Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Clinical Packet
November 8, 2023

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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 ensure any restriction on pharmaceutical use does not increase overall health care costs to Medicaid.

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

Preferred Drug List/Program Definitions

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

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

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

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

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

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

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

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

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

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

Accumulation Edit
Brand Limit Switchover
Dispense As Written Override
Early Refill
Ingredient Duplication
Maximum Unit/Max Cost Limitations
Therapeutic Duplication

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

Prior Authorization Criteria Definitions

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

Prior Treatment Trials: Prior authorization requires that two (2) prescribed generic 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 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 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, 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

Antihistamines (First Generation)

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 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.

Stable Therapy

- Approval may be given for children age 18 years and under who have documented stable therapy on the requested medication for 60 consecutive days or greater.

Medical Justification

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

PA Approval Timeframes

- Approval may be given for up to 12 months.

Electronic Prior Authorization (EPA)

- Antihistamines are included in the electronic PA program.

Verbal PA Requests

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

Estrogens

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 estrogens in this class, either generic, OTC or brand, within the past 6 months, or have a documented allergy or contraindication to all preferred agents in this class.

Stable Therapy

- Approval may be given for children age 18 years and under who have documented stable therapy on the requested medication for 60 consecutive days or greater.

Medical Justification

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

PA Approval Timeframes

- Approval may be given for up to 12 months.

Electronic Prior Authorization (EPA)

- Estrogens are included in the electronic PA program.

Verbal PA Requests

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

Antidiabetic 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 antidiabetic agents, either generic, OTC or brand, within the past 12 months, or have a documented allergy or contraindication to all preferred agents in this class.

- If the request is for Symlin®, the patient must also be on insulin therapy and have a hemoglobin A_{1c} greater than 7% despite more than 90 days of insulin therapy.

- If the request is for Korlym®, the patient must be ≥18 years of age with endogenous Cushing's syndrome with type 2 diabetes mellitus or glucose intolerance and have failed surgery or are not candidates for surgery.

Stable Therapy

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

Medical Justification

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

PA Approval Timeframes

- Approval may be given for up to 12 months.

Electronic Prior Authorization (EPA)

- Antidiabetic agents, excluding Symlin® and Korlym®, are included in the electronic PA program.

Verbal PA Requests

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

Prenatal Vitamins

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 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.

Stable Therapy

- Approval may be given for children age 18 years and under who have documented stable therapy on the requested medication for 60 consecutive days or greater.

Medical Justification

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

PA Approval Timeframes

- Approval may be given for up to 12 months.

Electronic Prior Authorization (EPA)

- 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, 2023
1:00 p.m. – 3:00 pm

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1. Opening remarks…….…….....…….Chair
2. Approval of August 2, 2023 P&T Committee Meeting minutes…….…....…Chair
3. Pharmacy program update…….…….....…….....Alabama Medicaid
4. Oral presentations by manufacturers/manufacturers' representatives
   (prior to each respective class review)
5. Pharmacotherapy class re-reviews.….....UMass Medical School Clinical Pharmacy Services
   - First Generation Antihistamines
     - Ethanolamine Derivatives-AHFS 040404
     - Ethylenediamine Derivatives-AHFS 040408
     - Propylamine Derivatives-AHFS 040420
   - Estrogens-AHFS 681604
   - Alpha Glucosidase Inhibitors-AHFS 682002
   - Amylinomimetics-AHFS 682003
   - Biguanides-AHFS 682004
   - Dipeptidyl Peptidase-4 (DPP-4) Inhibitors-AHFS 682005
   - Incretin Mimetics-AHFS 682006
   - Insulins-AHFS 682008
   - Meglitinides-AHFS 682016
   - Sodium-glucose Cotransport 1 Inhibitors-AHFS 682017
   - Sodium-glucose Cotransport 2 Inhibitors-AHFS 682018
   - Sulfonylureas-AHFS 682020
   - Thiazolidinediones-AHFS 682028
   - Antidiabetic Agents, Miscellaneous-AHFS 682092
   - Multivitamin Preparations: Prenatal Vitamins-AHFS 882800
   - Immunomodulatory Agents used to treat Multiple Sclerosis-AHFS 922000
   - Antigout Agents-AHFS 921600
   - Genitourinary Smooth Muscle Relaxants: Antimuscarinics-AHFS 861204
   - Genitourinary Smooth Muscle Relaxants: Beta-3 Adrenergic Agents-AHFS 861208
6. Results of voting announced……..……..…....…….……...Chair
7. New business
   - Election of new Chair and Vice-Chair
8. Next meeting dates:
   - February 7, 2024
   - May 8, 2024
   - August 7, 2024
   - November 6, 2024
9. Adjourn

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of First Generation Antihistamines
Ethanolamine Derivatives, AHFS Class 040404
Ethylenediamine Derivatives, AHFS Class 040408
Propylamine Derivatives, AHFS Class 040420
November 8, 2023

I. Overview

The H_1-antihistamines are approved for the treatment of allergic and non-allergic conditions; however, they are primarily used for the management of allergic rhinitis, urticaria, and angioedema. Allergic rhinitis is a common disorder that is associated with significant morbidity, including lost school/work days, interference with activities of daily living, and a decrease in quality of life. Nasal symptoms include sneezing, itching, rhinorrhea, and congestion. Rhinitis may also be accompanied by symptoms involving the eyes, ears, and throat.[1] Urticaria is a common disorder characterized by pruritic, raised, erythematous plaques. Lesions may appear on any part of the body; however, they frequently appear on the trunk and extremities. As is seen with allergic rhinitis, intense itching may interfere with sleep, school/work productivity, and quality of life. Angioedema is characterized by swelling of deeper subcutaneous tissues, with less circumscribed lesions. It often involves the face, eyelids, lips, and tongue and may be life-threatening if laryngeal edema or tongue swelling obstructs the airway.[2]

H_1-antihistamines reduce the physiologic effects elicited by histamine at the H_1-receptor; however, they do not prevent the release of histamine or bind to histamine that has already been released. They are classified as first generation and second generation agents. First generation antihistamines bind to both central and peripheral H_1-receptors, whereas second generation agents are more selective for peripheral H_1-receptors. As a result, the first generation antihistamines may cause sedation, performance impairment in school and driving, as well as anticholinergic effects.[3]

The first generation antihistamines include ethanolamine derivatives (carbinoxamine, clemastine, and diphenhydramine), ethylenediamine derivatives (no current agents), and propylamine derivatives (chlorpheniramine and dexchlorpheniramine). They are available as single entity agents, as well as in combination with phenylephrine, an oral decongestant.

The first generation antihistamines that are included in this review are listed in Table 1. This review encompasses all systemic dosage forms and strengths. The eye, ear, nose, and throat anti-allergic agents (American Hospital Formulary Service 520200) were previously reviewed and are not included in this review. All of the first generation antihistamines with the exception of dexchlorpheniramine are available in a generic formulation. Cough and cold products are an excludable/optional drug class in accordance with the Omnibus Budget Reconciliation Act of 1990 (OBRA 90). Brand cough and cold products are not covered by Alabama Medicaid; therefore, these products were not included in this review. The second generation antihistamines (acrivastine, cetirizine, desloratadine, fexofenadine, levocetirizine, and loratadine) are not included on the mandatory preferred drug list. Brand products currently require prior authorization. Covered generics (unless otherwise specified) do not require prior authorization. Although the second generation antihistamines may be mentioned throughout this review, they are not being considered for preferred status at this time. This class was last reviewed in November 2021.

Table 1. First Generation Antihistamines Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Ethanolamine Derivatives			
Carbinoxamine	extended-release suspension, solution*, tablet*	Karbinal ER®, Ryvent®	carbinoxamine
Clemastine	syrup, tablet	N/A	clemastine
Diphenhydramine	elixir, injection	N/A	diphenhydramine
Propylamine Derivatives			

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Dexchlorpheniramine	solution	Ryclora®	none
Phenylephrine and chlorpheniramine	drops	N/A	phenylephrine and chlorpheniramine

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

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the first generation antihistamines are summarized in Table 2.

Table 2. Treatment Guidelines Using the First Generation Antihistamines

Clinical Guideline	Recommendation(s)
American Academy of Allergy, Asthma, and Immunology/ American College of Allergy, Asthma, and Immunology/ Joint Council on Allergy, Asthma, and Immunology: **The Diagnosis and Management of Anaphylaxis: A Practice Parameter Update (2020)[4]**	• Severe anaphylaxis and/or the need for >1 dose of epinephrine to treat anaphylaxis are risk factors for biphasic anaphylaxis. Additional risk factors include wide pulse pressure, unknown anaphylaxis trigger, cutaneous signs and symptoms, and drug trigger in children. • Extended observation is suggested for patients with resolved severe anaphylaxis and/or those with need for >1 dose of epinephrine. • Antihistamines and/or glucocorticoids are not reliable interventions to prevent biphasic anaphylaxis but may be considered as secondary treatment. • Evidence supports a role for antihistamine and/or glucocorticoid premedication in specific chemotherapy protocols and rush aeroallergen immunotherapy. • Evidence is lacking to support the routine use of antihistamines and/or glucocorticoid premedication in patients receiving low- or iso-osmolar contrast material to prevent recurrent radiocontrast media anaphylaxis. • Administer epinephrine as the first-line pharmacotherapy for uniphasic and/or biphasic anaphylaxis. • Do not delay the administration of epinephrine for anaphylaxis. • After diagnosis and treatment of anaphylaxis, all patients should be kept under observation until symptoms have fully resolved. • All patients with anaphylaxis should receive education about anaphylaxis, risk of recurrence, trigger avoidance, self-injectable epinephrine, and thresholds for further care, and they should be referred to an allergist for follow-up evaluation.
American Academy of Dermatology Clinical Guidelines Task Force: **Guidelines of Care for the Management of Atopic Dermatitis (2014)[5-6]**	<u>Topical corticosteroids</u> • Topical corticosteroids (TCs) are used in the management of atopic dermatitis in both adults and children and are the mainstay of anti-inflammatory therapy. • TCs are typically introduced into the treatment regimen after failure of lesions to respond to good skin care and regular use of moisturizers alone. • TCs are used for both active inflammatory disease and for prevention of relapses. • There are no data to support one or a few specific agents as being more efficacious than others. • Most studies involve twice daily application. This is the most common clinical practice and also the generally recommended frequency. However, there is evidence to support that once daily application of some potent corticosteroids may be as effective as twice daily application. Some newer formulations also use once daily application. <u>Topical calcineurin inhibitors</u> • The two available topical calcineurin inhibitors (TCIs), tacrolimus ointment and pimecrolimus cream, have been shown to be more effective than vehicle in short-term and long-term studies in adults and children with active disease.

Clinical Guideline	Recommendation(s)
	• Tacrolimus is approved for moderate to severe disease, where pimecrolimus is indicated for mild to moderate atopic dermatitis, and six-week comparative studies support a greater effect for tacrolimus for all severities. • Twice daily application of the tacrolimus ointments and pimecrolimus cream are significantly more effective at decreasing signs of inflammation, affected body surface area, and associated pruritus of lesional areas on the head/neck and non-head/neck locations than vehicle or once-daily application in adults, children, and infants. • Proactive, intermittent application of TCI two to three times weekly to recurrent sites of disease has also been shown to be effective in reducing relapses. <u>Topical antimicrobials and antiseptics</u> • Patients with atopic dermatitis are commonly colonized with *Staphylococcus aureus*. • No clear benefit for topical antibiotics/antiseptics, antibacterial soaps, or antibacterial bath additives has been established. Thus, topical antimicrobial preparations are not generally recommended in the treatment of atopic dermatitis. <u>Topical antihistamines</u> • Topical antihistamines have been tried doe the treatment of atopic dermatitis but have demonstrated little utility and are not recommended. <u>Systemic agents</u> • Systemic agents are recommended in the subset of atopic dermatitis patients in whom optimized topical regimens and/or phototherapy do not adequately control the disease, or when quality of life is substantially impacted. • All immunomodulatory agents should be adjusted to the minimal effective dose once response is attained and sustained. • Adjunctive therapies should be continued to use the lowest dose and duration of systemic agent possible. • Insufficient data exist to firmly recommend optimal dosing, duration of therapy, and precise monitoring protocols for any systemic immunomodulating medication. • Treatment decisions should be based on each individual patient's atopic dermatitis status (current and historical), comorbidities, and preferences. • Cyclosporine is effective and recommended as a treatment option for patients with atopic dermatitis refractory to conventional topical treatment. • Azathioprine is recommended as a systemic agent for the treatment of refractory atopic dermatitis. • Methotrexate is recommended as a systemic agent for the treatment of refractory atopic dermatitis. Folate supplementation is recommended during treatment with methotrexate. • Mycophenolate mofetil may be considered as an alternative, variably effective therapy for refractory atopic dermatitis. • Interferon gamma is moderately and variably effective and may be considered as an alternative therapy for refractory atopic dermatitis in adults and children who have not responded to, or have contraindications to the use of, other systemic therapies or phototherapy. • Systemic steroids should be avoided if possible for the treatment of atopic dermatitis. Their use should be exclusively reserved for acute, severe exacerbations and as a short-term bridge therapy to other systemic, steroid-sparing therapy. • The use of systemic antibiotics in the treatment of noninfected atopic dermatitis is not recommended. Systemic antibiotics are appropriate and can be recommended for use in patients with clinical evidence of bacterial infections in

Clinical Guideline	Recommendation(s)
	addition to standard and appropriate treatments for atopic dermatitis disease itself (which may include the concurrent use of topical corticosteroids). Systemic antiviral agents should be used for the treatment of eczema herpeticum. • There is insufficient evidence to recommend the general use of oral antihistamines as part of the treatment of atopic dermatitis. Short-term, intermittent use of sedating antihistamines may be beneficial in the setting of sleep loss secondary to itch, but should not be substituted for management of atopic dermatitis with topical therapies. Nonsedating antihistamines are not recommended as a routine treatment for atopic dermatitis in the absence of urticaria or other atopic conditions such as rhinoconjunctivitis.
American Academy of Allergy, Asthma, and Immunology/ American College of Allergy, Asthma, and Immunology/ Joint Council on Allergy, Asthma, and Immunology: **Disease Management of Atopic Dermatitis: An Updated Practice Parameter (2013)[7]**	<u>General considerations</u> • The intensity of management and treatment of atopic dermatitis is dictated by the severity of illness. The clinician should establish treatment goals with the patient, which may include reduction in number and severity of flares and increase in disease-free periods. • Clinicians should use a systematic, multipronged approach that includes skin hydration, topical anti-inflammatory medications, antipruritic therapy, antibacterial measures, and elimination of exacerbating factors. <u>Skin hydration</u> • Atopic dermatitis is characterized by reduced skin barrier function, which leads to enhanced water loss and dry skin; therefore, hydration with warm soaking baths for at least 10 minutes followed by application of a moisturizer is recommended as first-line therapy. <u>Topical corticosteroids</u> • If atopic dermatitis is not controlled by moisturizers alone, a topical corticosteroid is recommended. • Low-potency corticosteroids are recommended for maintenance therapy, whereas intermediate and high-potency corticosteroids should be used for the treatment of clinical exacerbation over short periods of time. Clinicians should not prescribe potent fluorinated corticosteroids for use on the face, eyelids, genitalia, and intertriginous areas or in young infants. Ultrahigh-potency corticosteroids are recommended only for very short periods (1 to 2 weeks) and in nonfacial non-skinfold areas. • When prescribing topical steroids, clinicians should remember that the degree of corticosteroid absorption through the skin and hence the potential for systemic adverse effects are directly dependent on the surface area of the skin involved, thickness of the skin, the use of occlusive dressing, and the potency of the corticosteroid preparation. <u>Topical calcineurin inhibitors</u> • Clinicians can consider the use of tacrolimus ointment, which has been shown to be effective and safe in both adults and children older than two years for the treatment of atopic dermatitis, with most patients experiencing a reduction of pruritus within three days of initiating therapy. Tacrolimus ointment, which, unlike topical steroids, does not cause atrophy for eczema on the face, eyelid, and skin folds, is an option for patients unresponsive to low-potency topical steroids. Topical tacrolimus can cause transient localized burning and itching during the first week of therapy. This might limit its usefulness in certain patients. Once a flare is controlled, the clinician might consider prescribing tacrolimus ointment twice daily, twice weekly to eczema-prone areas to prevent future flares. • Clinicians should consider the use of topical pimecrolimus cream, which is a calcineurin inhibitor that safely decreases the number of flares, reduces the need for corticosteroids, does not cause skin atrophy, and controls pruritus.

Clinical Guideline	Recommendation(s)
	Tar preparations • Although tar preparations are widely used, there are no randomized controlled studies that have demonstrated their efficacy. Tar should not be recommended for acutely inflamed skin because this might result in additional skin irritation. Antihistamines • Some patients may benefit from the use of antihistamines for the relief of pruritus. Treatment with topical antihistamines is not recommended because of potential cutaneous sensitization. Vitamin D • Patient may benefit from supplementation with vitamin D, particularly if they have a documented low level or low vitamin D intake. Dilute bleach baths • Consider the addition of dilute bleach baths twice weekly to reduce the severity of atopic dermatitis, especially in patients with recurrent skin infections. Microbes • Skin infections with *Staphylococcus aureus* are a recurrent problem in patients with atopic dermatitis, and patients with moderate-to-severe dermatitis have been found to make IgE antibodies against staphylococcal toxins present in their skin. • A short course of an appropriate systemic antibiotic should only be prescribed for patients who are clinically infected with *Staphylococcus aureus*. In areas with high levels of methicillin-resistant *Staphylococcus aureus*, the clinician might want to obtain a skin culture and initiate treatment with clindamycin, doxycycline, or sulfamethoxazole-trimethoprim while awaiting culture results. • Atopic dermatitis can be complicated by recurrent viral skin infections, such as herpes simplex, warts, and molluscum contagiosum. Disseminated herpes simplex or eczema herpeticum should promptly be treated with systemic antiviral agents. • Atopic dermatitis patients and their household should not be immunized with the smallpox vaccine because they can have a severe, widespread, potentially fatal cutaneous infection called eczema vaccinatum, which is similar in appearance to eczema herpeticum. • Consider fungal infections that can contribute to exacerbations. The diagnosis of dermatophytes can be made by using KOH preparation or culture. *Malassezia* species, which is a particular problem in young adults with refractory head and neck eczema, can be diagnosed clinically or with a KOH preparation. Specific IgE to *Malassezia* species might also be obtained.
American Academy of Ophthalmology Preferred Practice Pattern Guidelines: **Conjunctivitis (2018)**[8]	Seasonal allergic conjunctivitis • Mild allergic conjunctivitis can be treated with an over-the-counter antihistamine/vasoconstrictor agent or with the more effective second-generation topical histamine H_1- receptor antagonists. • Mast-cell stabilizers can be utilized if the condition is recurrent or persistent. • Combination antihistamine and mast-cell stabilizer medications can be utilized for either acute or chronic disease. • If the symptoms are not adequately controlled, a brief course (one to two weeks) of a topical corticosteroid with a low side effect profile can be added to the regimen. • Oral antihistamines are commonly used but may induce or worsen dry eye syndrome, impair the tear film's protective barrier, and actually worsen allergic conjunctivitis. • Concomitant use of cooled artificial tears may alleviate coexisting tear deficiency and dilute allergens and inflammatory mediators on the ocular surface.

Clinical Guideline	Recommendation(s)
	• In severe cases, topical cyclosporine or tacrolimus can be considered. • Use of topical mast-cell stabilizers can also be helpful in alleviating symptoms of allergic rhinitis, and mast-cell inhibitors formulated as a nasal spray and aerosols are also helpful in alleviating the symptoms of allergic rhinitis and asthma in some patients. <u>Vernal/atopic conjunctivitis</u> • General treatment measures include minimizing exposure to allergens or irritants and using cool compresses and ocular lubricants. • Topical and oral antihistamines and topical mast-cell stabilizers can be useful to maintain comfort. • Topical corticosteroids are usually necessary to control severe signs and symptoms during acute exacerbations. • Topical cyclosporine (2.0%) has demonstrated a reduction in signs and symptoms compared with placebo after two weeks of use in patients with vernal keratoconjunctivitis. • Commercially available 0.05% topical cyclosporine has also been shown to be effective in more frequent dosing for the treatment of severe vernal/atopic conjunctivitis and it has been shown to be effective in preventing seasonal recurrences. • Use of cyclosporine may allow for reduced use of topical steroids. • For severe sight-threatening atopic keratoconjunctivitis that is not responsive to topical therapy, supratarsal injection of corticosteroid can be considered. • Systemic immunosuppression is rarely warranted, but options include montelukast, aspirin, interferons, and oral T-cell inhibitors, such as cyclosporine and tacrolimus. • In patients two years of age and older, eyelids can be treated with pimecrolimus cream (1.0%) or tacrolimus ointment applied to the affected eyelid skin. Tacrolimus drops/ointment 0.03% is used for children two to 15 years of age; either 0.03% or 0.1% is used for patients 16 years and older. Both agents are rarely associated with development of skin cancer or lymphoma.
American Academy of Allergy, Asthma, and Immunology/ American College of Allergy, Asthma, and Immunology/ Joint Council on Allergy, Asthma, and Immunology: **Rhinitis: A Practice Parameter Update (2020)**[1]	• Complete a detailed history and a physical examination in a patient presenting with symptoms of rhinitis. • For patients presenting with rhinitis symptoms, a review of all current medications should be completed to assess whether drug-induced rhinitis may be present. • Aeroallergen skin prick testing or serum-specific IgE testing is recommended to confirm the diagnosis of allergic rhinitis in a patient with a history consistent with allergic rhinitis. • Do not perform food skin prick testing or serum-specific IgE for foods in their routine evaluation of a patient presenting with the signs and symptoms compatible with the diagnosis of allergic rhinitis. • Use of a validated instrument (e.g., scoring system, scale, or questionnaire) should be considered to help determine the severity of rhinitis and to monitor the degree of disease control. • Recommendations are against prescribing a first-generation antihistamine and are in favor of a second-generation antihistamine when prescribing an oral antihistamine for the treatment of allergic rhinitis. • Clinicians should not select the oral leukotriene receptor antagonist montelukast for the initial treatment of allergic rhinitis due to reduced efficacy when compared with that of other agents. Furthermore, serious neuropsychiatric events that may include suicidal thoughts or actions have been reported in some patients taking montelukast. As advised by the FDA, montelukast should be used to treat allergic rhinitis only in patients who are not treated effectively with or cannot tolerate other alternative therapies.

Clinical Guideline	Recommendation(s)
	• Clinicians should not select an oral leukotriene receptor antagonist for the treatment of nonallergic rhinitis. • For the treatment of very severe or intractable allergic rhinitis, the clinician may consider a short course (five to seven days) of oral corticosteroids. • For the treatment of very severe or intractable allergic rhinitis, the clinician should not prescribe a depot parenteral corticosteroid for allergic rhinitis due to the potential risks of systemic and local corticosteroid side effects. • Clinicians should offer intranasal antihistamines as an initial treatment option for patients with seasonal allergic rhinitis. • Clinicians should offer intranasal antihistamines as a first-line monotherapy option for patients with nonallergic rhinitis. • Clinicians should offer intranasal antihistamines as a first-line option for patients with intermittent allergic rhinitis. • When choosing monotherapy for persistent allergic rhinitis, intranasal corticosteroids should be the preferred medication. • For the initial treatment of moderate/severe seasonal allergic rhinitis in patients ≥15 y of age, clinicians should use an intranasal corticosteroid over a leukotriene receptor antagonist. • The use of intranasal decongestants should be short term and used for intermittent or episodic therapy of nasal congestion. • In patients having severe mucosal edema, which impairs the delivery of other intranasal agents, an intranasal decongestant should be considered for up to five days of use. • Oral decongestant agents should be used with caution in older adults and children younger than four years old, and in patients of any age who have a history of cardiac arrhythmia, angina pectoris, cerebrovascular disease, uncontrolled hypertension, bladder outlet obstruction, glaucoma, hyperthyroidism, or Tourette syndrome. • Oral decongestants should be avoided during the first trimester of pregnancy. • Patients with perennial allergic rhinitis and nonallergic rhinitis who have rhinorrhea as their main nasal symptom should be offered intranasal ipratropium. • Intranasal cromolyn can be offered as an option to be taken just prior to allergen exposure to reduce symptoms of allergic rhinitis from episodic allergen exposures. • Clinicians may consider the combination of an intranasal corticosteroids and an intranasal antihistamine for the initial treatment of moderate/severe nasal symptoms of seasonal allergic rhinitis in patients ≥12 years old. • Clinicians may consider the combination of an intranasal corticosteroids and an intranasal antihistamine for moderate/severe seasonal allergic rhinitis and perennial allergic rhinitis that is resistant to pharmacologic monotherapy. • Clinicians should consider the combination of an intranasal corticosteroids and an intranasal antihistamine for moderate/severe nonallergic rhinitis that is resistant to pharmacologic monotherapy. • For patients taking an intranasal corticosteroid who have persistent rhinorrhea, the clinician may consider the addition of intranasal ipratropium. • Patients with persistent nasal congestion unresponsive to an intranasal corticosteroid or to an intranasal corticosteroids-intranasal antihistamines combination may be offered combination therapy with addition of an intranasal decongestant for up to four weeks. • For patients with allergic rhinitis and nasal congestion uncontrolled with an oral antihistamine, clinicians should consider the addition of pseudoephedrine, when tolerated. • For seasonal allergic rhinitis clinicians should not combine the oral leukotriene receptor antagonist montelukast with an oral antihistamine for symptoms not controlled with an oral antihistamine.

Clinical Guideline	Recommendation(s)
	• Clinicians should not prescribe, as initial treatment, a combination of an oral antihistamine and an intranasal steroid in preference to monotherapy with an intranasal steroid in patients ≥12 years of age with symptoms of seasonal allergic rhinitis. • Clinicians should not prescribe the combination of an oral antihistamine and an intranasal corticosteroid in preference to monotherapy with an intranasal steroid in all patients with seasonal allergic rhinitis and perennial allergic rhinitis. • The guideline suggests against the addition of the oral leukotriene receptor antagonist montelukast to an intranasal corticosteroid for allergic rhinitis, due to the lack of adequate evidence of improved efficacy and concerns for serious neuropsychiatric events from montelukast. • Clinicians may offer an intranasal corticosteroid as a first-line therapy for nonallergic rhinitis. • Clinicians may offer an intranasal antihistamine as a first-line therapy for nonallergic rhinitis. • Allergen immunotherapy (subcutaneous or sublingual tablets) may be offered through shared decision making to patients with moderate/severe allergic rhinitis who (1) are not controlled with allergen avoidance and/or pharmacotherapy or (2) choose immunotherapy as the preferred method of treatment (e.g., due to the desire to avoid the adverse effects, costs, or long-term use of pharmacotherapy) and/or (3) desire the potential benefit of immunotherapy to prevent or reduce the severity of comorbid conditions, such as asthma. • Allergen immunotherapy (subcutaneous or sublingual tablets) may be considered for patients with controlled mild/moderate asthma with coexisting allergic rhinitis. • A recommendation for or against the use of acupuncture for the treatment of allergic rhinitis cannot be made. • A recommendation for or against the use of specific herbal products for the treatment of allergic rhinitis cannot be made.

American Academy of Allergy, Asthma, and Immunology/ American College of Allergy, Asthma, and Immunology/ Joint Council on Allergy, Asthma, and Immunology: **Treatment of Seasonal Allergic Rhinitis - An Evidence-Based Focused 2017 Guideline Update (2017)[9]**	• <u>For initial treatment of nasal symptoms of seasonal allergic rhinitis in patients ≥12 years of age:</u>
	  ○ Routinely prescribe monotherapy with an intranasal corticosteroid rather than a combination of an intranasal corticosteroid with an oral antihistamine.
	  ○ Recommend an intranasal corticosteroid over a leukotriene receptor antagonist (for ≥15 years of age). For moderate to severe symptoms, may recommend the combination of an intranasal corticosteroid and an intranasal antihistamine.

Global Allergy and Asthma European Network: **Allergic Rhinitis and its Impact on Asthma (ARIA) Guidelines: 2016 Revision (2016)[10]**	<u>Should a combination of an oral H_1-antihistamine and intranasal corticosteroid vs intranasal corticosteroid alone be used for treatment of allergic rhinitis?</u> • In patients with seasonal allergic rhinitis, utilize either a combination of an intranasal corticosteroid with an oral H_1-antihistamine or an intranasal corticosteroid alone. • In patients with perennial allergic rhinitis, utilize an intranasal corticosteroid alone rather than a combination of an intranasal corticosteroid with an oral H_1-antihistamine. <u>Should a combination of an intranasal H_1-antihistamine and intranasal corticosteroid vs an intranasal corticosteroid alone be used for treatment of allergic rhinitis?</u>

Clinical Guideline	Recommendation(s)
	• In patients with seasonal allergic rhinitis, utilize either a combination of an intranasal corticosteroid with an intranasal H_1-antihistamine or an intranasal corticosteroid alone. • In patients with perennial allergic rhinitis, utilize either a combination of an intranasal corticosteroid with an intranasal H_1-antihistamine or an intranasal corticosteroid alone. <u>Should a combination of an intranasal H_1-antihistamine and intranasal corticosteroid vs an intranasal H_1-antihistamine alone be used for treatment of allergic rhinitis?</u> • In patients with seasonal allergic rhinitis, utilize a combination of an intranasal corticosteroid with an intranasal H_1-antihistamine rather than an intranasal H_1-antihistamine alone. <u>Should a leukotriene receptor antagonist vs an oral H_1-antihistamine be used for treatment of allergic rhinitis?</u> • In patients with seasonal allergic rhinitis, utilize either a leukotriene receptor antagonist or an oral H_1-antihistamine. • In patients with perennial allergic rhinitis, utilize an oral H_1-antihistamine rather than a leukotriene receptor antagonist. <u>Should an intranasal H_1-antihistamine vs an intranasal corticosteroid be used for treatment of allergic rhinitis?</u> • In patients with seasonal allergic rhinitis, utilize an intranasal corticosteroid rather than an intranasal H_1-antihistamine. • In patients with perennial allergic rhinitis, utilize an intranasal corticosteroid rather than an intranasal H_1-antihistamine. <u>Should an intranasal H_1-antihistamine vs an oral H_1-antihistamine be used for treatment of allergic rhinitis?</u> • In patients with seasonal allergic rhinitis, utilize either an intranasal H_1-antihistamine or oral H_1-antihistamine. • In patients with perennial allergic rhinitis, utilize either an intranasal H_1-antihistamine or oral H_1-antihistamine.
American Academy of Otolaryngology–Head and Neck Surgery Foundation: **Clinical Practice Guideline: Allergic Rhinitis (2015)**[11]	• Advise avoidance of known allergens or environmental controls (e.g., removal of pets, the use of air filtration systems, bed covers) in allergic rhinitis patients who have identified allergens that correlate with clinical symptoms. • Recommend intranasal steroids for patients with a clinical diagnosis of allergic rhinitis whose symptoms affect their quality of life. • Recommend oral second-generation/less sedating antihistamines for patients with allergic rhinitis and primary complaints of sneezing and itching. • Offer intranasal antihistamines for patients with seasonal, perennial, or episodic allergic rhinitis. • Do <u>not</u> offer oral leukotriene receptor antagonists as primary therapy for patients with allergic rhinitis. • Combination pharmacologic therapy may be used in patients with allergic rhinitis who have inadequate response to pharmacologic monotherapy. • Offer immunotherapy (sublingual or subcutaneous) for patients with allergic rhinitis who have inadequate response to symptoms with pharmacologic therapy with or without environmental controls.
American Academy of Otolaryngology–Head and Neck Surgery Foundation:	<u>Symptomatic relief of viral rhinosinusitis</u> • Management of viral rhinosinusitis is primarily symptomatic, with an analgesic or antipyretic provided for pain or fever, respectively. • Topical or systemic decongestants may offer additional symptomatic relief. • Antihistamines have been used to treat viral rhinosinusitis due to their drying effect; however, no studies have been published that assess the impact of

Clinical Guideline	Recommendation(s)
Clinical Practice Guideline (update): Adult Sinusitis (2015)[12]	antihistamines specifically on viral rhinosinusitis outcomes. Adverse effects of antihistamines, especially first-generation H_1-antagonists, include drowsiness, behavioral changes, and impaired mucus transport in the nose and sinuses because of drying. <u>Symptomatic relief of acute bacterial rhinosinusitis</u> • Symptomatic treatments for acute bacterial rhinosinusitis include analgesics, saline irrigation, and topical nasal steroids. Use of interventions with questionable or unproven efficacy (antihistamines, systemic steroids) is discouraged. Commonly used interventions (decongestants, guaifenesin) with unknown effects on acute bacterial rhinosinusitis symptoms may be considered. • Adjunctive treatments for rhinosinusitis that may aid in symptomatic relief include analgesics, decongestants (α-adrenergic), corticosteroids, saline irrigation, and mucolytics. None of these products has been specifically approved by the Food and Drug Administration (FDA) for use in acute rhinosinusitis (as of March 2014), and only some have data from controlled clinical studies supporting this use. • Antihistamines have no role in the symptomatic relief of acute bacterial rhinosinusitis in nonatopic patients. There are no studies that support their use in an infectious setting, and antihistamines may worsen congestion by drying the nasal mucosa. • Antihistamines may be considered in patients with acute bacterial rhinosinusitis whose symptoms suggest a significant allergic component. <u>Watchful waiting for acute bacterial rhinosinusitis</u> • Observation without use of antibiotics is an option for selected adults with uncomplicated acute bacterial rhinosinusitis (regardless of severity). <u>Choice of antibiotic for acute bacterial rhinosinusitis</u> • If a decision is made to treat acute bacterial rhinosinusitis with an antibiotic, the clinician should prescribe amoxicillin with or without clavulanate as first-line therapy for five to 10 days for most adults. <u>Treatment failure for acute bacterial rhinosinusitis</u> • If the patient worsens or fails to improve with the initial management option by seven days after diagnosis, the clinician should reassess the patient to confirm acute bacterial rhinosinusitis, exclude other causes of illness, and detect complications. • If acute bacterial rhinosinusitis is confirmed in the patient initially managed with observation, the clinician should begin antibiotic therapy. • If the patient was initially managed with an antibiotic, the clinician should change the antibiotic.
American Academy of Allergy, Asthma, and Immunology/ American College of Allergy, Asthma, and Immunology/ Joint Council on Allergy, Asthma, and Immunology: **The Diagnosis and Management of Rhinosinusitis: A Practice Parameter Update**	<u>Acute bacterial rhinosinusitis</u> • Acute bacterial rhinosinusitis is defined as symptoms and signs for less than 12 weeks. The diagnosis of acute rhinosinusitis is based primarily on the clinical history, the physical examination, and possibly other ancillary evaluations, including endoscopy or radiographic imaging. In most instances the diagnosis is made presumptively, and treatment is initiated. • Patients with obvious acute bacterial rhinosinusitis should be carefully reviewed for any possible evidence of complicating factors, including the presence of facial swelling, erythema over an involved sinus, visual changes, abnormal extraocular movements, proptosis, periorbital inflammation, any suggestion of intracranial involvement, or central nervous system involvement manifested as abnormal neurologic signs.

Clinical Guideline	Recommendation(s)
(2014)[13]	• Empiric treatment with an antibiotic approved by the FDA should be started once the diagnosis is made. Empiric therapy is administered for seven to 14 days. FDA-approved antibiotics include amoxicillin, amoxicillin-clavulanate, cefaclor, cefprozil, cefuroxime, cefdinir, cefixime, azithromycin, levofloxacin, trimethoprim-sulfamethoxazole, doxycycline, and clindamycin. Fluoroquinolones and doxycycline should be avoided in children. Nasal steroids may be of benefit, especially in allergic individuals. • A systematic review of antihistamines and decongestants in common colds found that there is insufficient evidence to suggest that antihistamines or decongestants are of benefit for the common cold. Antihistamines may slightly alleviate rhinorrhea and sneezing, but the overall benefit is minimal. Decongestants decrease congestion over six to 10 hours, but there is no evidence to suggest benefit for longer than 10 hours. • The following comfort measures might be helpful: adequate rest, adequate hydration, analgesics as needed, warm facial packs, steamy showers, and sleeping with the head of the bed elevated. Patients should be instructed to follow up if symptoms worsen (e.g., especially with headache or high fever) or if symptoms have not improved within three to five days of treatment. • For partial response, continue antibiotic treatment for another 10 to 14 days or consider a different antibiotic. • For poor response, which worsens after three to five days, consider broadening the microbial coverage provided by the antibiotic or switch to a different antimicrobial that covers resistant bacteria. • Rhinosinusitis that fails to improve after 21 to 28 days of initial antibiotic treatment might be caused by pathogens not adequately covered by prior antibiotics, nasal polyps, tumor, or noncompliance. <u>Chronic rhinosinusitis</u> • Clinicians should use systemic antibiotics for acute exacerbations of chronic rhinosinusitis. However, in some patients, this may not be necessary. • Consider a three- to six-week course of topical antibiotics for chronic rhinosinusitis. • Consider the use of systemic antibiotics plus a short course of oral steroids in the treatment of chronic rhinosinusitis. Greater benefit with antibiotics has been reported in patients without nasal polyps than with nasal polyps. • Consider a short course of oral steroids for the treatment of patients without nasal polyps. • Use short-term treatment with oral steroids in patients with nasal polyps because it decreases nasal polyp size and symptoms. • Use intranasal corticosteroid (INS; sprays and aerosols) for the treatment of patients with or without nasal polyps. • Use nasal saline irrigation as an adjunctive treatment for the therapy of chronic rhinosinusitis. • Consider antihistamines for treatment of symptoms associated with acute rhinosinusitis in patients with coexistent chronic rhinosinusitis. • Neither oral nor topical decongestants are beneficial for maintenance treatment of chronic rhinosinusitis.
American Academy of Allergy, Asthma, and Immunology/ American College of Allergy, Asthma, and Immunology/ Joint Council on Allergy,	<u>Acute urticaria and angioedema</u> • Antihistamines are efficacious in most cases and are recommended as first-line therapy. Although first-generation antihistamines are rapidly acting and effective, in both pediatric and adult patients they may be associated with sedation and impaired motor skills due to their ability to cross the blood-brain barrier, while these impairments are less evident or not evident with second-generation antihistamines as a class.

Clinical Guideline	Recommendation(s)
Asthma, and Immunology: **Diagnosis and Management of Urticaria: A Practice Parameter (2014)[2]**	• In patients with poor response to antihistamines, a brief course of oral corticosteroids may also be required while attempting to eliminate suspected triggers and develop an effective treatment plan. <u>Chronic urticaria</u> • H_1-antagonists are effective in the majority of patients but may not achieve complete control in all patients. Second-generation antihistamines are safe and effective therapies in chronic urticaria and are considered first-line agents. • For patients not responding to monotherapy with a second generation antihistamine at Food and Drug Administration- approved doses, several treatment options can be employed. Higher doses of second-generation antihistamines may provide more efficacy but data are limited and conflicting for certain agents. Addition of H_2-antagonists or leukotriene receptor antagonists may be considered for patients with unsatisfactory responses to 2nd generation antihistamine monotherapy. First-generation antihistamines may also be considered in patients who do not achieve control of their condition with higher dose second-generation antihistamines. • Treatment with a potent antihistamine, hydroxyzine or doxepin, may be considered in patients who remain poorly controlled with dose advancement of second-generation antihistamines, and/or addition of one of more of the following: H_2-antihistamines, first-generation H_1-antihistamine at bedtime, and/or anti-leukotrienes. • Systemic corticosteroids are frequently used for refractory patients, but no controlled studies have demonstrated efficacy. In some patients, short-term use (e.g., one to three weeks duration) may be required to gain control of their disease until other therapies can achieve control. Because of the risk of adverse effects with systemic corticosteroids, long-term use for treatment of chronic urticaria patients should be avoided. Patients who are not adequately controlled on maximal antihistamine therapy may be considered to have refractory chronic urticaria. • A number of alternative therapies have been studied for the treatment of chronic urticaria; these therapies merit consideration for patients with refractory disease. o Omalizumab and cyclosporine have the greatest published experience for efficacy compared to all other alternative agents. The therapeutic utility of omalizumab for refractory chronic urticaria has been supported by findings from large double-blind randomized controlled trials and is associated with a relatively low rate of clinically significant adverse effects. o There is evidence from observational studies with cyclosporine, including long-term use that suggests cyclosporine is efficacious for refractory chronic urticaria and capable of inducing remission. There is also evidence for efficacy of cyclosporine from randomized controlled trials; however, taken in the context of study limitations, potential harms and cost, the quality of evidence from these randomized controlled trials supporting cyclosporine is low, leading to a weak recommendation for use of cyclosporine. o Many other alternative therapies have been used in refractory chronic urticaria; however the level of evidence supporting their use is lower than with omalizumab or cyclosporine. Anti-inflammatory agents including dapsone, sulfasalazine, hydroxychloroquine, and colchicine have limited evidence for efficacy and some require laboratory monitoring for adverse effects. These agents are generally well tolerated and may be considered for properly selected patients with antihistamine refractory chronic urticaria. Other agents have been used in patients with refractory chronic urticaria, including but not limited to: theophylline, attenuated androgens, anticoagulants, NSAIDs, beta-agonists, cyclophosphamide, gold, plasmapheresis, cromolyn, and nifedipine; however, these agents should be reserved for patients with refractory urticaria who have failed other anti-

Clinical Guideline	Recommendation(s)
	inflammatory, immunosuppressant or biologic agents. Other unproven therapies, which are not recommended, include allergen immunotherapy, herbal therapies, vitamins, supplements, and acupuncture.
European Academy of Allergy and Clinical Immunology/ Global Allergy and Asthma European Network/ European Dermatology Forum/ Asia Pacific Association of Allergy, Asthma and Clinical Immunology: **Guideline for the definition, classification, diagnosis, and management of urticaria (2022)**[14]	Basic considerations • Urticaria is a frequent, mast cell-driven disease, presenting with wheals, angioedema, or both. • Urticaria is classified based on its duration as acute (≤ 6 weeks) or chronic (> 6 weeks). • Urticaria is classified as spontaneous (no specific eliciting factor involved) or inducible (specific eliciting factor involved). Management of urticaria • The goal of treatment is to treat the disease until it is gone and as efficiently and safely as possible aiming for complete control and a normalization of quality of life. Treatment should follow the basic principles of treating as much as needed and as little as possible. • The therapeutic approach to chronic urticaria should involve the search for and, if possible, elimination of underlying causes, which means healing the disease; the avoidance of eliciting factors, reducing disease activity; tolerance induction, reducing disease activity; and the use of pharmacological treatment to prevent mast cell mediator release and/or the effects of mast cell mediators, reducing disease activity. • Regular (rather than as needed) treatment with 2nd generation H_1-antihistamines are recommended as first-line treatment for all types of urticaria. • Updosing of a 2nd generation H_1-antihistamine up to fourfold in patients with chronic urticaria unresponsive to a standard-dosed 2nd generation H_1-antihistamines is recommended as second-line treatment before other treatments are considered. • Using different H_1-antihistamines at the same time is not suggested. • If there is no improvement, using higher than four-fold standard-dosed H_1-antihistamines in chronic urticaria is not recommended. • Adding on omalizumab for the treatment of patients with chronic urticaria unresponsive to high dose 2nd generation H_1-antihistamines is recommended. • Using cyclosporine for the treatment of patients with chronic urticaria unresponsive to high dose of 2nd generation H_1-antihistamine and omalizumab is suggested. • The long-term use of systemic glucocorticosteroids in chronic urticaria is NOT recommended. • A short course of rescue systemic glucocorticosteroids may be considered in patients with an acute exacerbation of chronic urticaria. • There is inadequate evidence to make a recommendation for or against the combined use of H_1- and H_2-antihistamines in patients with chronic urticaria. • There is inadequate evidence to make a recommendation with respect to further treatment options as standard therapies, but these may be considered in special cases, which also include those where financial or legal limitations for the recommended algorithm treatment exist.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the first generation antihistamines 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 First Generation Antihistamines[3]

Generic Name(s)	Allergic Reactions to Blood/Plasma	Allergic Conjunctivitis	Allergic Rhinitis	Anaphylactic Reactions†	Angioedema*	Dermato-graphism	Sinusitis	Upper Respiratory Conditions‡	Urticaria*	Vasomotor Rhinitis
Ethanolamine Derivatives										
Carbinoxamine	✔	✔	✔	✔	✔	✔			✔	✔
Clemastine			✔		✔				✔	
Diphenhydramine§	✔	✔	✔	✔	✔	✔			✔	✔
Propylamine Derivatives										
Dexchlorpheniramine	✔	✔	✔	✔	✔	✔			✔	✔
Phenylephrine and chlorpheniramine			✔				✔	✔		

*Mild, uncomplicated allergic skin manifestations.
†Adjunctive to epinephrine and other standard measures after the acute manifestations have been controlled.
‡Upper respiratory conditions may include the common cold.
§Diphenhydramine is also approved for Antiparkinsonism, insomnia, motion sickness, and for use as an antitussive.

IV. Pharmacokinetics

The pharmacokinetic parameters of the first generation antihistamines are listed in Table 4. There is insufficient information on the pharmacokinetic properties of the fixed-dose combination products. Therefore, only information on the individual components was included in the table.

Table 4. Pharmacokinetic Parameters of the First Generation Antihistamines[15]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Ethanolamine Derivatives					
Carbinoxamine	Good	Not reported	Liver	Renal	10 to 20
Clemastine	39	Not reported	Liver	Renal	21
Diphenhydramine	65 to 100	76 to 85	Liver (50)	Renal (50 to 65)	4 to 8
Propylamine Derivatives					
Chlorpheniramine	Good	Not reported	Liver, extensive	Renal (50)	20
Dexchlorpheniramine	Well-absorbed	Not reported	Liver, extensive	Renal (50)	20
Decongestants					
Phenylephrine	38	Not reported	Intestinal wall, extensive; Liver, moderate	Renal (80 to 86)	2 to 3

V. Drug Interactions

Significant drug interactions with the first generation antihistamines are listed in Table 5. Drug interactions are due to the individual components of the combination products; therefore, only information on the individual ingredients was included in the table.

Table 5. Significant Drug Interactions with the First Generation Antihistamine[15]

Generic Name(s)	Interaction	Mechanism
First generation antihistamines	Tranylcypromine	Concurrent use of tranylcypromine and non-selective H_1 receptor antagonists may result in increased risk of anticholinergic effects.
Carbinoxamine	Monoamine oxidase inhibitors	Carbinoxamine anticholinergic effects (e.g., drying) may be increased and prolonged with monoamine oxidase inhibitor coadministration.
Carbinoxamine	CNS Depressants	Concurrent use may result in additive CNS effects.
Chlorpheniramine	Almotriptan	Concurrent use may result in increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes).
Chlorpheniramine	Amitriptyline	Concurrent use may result in an increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes).
Chlorpheniramine	Amoxapine	Concurrent use may result in increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes).
Chlorpheniramine	Fentanyl	Concurrent use may result in increased risk for serotonin syndrome and CNS depression.
Chlorpheniramine	Hydroxytryptophan	Concurrent use may result in increased risk of serotonin syndrome (hypertension, tachycardia, hyperthermia, myoclonus, mental status changes).
Chlorpheniramine	Phenytoin	Concurrent use of chlorpheniramine and phenytoin may result in an increased risk of phenytoin toxicity (ataxia, hyperreflexia, nystagmus, tremor).

Generic Name(s)	Interaction	Mechanism
Chlorpheniramine	Tramadol	Concurrent use may result in increased risk of seizures and serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes).
Chlorpheniramine	Trazodone	Concurrent use may result in increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes).
Diphenhydramine	CNS Depressants	Concurrent use may result in additive CNS effects.
Diphenhydramine	Linezolid	Concurrent use of diphenhydramine and linezolid may result in increased anticholinergic toxicity effects.
Phenylephrine	Monoamine oxidase inhibitors	Coadministration of a monoamine oxidase inhibitor and an indirect- or mixed-acting sympathomimetic may cause hypertensive crisis.
Phenylephrine	Linezolid	Pharmacologic effects of sympathomimetics may be increased by linezolid. Headache, hyperpyrexia, and hypertension may occur.
Phenylephrine	Rauwolfia alkaloids (e.g., reserpine)	Reserpine depletes stores of catecholamines, increasing the receptor sensitivity to the direct-acting sympathomimetics while antagonizing the effects of the indirect-acting agents which release norepinephrine from the neurons. Coadministration may result in hypertension.
Phenylephrine	Tricyclic antidepressants	Tricyclic antidepressants potentiate the pressor response of the direct-acting sympathomimetics; dysrhythmias have occurred. The pressor response to the indirect-acting sympathomimetics is decreased by the tricyclic antidepressants.

VI. Adverse Drug Events

The most common adverse drug events reported with the first generation antihistamines are listed in Table 6. These agents have the potential to cause sedation, performance impairment, and anticholinergic adverse effects.[15]

Table 6. Adverse Drug Events (%) Reported with the First Generation Antihistamines[3]

Adverse Events	Ethanolamine Derivatives			Propylamine Derivatives		Decongestants
	Carbinoxamine	Clemastine	Diphenhydramine	Chlorpheniramine	Dexchlorpheniramine	Phenylephrine
Cardiovascular						
Arrhythmias	-	-	-	-	-	✔
Bradyarrhythmia	-	✔	-	-	-	-
Cardiac dysrhythmia	-	-	-	✔	-	-
Cardiovascular finding	-	-	✔	-	-	-
Hypertension	-	-	-	-	-	✔
Hypotension	✔	✔	✔	✔	-	-
Myocardial infarction	-	-	-	-	-	✔
Myocardial perfusion	-	-	-	-	-	✔
Palpitations	✔	✔	✔	✔	-	-
Pulmonary edema	-	-	-	-	-	✔
Raynaud's phenomenon	-	-	✔	-	-	-
Tachycardia	✔	✔	✔	✔	-	✔
Central Nervous System						
Anxiety	-	-	-	-	-	✔
Ataxia	✔	✔	✔	-	✔	-
Central nervous system stimulation	-	✔	-	-	-	-
Chills	✔	✔	✔	-	✔	-
Confusion	✔	✔	✔	✔	✔	-
Dizziness	✔	✔	✔	✔	✔	-
Drowsiness	✔	✔	-	-	✔	-
Dyskinesia	-	-	✔	✔	-	-
Dystonia	-	-	✔	-	-	-
Electro-encephalograph finding	-	-	-	✔	-	-
Fatigue	✔	✔	✔	✔	✔	-
Headache	✔	✔	✔	✔	-	-
Hypesthesia	-	-	-	-	-	✔
Insomnia	✔	✔	-	-	✔	✔
Nervousness	✔	✔	✔	✔	✔	✔
Neurological finding	-	-	✔	-	-	-

Adverse Events	Ethanolamine Derivatives			Propylamine Derivatives		Decongestants
	Carbinoxamine	Clemastine	Diphenhydramine	Chlorpheniramine	Dexchlorpheniramine	Phenylephrine
Myofascial pain	-	-	-	-	-	✔
Sedation	✔	✔	✔	✔	✔	-
Somnolence	-	✔	✔	✔	-	-
Vertigo	-	✔	✔	✔	✔	-
Dermatologic						
Contact dermatitis	-	-	-	✔	-	✔
Dermatitis	-	-	✔	-	-	-
Dermatologic finding	-	-	✔	-	-	-
Diaphoresis	✔	✔	✔	-	✔	-
Photosensitivity	✔	✔	✔	✔	✔	-
Pruritus	-	✔	-	-	-	-
Rash	✔	✔	✔	✔	✔	-
Urticaria	✔	✔	✔	✔	✔	-
Endocrine/Metabolic Effects						
Acute intermittent porphyria	-	✔	✔	-	-	-
Increased uric acid	✔	-	-	-	-	-
Gastrointestinal						
Anorexia	✔	✔	✔	✔	✔	-
Constipation	✔	✔	✔	✔	✔	-
Diarrhea	✔	✔	✔	✔	✔	-
Dry mouth	-	✔	✔	-	✔	-
Epigastric distress	✔	✔	✔	✔	✔	-
Gastric pain	-	✔	-	-	-	-
Heartburn	-	-	-	-	-	-
Nausea	✔	✔	✔	✔	✔	-
Vomiting	✔	✔	✔	✔	✔	-
Hematologic						
Agranulocytosis	✔	✔	-	✔	✔	-
Hemolytic anemia	✔	✔	-	✔	✔	-
Leukocytosis	-	-	-	-	-	✔
Thrombocytopenia	✔	✔	-	✔	✔	-
Immunologic						
Anaphylaxis	✔	✔	✔	✔	✔	-
Cell-mediated immune reaction	-	-	-	-	-	✔
Immune hypersensitivity reaction	-	-	✔	-	-	-
Immune system finding	-	-	✔	-	-	-

Adverse Events	Ethanolamine Derivatives			Propylamine Derivatives		Decongestants
	Carbinoxamine	Clemastine	Diphenhydramine	Chlorpheniramine	Dexchlorpheniramine	Phenylephrine
Musculoskeletal						
Fracture of bone	-	-	✔	-	-	-
Musculoskeletal finding	-	-	✔	-	-	-
Myasthenia gravis	-	-	✔	-	-	-
Ophthalmic						
Aqueous pigment floater	-	-	-	-	-	✔
Conjunctivitis	-	-	-	-	-	✔
Diplopia	✔	✔	✔	✔	✔	-
Miosis	-	-	-	-	-	✔
Mydriasis	-	-	-	-	-	✔
Psychiatric						
Agitation	✔	-	-	-	-	-
Excitability	✔	-	✔	-	-	-
Hallucinations	✔	-	-	✔	-	✔
Motor nervous system finding	-	-	✔	-	-	-
Panic	-	-	-	-	-	✔
Paranoid delusions	-	-	-	-	-	✔
Psychiatric sign or symptom	-	-	✔	-	-	-
Psychosis	-	-	-	-	-	✔
Psychotic disorder	-	-	✔	-	-	-
Toxic psychosis	-	-	-	-	-	✔
Renal						
Dysuria	✔	✔	✔	✔	✔	-
Polyuria	✔	✔	✔	✔	✔	-
Urogenital finding	✔	-	-	-	-	-
Respiratory						
Nasal dryness	✔	✔	✔	✔	✔	-
Pulmonary edema	-	-	-	-	-	✔
Pulmonary embolism	-	-	-	-	-	✔
Respiratory finding	-	-	✔	-	-	-
Shortness of breath	-	✔	-	-	✔	-
Other						
Anticholinergic effects	-	-	✔	-	-	-
Death	-	-	✔	-	-	-
Drug abuse	-	-	✔	-	-	-
Drug dependence	-	-	✔	-	-	-
Sense of smell altered	-	-	-	-	-	✔

Adverse Events	Ethanolamine Derivatives			Propylamine Derivatives		Decongestants
	Carbinoxamine	Clemastine	Diphenhydramine	Chlorpheniramine	Dexchlorpheniramine	Phenylephrine
Withdrawal sign or symptom	-	-	✔	-	-	-

✔ Percent not specified.
- Event not reported.

VII. Dosing and Administration

The usual dosing regimens for the first generation antihistamines are listed in Table 7.

Table 7. Usual Dosing Regimens for the First Generation Antihistamines[3,16]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Ethanolamine Derivatives			
Carbinoxamine	Allergic rhinitis and other allergic conditions: Extended-release suspension: 6 to 16 mg every 12 hours Solution, tablet: 4 to 8 mg three to four times daily	Allergic rhinitis and other allergic conditions: Extended-release suspension: ≥12 years of age: 6 to 16 mg every 12 hours; 6 to 11 years of age: 6 to 12 mg every 12 hours; 4 to 5 years of age: 3 to 8 mg every 12 hours; 2 to 3 years of age: 3 to 4 mg every 12 hours Solution, tablet: ≥12 years of age: 4 to 8 mg three to four times daily 6 to 11 years of age: 2 to 4 mg three to four times daily Solution: 2 to 5 years of age: 1 to 2 mg three or four times daily	Extended-release suspension: 4 mg/5 mL Solution: 4 mg/5 mL Tablet: 4 mg 6 mg
Clemastine	Allergic rhinitis: Syrup, tablet: initial, 1.34 mg two times daily or 2.68 mg as a single dose; maximum, 8.04 mg/day Allergic urticaria and angioedema: Syrup, tablet: initial, 2.68 mg one to three times daily; maximum, 8.04 mg/day Upper respiratory conditions: Syrup, tablet: 1.34 mg two times daily; maximum, 2.68 mg/day	Allergic rhinitis: Syrup, tablet: ≥12 years of age: initial, 1.34 mg two times daily; maximum, 8.04 mg/day; 6 to <12 years of age: initial, 0.67 mg two times daily; maximum, 4.02 mg/day Allergic urticaria and angioedema: Syrup, tablet: ≥12 years of age: initial, 2.68 mg one to three times daily; maximum, 8.04 mg/day; 6 to <12 years of age: initial, 1.34 mg two times daily; maximum, 4.02 mg/day Upper respiratory conditions: Syrup, tablet: ≥12 years of age: 1.34 mg two times daily; maximum, 2.68 mg/day	Syrup: 0.67 mg/5 mL Tablet: 2.68 mg
Diphenhydramine	Allergic rhinitis and upper respiratory conditions: Oral: 25 to 50 mg three to four times daily; maximum, 300 mg/day Antitussive: Oral: 25 mg six times daily; maximum, 150 mg/day Insomnia: Oral: 50 mg at bedtime	Allergic rhinitis and upper respiratory conditions: Oral: ≥12 years of age: 25 to 50 mg four to six times daily; maximum, 300 mg/day; 6 to <12 years of age: 12.5 to 25 mg four to six times daily; maximum, 150 mg/day Antitussive: Oral: ≥12 years of age: 25 mg four to six times daily; maximum, 150 mg/day	Elixir: 12.5 mg/5 mL Injection: 50 mg/mL

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Motion sickness: Oral: 25 to 50 mg three to four times daily; maximum, 300 mg/day Parkinsonian syndrome: Oral: initial, 25 mg three to four times daily; maintenance, 50 mg four times daily Other: Injection: 10 to 15 mg IM or IV; maximum, 400 mg/day	Motion sickness: Oral: ≥12 years of age: 25 to 50 mg four to six times daily; maximum, 300 mg/day; 6 to <12 years of age: 12.5 to 25 mg 30 to 60 minutes prior to travel and four to six times daily; maximum, 150 mg/day; 2 to <6 years of age: 6.25 mg 30 to 60 minutes prior to travel and four to six times daily; maximum, 37.5 mg/day Insomnia: Oral: ≥12 years of age: 1 mg/kg 30 minutes prior to bedtime; maximum, 50 mg/day Other: Injection: 5 mg/kg/day or 150 mg/m^2 IM or IV; maximum, 300 mg/day	
Propylamine Derivatives			
Dexchlorpheniramine	Hypersensitivity reactions: Solution: 2 mg every four to six hours	Hypersensitivity reactions: Solution: ≥12 years of age: 2 mg every four to six hours; 6 to 11 years of age: 1 mg every four to six hours; 2 to 5 years of age: 0.5 mg every four to six hours	Solution: 2 mg/5 mL
Phenylephrine HCl and chlorpheniramine maleate	Antihistamine/Decongestant: Drops (2-1 mg/mL): 4 mL every four hours; maximum, 24 mL per day	Antihistamine/Decongestant: Drops (2-1 mg/mL): ≥12 years of age: 4 mL every four hours; maximum, 24 mL per day; 6 to <12 years of age: 2 mL four to six times daily; maximum, 8 to 12 mL per day	Drops: 2-1 mg/mL

HCl=hydrochloride, IM=intramuscular, IV=intravenous

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the first generation antihistamines are summarized in Table 8.

Table 8. Comparative Clinical Trials with the First Generation Antihistamines

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Allergic Rhinitis				
Druce et al.[17] (1998) Brompheniramine ER 12 mg BID vs loratadine 10 mg QD vs placebo	DB, MC, PC, PG, RCT Patients >12 years of age with allergic rhinitis	N=338 7 days	Primary: Global evaluation scores, evaluation of symptom relief, total symptom severity scores, nasal symptom scores, adverse events Secondary: Not reported	Primary: At day three and day seven, physician and subject global evaluation scores for brompheniramine were significantly better than those for loratadine (P<0.001) and placebo (P<0.001). Loratadine was more effective than placebo; however, this was not statistically significant. On the subjects' daily overall evaluations of symptom relief, brompheniramine was significantly better than loratadine and placebo on all seven days (P value not reported). Loratadine was significantly better than placebo on day four. The total symptom severity scores improved to a greater degree with brompheniramine compared to loratadine or placebo at day three, day seven, and the average over the two visits (P<0.05). Treatment with loratadine improved symptoms to a greater degree than placebo (P<0.05 only when symptoms were averaged over day three and day seven). The mean individual symptom severity scores paralleled the pattern seen for the summed symptom severity scores in the three groups. Improvement in nasal symptoms was significantly greater in the patients taking brompheniramine than in those taking loratadine (P<0.01) or placebo (P<0.001) at day three, day seven, and when averaged over the two visits. Improvement in nasal symptoms in the loratadine treatment group was greater than that in the placebo treatment group at day three (P<0.05). At visit two, adverse events were reported by 53% of the patients taking brompheniramine, 33% of those taking loratadine, and 36% of those taking placebo (P=0.006). At visit three, adverse events were reported by 34% of the patients taking brompheniramine, 20% of those taking loratadine, and 29% of those taking placebo (P=0.05). At visit two, the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				frequency of somnolence was 28, 9, and 6% in the brompheniramine, loratadine, and placebo groups, respectively (P<0.001). At visit three, the frequency of somnolence was reduced to 10, 2, and 3% for the brompheniramine, loratadine, and placebo groups, respectively (P=0.011). Secondary: Not reported
Crawford et al.[18] (1998) Chlorpheniramine 8 mg BID for 2 weeks vs astemizole 10 mg QD for 2 weeks vs loratadine 10 mg QD for 2 weeks vs terfenadine† 60 mg BID for 2 weeks Pseudoephedrine 60 mg every 8 hours as needed was permitted throughout the study.	OL, XO Patients with perennial allergic rhinitis	N=14 8 weeks	Primary: Nasal-examination score, rhinitis symptom score, overall efficacy score, pseudoephedrine use, adverse events Secondary: Not reported	Primary: The physician assessed nasal-examination score for each of the four antihistamines was significantly better than the baseline nasal-examination score (P<0.05). The nasal-examination score for astemizole was significantly better than loratadine (P<0.05). No other significant differences in nasal-examination score were noted among the treatment groups. There were no significant differences among antihistamines when comparing patient-reported rhinitis symptom scores, overall efficacy scores, or pseudoephedrine use. Sedation was noted most frequently by patients taking chlorpheniramine. Headache was the most frequent adverse event with terfenadine. Secondary: Not reported
von Maur et al.[19] (1985)	OL	N=782 5 years	Primary: Patient preference and long-term	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Chlorpheniramine 2 to 4 mg QID for 2 weeks vs diphenhydramine 12.5 to 25 mg QID for 2 weeks vs hydroxyzine 10 to 25 mg QID for 2 weeks vs tripelennamine† 37.5 to 50 mg TID for 2 weeks vs trimeprazine† 2.5 mg TID for 2 weeks	Adults and children with seasonal or perennial allergic rhinitis		choice of antihistamine Secondary: Not reported	The order of antihistamine preference was chlorpheniramine, diphenhydramine, tripelennamine, hydroxyzine, and trimeprazine (P<0.001). At the end of one year, 78% of patients remained on their preferred antihistamine. By three years, 71% of patients were still on the antihistamine of first choice. By five years, 57% of patients were still on the antihistamine class that had been selected five years before. Secondary: Not reported
Prevost et al.[20] (1994) Chlorpheniramine 12 mg and pseudoephedrine 120 mg BID vs	DB, MC, PG, RCT Patients 18 to 65 years of age with seasonal allergic rhinitis	N=134 14 days	Primary: Nasal and non-nasal symptoms Secondary: Not reported	Primary: There was a significant decrease from baseline in mean TTSs in both treatment groups (P<0.01). On day three, improvement in mean TSS was 54% in the loratadine/pseudoephedrine group and 57% in the chlorpheniramine /pseudoephedrine group. On day 14, there was a 65% improvement in the patients treated with loratadine/pseudoephedrine and 64% improvement in the chlorpheniramine/pseudoephedrine group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
loratadine 5 mg and pseudoephedrine 120 mg BID Products were ER fixed-dose combinations.				Reduction in mean total nasal and non-nasal symptom scores was comparable between the two treatment groups. By day 14, nasal symptom improvement was 60% in the loratadine/pseudoephedrine group and 61% in the chlorpheniramine/pseudoephedrine group. Improvement was comparable for nasal discharge (53 vs 45%, respectively), stuffiness (52 vs 44%, respectively), and sneezing (61 vs 54%, respectively) on day three. Improvement in mean total non-nasal symptom scores was comparable and not significantly different between the two treatment groups on day three (P value not reported). At day 14, improvement in non-nasal symptom scores was 69% in both study groups. Patients in the chlorpheniramine/pseudoephedrine group showed greater relief of red eyes at day three (63 vs 54%) and day 14 (75 vs 68%). Patients treated with loratadine/pseudoephedrine showed greater improvement in ear/palate itch (60 vs 50%) at day 14. The most frequently reported side effects were headache (16% in both groups) and insomnia (16% in the loratadine/pseudoephedrine group and 18% in the chlorpheniramine/pseudoephedrine group). There was a greater incidence of fatigue (6 vs 25%, P<0.01), dry mouth (7 vs 19%; P=0.07), and sedation (7 vs 22%; P<0.03) in the group receiving chlorpheniramine/pseudoephedrine compared to those receiving loratadine/pseudoephedrine. Secondary: Not reported
Gibbs et al.[21] (1998) <u>Study 2</u> Clemastine 1.34 mg TID for 5 days vs acrivastine 8 mg TID for 5 days	RCT, XO Adults with seasonal allergic rhinitis	N=54 21 days	Primary: Nasal and non-nasal symptoms Secondary: Not reported	Primary: *Study 2* The acrivastine was significantly better than placebo for the relief of itchy nose, blocked nose and watery eyes symptoms, and for calculated overall symptom score (mean of all seven symptoms). Clemastine was significantly better than placebo for alleviation of the symptoms of itchy nose, running nose, itchy eyes and watery eyes, and for calculated overall symptom score. There were no significant differences between the two antihistamines.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo for 5 days <u>Study 1</u> Acrivastine 4 mg TID for 5 days vs acrivastine 8 mg TID for 5 days vs placebo for 5 days				In study 2, drowsiness was reported by seven (39%) patients receiving clemastine compared to one patient receiving acrivastine (P<0.05). *Study 1* High- and low-dose acrivastine led to significantly lower scores than placebo for all symptoms, except blocked nose (P>0.01). There was no significant difference in symptom scores between the two doses of acrivastine. Sixty-three percent of patients rated symptom control as excellent or good during treatment with 8 mg acrivastine compared with 46% for 4 mg acrivastine and 36% for placebo (8 mg acrivastine vs placebo; P=0.058). There were no statistically significant differences in the proportion of patients who would have requested further treatment had it been available on prescription although slightly more patients on 4 mg acrivastine (61%) and 8 mg acrivastine (62%) than on placebo (54%) indicated this desire. Only 20% of patients preferred treatment with placebo. This is compared to 40% of patients preferring acrivastine 4 mg and 40% preferring acrivastine 8 mg. Secondary: Not reported
Sheriff et al.[22] (1976) Clemastine 1.34 mg given as 1 to 2 tablets 2 to 3 times daily vs chlorpheniramine 4 mg given as 1 to 2 tablets 2 to 3 times daily	DB, PG, RCT Patients 7 to 40 years of age with seasonal allergic rhinitis	N=51 2 weeks	Primary: Mean total number of tablets taken, mean TSSs, mean number of days the patient felt drowsy, investigator's and patient's assessment of effectiveness of treatment Secondary: Not reported	Primary: The mean number of tablets taken was similar with clemastine (27.8) and chlorpheniramine (28.1; P value not significant). The mean TSSs were similar with clemastine (16.2) and chlorpheniramine (14.0; P value not significant). The mean number of days drowsy was similar with clemastine (1.58) and chlorpheniramine (1.08; P value not significant). The effectiveness of clemastine and chlorpheniramine as defined by the investigator's assessments and by the patients' daily record forms were similar among the two treatment groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Thomas et al.[23] (1977) Clemastine 2.68 mg as a single dose vs chlorpheniramine 4 mg as a single dose vs placebo	DB, RCT Patients >15 years of age with seasonal allergic rhinitis	N=46 1 day	Primary: Alteration in airway resistance, nasal congestion, nasal obstruction, nasal airway patency, investigator's and patient's subjective assessments of improvement Secondary: Not reported	Primary: Treatment with clemastine and chlorpheniramine resulted in significant changes in the plethysmographic oral resistance evaluations compared to baseline. There were no significant differences noted with placebo compared to baseline. Clemastine was significantly better than placebo for hours two and six ($P<0.10$) and for the mean response over all time points ($P<0.05$). There were no significant differences for patients receiving chlorpheniramine compared to placebo. Differences in nasal resistance and total airway resistance among the three treatment groups were not significant. Treatment with clemastine and chlorpheniramine resulted in significant improvements in nasal congestion compared to baseline. Both clemastine and chlorpheniramine also demonstrated greater improvements in nasal congestion compared to placebo at all time points and overall ($P<0.05$). There were no significant differences in nasal obstruction among the three treatment groups. Treatment with clemastine and chlorpheniramine led to improvements in the investigator's subjective evaluation of nasal congestion at each time point. There was no difference noted with placebo. More patients treated with clemastine showed improvement (64 to 73%) compared to placebo (9 to 18%; $P<0.05$). There was no significant difference in nasal congestion with chlorpheniramine compared to placebo. There were no significant differences in the overall improvement index of physician-evaluated signs among the three treatment groups. Patients' self-evaluation of changes in symptoms showed improvement in all treatment groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The most common adverse reaction was drowsiness. The number of patients with severe drowsiness was higher in the chlorpheniramine group than in the placebo group (P<0.10). Secondary: Not reported
Todd et al.[24] (1975) <u>Study 1</u> Clemastine 1.34 mg BID to QID vs chlorpheniramine 4 mg BID to QID <u>Study 2</u> Clemastine elixir 0.5 mg BID vs chlorpheniramine syrup 2 mg BID	DB, PG, RCT <u>Study 1</u> Adults with allergic rhinitis <u>Study 2</u> Children with allergic rhinitis	<u>Study 1</u> N=58 3 weeks <u>Study 2</u> N=42 3 weeks	Primary: Physician's assessment of improvement after treatment Secondary: Not reported	Primary: *Study 1* In the physician's assessment of improvement, 50% of clemastine-treated patients were to be greatly improved compared to 23% (improved), 13% (no change), and 13% (worse). This is compared to 28% of patients in the chlorpheniramine group who were considered to be greatly improved, 43% (improved), 14% (no change), and 14% (worse). There were no P values reported. Adverse events were minimal with both preparations. Drowsiness when reported was mainly of a transient nature with no significant difference in incidence or severity between the compounds. *Study 2* In the physician's assessment of improvement, 32% of clemastine-treated patients were to be greatly improved compared to 21% (improved), 11% (no change), and 32% (worse). This is compared to 31% of patients in the chlorpheniramine group who were considered to be greatly improved, 13% (improved), 4% (no change), and 52% (worse). There were no P values reported. There were no reports of drowsiness or tiredness from any of the 19 patients receiving clemastine. Of the 23 patients receiving chlorpheniramine, three complained of drowsiness. Secondary: Not reported
Dockhorn et al.[25] (1987)	DB, MC, PC, PG, RCT	N=330 14 days	Primary: Assessment of nasal and non-nasal symptoms,	Primary: Improvement in mean total symptoms scores and nasal symptom scores were significantly greater with loratadine and clemastine than placebo at each time point (P<0.01). There was no significant difference between the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Clemastine 1.34 mg BID vs loratadine 10 mg QD vs placebo	Patients with seasonal allergic rhinitis		overall condition or rhinitis, and therapeutic response to treatment Secondary: Not reported	loratadine and clemastine treatment groups (P value not significant) at day three, day 14, or study end point. At day seven, the improvement in the loratadine group was significantly greater than that of the clemastine group (P=0.04 for TSSs and P=0.05 for nasal symptom scores). Non-nasal symptom scores were not reported. In the physician evaluation of therapeutic response, loratadine and clemastine led to a more favorable response to treatment than placebo. By day three, an excellent response was seen in 22% of loratadine-treated patients, 9% of the clemastine-treated patients, and 3% of the placebo-treated patients. Likewise, 22, 43, and 23%, respectively, were rated as have a good response to treatment. In the end point analysis, the percentage of patients with a good or excellent response to treatment was 29 and 27%, respectively with loratadine; 13 and 42%, respectively with clemastine; 5 and 27%, respectively with placebo. A greater percentage of patients reported at least one adverse event with clemastine (37%) than with loratadine (21%) or placebo (20%; P<0.01). Sedation was reported by a greater percentage of patients receiving clemastine (22%) than loratadine (6%) or placebo (5%; P<0.01). There was no difference in dry mouth among the treatment groups. Secondary: Not reported
Frølund et al.[26] (1990) Clemastine 1.34 mg BID vs loratadine 10 mg QD vs	DB, MC, PG, RCT Patients 18 to 65 years of age with perennial allergic rhinitis	N=155 3 weeks	Primary: Total, nasal and non-nasal symptom severity Secondary: Not reported	Primary: The loratadine and clemastine groups showed a significant improvement compared to placebo when nasal membranes, secretion, and patency were assessed with rhinoscopy (P<0.05). Loratadine and clemastine significantly reduced patients' total nasal and total eye symptoms compared to placebo (P<0.05). A similar reduction was seen for all four nasal symptoms (discharge, stuffiness, itching, and sneezing). For eye symptoms, this decrease was found for redness and itching (P<0.05), but no significant decrease was observed for tearing. Loratadine improved total symptoms scores at day seven compared to clemastine (P<0.05). Loratadine also improved nasal itching and nasal

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo				stuffiness more effectively than clemastine at day seven (P<0.05). There were no significant changes between the treatment groups at other time points. The diary cards showed there was a significant onset of relief of symptoms within the first day of treatment with loratadine and clemastine compared to placebo. A faster onset of symptom relief was also seen in the loratadine group compared with the clemastine group within the first day (P<0.05). There were fewer adverse events reported with loratadine compared to clemastine (P<0.05) and placebo (P<0.05). Secondary: Not reported
Irander et al.[27] (1990) Clemastine 1.34 mg BID vs loratadine 40 mg QD vs placebo	DB, RCT Patients >18 years of age with a history of rhino-conjunctivitis during the birch pollen season	N=107 2 weeks	Primary: Rhino-conjunctivitis symptoms Secondary: Not reported	Primary: Loratadine significantly reduced all rhino-conjunctivitis symptoms compared to placebo, except for nasal stuffiness (P value not significant). Clemastine significantly reduced sneezing, nasal discharge, and tearing compared to placebo; however, there was no difference in nasal itching/stuffiness, ocular itching/redness, or palatal itching (P value not significant). There was no significant difference in the majority of the rhino-conjunctivitis symptoms between clemastine and loratadine, except for ocular itching/redness (P<0.05). Sedation was the most common adverse event. There was no difference in sedation with loratadine compared to placebo; however, a significantly higher incidence was noted in patients treated with clemastine (P<0.05). Dizziness, headache, insomnia, dryness of the mouth and nausea were reported rarely. Secondary: Not reported
Boner et al.[28]	RCT	N=40	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(1989) Dex-chlorpheniramine 1 mg every 8 hours vs loratadine 5 mg QD Children under 6 years and those weighing less than 20 kg received half the dose.	Children 4 to 12 years of age with moderate-to-severe seasonal allergic rhinitis	14 days	Symptom severity Secondary: Not reported	Symptom severity (on physical exam and subjective symptoms) improved with both drugs during the 14-day treatment period (P<0.01). There was no significant difference between the dexchlorpheniramine or loratadine treatment groups (P=0.295). Rhinoscopy showed a reduction in nasal secretions/stuffiness with both treatments and there was no significant difference between the treatment groups (P value not significant). The evaluation of therapeutic results by both the investigator and the patient/parent had similar positive results with both drugs at each visit (P>0.05). Four children receiving dexchlorpheniramine had somnolence on day one, two other patients complained of mild epistaxis during the first three days of treatment. Two children in the loratadine group had two episodes of moderate epistaxis, one on days one to two and the other on days six to eight, no child reported drowsiness. Secondary: Not reported
Raphael et al.[29] (2006) Diphenhydramine 50 mg TID vs desloratadine 5 mg QD vs placebo	DB, MC, PC, PG, RCT Patients 12 to 65 years of age with moderate-to-severe seasonal allergic rhinitis	N=610 1 week	Primary: Change from baseline in the TNSS Secondary: Change from baseline in TSS, individual symptom scores, global evaluation of response to treatment	Primary: Diphenhydramine had a 46.7% greater reduction in patient TNSSs compared with desloratadine (-1.81; P<0.001). Investigator TNSS results were similar to those recorded by patients. Secondary: Diphenhydramine had a 45.5% greater reduction in patient TSS compared with desloratadine (-3.35; P<0.001). Investigator TSS results were similar to those recorded by patients. Treatment with diphenhydramine led to significant reductions in all eight individual symptom scores compared to placebo and desloratadine, including nasal congestion. Treatment with desloratadine led to a greater reduction in six of the eight individual symptoms compared to placebo (nasal congestion, rhinorrhea, sneezing, nasal itching, redness of eyes, and itching ears/palate); however, only sneezing was significant (-027;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				P=0.04). Similar results were observed for investigator-scored individual symptoms. The daily nasal congestion scores were significantly reduced with diphenhydramine compared to desloratadine and placebo throughout the seven-day treatment period. Percentage improvement in the patient mean global response to treatment scores over placebo were 134.5% (P<0.001) for diphenhydramine and 29.4% (P=0.20) for desloratadine. Diphenhydramine had an 81.2% (P<0.001) greater improvement in the patient mean global response to treatment score compared with desloratadine. Adverse events were observed in 35.3, 16.3, and 8.3% of patients who received diphenhydramine, desloratadine, and placebo, respectively. The most common adverse events were somnolence, dry mouth, asthenia, headache, and dizziness.
Park et al.[30] (2011) Diphenhydramine 1 mg/kg vs cetirizine 0.25 mg/kg	DB, RCT Patients 3 to 19 years of age experiencing an allergic reaction during oral food challenge	N=64 70 allergic reactions Duration not specified	Primary: Proportion of patients experiencing sedation (sedation score of 1 or 2) Secondary: Mean resolution of urticaria and pruritus, administration of other medications	Primary: Overall, 28.6 and 17.1% of patients receiving diphenhydramine and cetirizine experienced sedation, reflecting a nonsignificant difference in sedation of 11.4% (95% CI, -8.4 to 30.2%). Secondary: The mean time to resolution of urticaria and pruritus was similar between the two treatments. Among patients receiving diphenhydramine, mean time to resolution was 42.3±13.15 minutes compared to 40.8±22.11 minutes among patients receiving cetirizine (P=0.86). For pruritus the corresponding times were 28.6±20.54 and 31.3±20.07 minutes (P=0.67). Furthermore, the mean time to first onset of resolution of urticaria and pruritus was similar between the two treatments. There was no difference in the administration of other medications between the two treatments. Other treatments included steroid and/or epinephrine.
Connell et al.[31] (1982)	DB, PC, RCT	N=184 2 days	Primary: TARs, nasal congestion scores,	Primary: There was no difference in the mean TARs among the four treatment groups. Triprolidine/pseudoephedrine was better than triprolidine

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Triprolidine 2.5 mg and pseudoephedrine 60 mg given every 6 hours as a fixed-dose combination vs triprolidine 2.5 mg given every 6 hours vs pseudoephedrine 60 mg given every 6 hours vs placebo	Patients >16 years of age with seasonal allergic rhinitis		hay fever symptom complex score, patient's perception of overall therapeutic benefit Secondary: Not reported	(P≤0.025) at 12.30 hours, 13.30 hours and 15.30 hours (borderline) on Day 1, and at 15.30 hours on Day 2. For the end point of mean nasal congestion scores vs hour after dosing, triprolidine/pseudoephedrine was better (P≤0.025) than: (1) triprolidine at 13.30 hours and 15.30 hours on Day 2; and (2) placebo at 10.30 hours, 11.30 hours (borderline), 12.30 hours (borderline), 13.30 hours (borderline), 14.30 hours, 15.30 hours (borderline), and 16.30 hours on Day 2. For the end point of hay fever symptom complex score, triprolidine/pseudoephedrine was better (P≤0.025) than: (1) pseudoephedrine at 12.30-14.30 hours, and 16.30 hours on Day 1, and at 13.30 hours (borderline), 15.30 and 16.30 hours on Day 2; and (2) placebo at 12.30-14.30 hours, and 15.30 hours (borderline) on Day 1, and at 08.30 hours, 10.30-11.30 hours (borderline) and 12.30-16.30 hours on Day 2. The mean symptom complex score was also better with triprolidine/pseudoephedrine compared to pseudoephedrine and placebo (P=0.01, respectively). The patients' perception of overall therapeutic benefit was assessed at 08.30 hours on Day 2 by the question "'Did the medication help?" For patients receiving triprolidine/pseudoephedrine, 52% said they noticed marked improvement compared to those receiving triprolidine (22%), pseudoephedrine (17%), or placebo (9%). The three most frequently reported adverse events were dry nose, drowsiness and headache. Secondary: Not reported
Diamond et al.[32] (1981) Triprolidine 2.5 mg and pseudoephedrine 60	DB, PC, RCT Patients >18 years of age with seasonal allergic rhinitis	N=151 1 day	Primary: NAR, symptom complex score, nasal congestion score, adverse events	Primary: Treatment with triprolidine/pseudoephedrine resulted in a greater reduction in NAR compared to triprolidine at all time points after one hour (P≤0.025) and a greater reduction in NAR compared to placebo at hours six and seven (P≤0.025). There was no statistical comparison with pseudoephedrine alone for this end point. When the area under the NAR-

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg as a fixed-dose combination given at 10:00 AM, 1:00 PM, and 4:00 PM (3 doses) vs triprolidine 2.5 mg given at 10:00 AM, 1:00 PM, and 4:00 PM (3 doses) vs pseudoephedrine 60 mg given 10:00 AM, 1:00 PM, and 4:00 PM (3 doses) vs placebo			Secondary: Not reported	time curves were compared, the overall response to treatment was greater with triprolidine/pseudoephedrine than triprolidine or placebo (P≤0.025). Reduction in the nasal congestion scores were greater with triprolidine/pseudoephedrine compared to placebo (hours six, seven and eight; P≤0.025) and triprolidine (hours six and eight; P≤0.025). There was no difference in nasal congestion scores between triprolidine/pseudoephedrine and pseudoephedrine alone. For the end point of symptom complex scores, triprolidine/ pseudoephedrine resulted in a greater reduction in symptoms compared to pseudoephedrine alone at hours three, six, seven and eight and a greater reduction in symptoms compared to placebo at hours three, four, six, seven and eight (P≤0.025, respectively). The mean symptom complex score was also better with triprolidine/pseudoephedrine compared to pseudoephedrine and placebo (P≤0.025, respectively). There was no difference in symptom complex scores between triprolidine/pseudoephedrine and triprolidine alone. Drowsiness was the most frequently reported adverse event. Secondary: Not reported
Empey et al.[33] (1975) Triprolidine 2.5 mg and pseudoephedrine 60 mg TID for 2 weeks vs triprolidine 2.5 mg TID for 2 weeks vs	DB, PC, XO Adults with seasonal allergic rhinitis	N=40 10 weeks	Primary: Symptoms (daily diary card), patient's overall impression of improvement, adverse events Secondary: Not reported	Primary: The mean number of days sneezing occurred was lower with triprolidine/pseudoephedrine (4.05 days) compared to triprolidine (6.1 days), pseudoephedrine (6.53 days) and placebo (7.33 days; P<0.05 for all comparisons). Triprolidine/pseudoephedrine was also more effective than pseudoephedrine and placebo in reducing the severity of sneezing (P<0.05). There was no difference in severity of sneezing between triprolidine/pseudoephedrine and triprolidine alone. The three active treatment groups were more effective than placebo in reducing the number of days of rhinorrhea and eye irritation occurred, as well as the severity of these symptoms (P<0.05 for all comparisons with placebo). There were no significant differences noted among the three active treatment groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
pseudoephedrine TID for 2 weeks vs placebo for 2 weeks				There was no significant difference in the number of days of nasal blockage, or the severity of this symptom, among the 4 treatment groups. Overall scores on the "better or worse than usual" assessment and the patient's choices of "best or joint best period" showed triprolidine/pseudoephedrine was preferred to triprolidine alone, pseudoephedrine alone, or placebo. Drowsiness, dry mouth and dizziness were the most commonly reported adverse events. Secondary: Not reported
Urticaria				
Jolliffe et al.[34] (1985) Brompheniramine SR 12 mg BID for 4 weeks vs clemastine 1 mg BID for 4 weeks vs placebo for 4 weeks	PC, XO Patients 18 to 62 years of age with chronic urticaria (with or without dermatographism)	N=24 12 weeks	Primary: Symptom severity and degree of improvement Secondary: Not reported	Primary: Investigators and patients found that both brompheniramine and clemastine were more effective than placebo with regards to symptom severity. In those patients who expressed a positive preference for one therapy, more patients preferred brompheniramine treatment to either clemastine ($P<0.025$) or placebo treatment ($P<0.005$). Drowsiness was experienced by four patients taking brompheniramine compared to three patients taking clemastine. Secondary: Not reported
Gale et al.[35] (1989) Chlorpheniramine 4 mg TID for 24 days	DB, RCT, XO Patients >16 years of age with chronic idiopathic urticaria	N=20 48 days	Primary: Patients' and physician's assessment of treatment of	Primary: There were no significant differences between acrivastine and chlorpheniramine in relieving itching, wheal, or overall discomfort in the patient assessment (P value not reported).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs acrivastine 8 mg TID for 24 days			chronic idiopathic urticaria Secondary: Not reported	There were no significant differences between acrivastine and chlorpheniramine in itching or wheal in the physician's assessment (P value not reported). Secondary: Not reported
Upper Respiratory Conditions				
Bye et al.[36] (1980) Triprolidine 2.5 mg and pseudoephedrine 60 mg 1 tablet TID vs triprolidine 2.5 mg 1 tablet TID vs pseudoephedrine 60 mg 1 tablet TID vs placebo Tablets were taken for as long as needed.	DB, PC, RCT Adults with symptoms of the common cold	N=466 (243 colds) 8 to 10 days	Primary: Symptoms (daily diary card), adverse events, overall impression of improvement Secondary: Not reported	Primary: The sneezing score was reduced with triprolidine/pseudoephedrine compared to placebo on days two, three and four of the cold (P<0.01). Sneezing was also reduced by pseudoephedrine on days two and three compared to placebo (P<0.01). Nasal obstruction was improved with pseudoephedrine and triprolidine/pseudoephedrine on day one only (P<0.01). The other specific symptoms were not significantly affected by the treatments. Difficulty in sleeping was significantly higher for patients taking pseudoephedrine compared to placebo. Significantly more patients receiving pseudoephedrine and triprolidine/pseudoephedrine reported “improvement” improved in symptoms compared to placebo (P<0.01). Secondary: Not reported
Central Nervous System Adverse Effects				
Seppälä et al.[37] (1981) Brompheniramine	DB, RCT, XO Healthy men 20 to 25 years of age	N=9 5 weeks	Primary: Psychomotor performance, subjective	Primary: No significant drug effects were seen on divided attention, tracking or on the speed anticipation test.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
12 mg for 3 doses vs carbinoxamine 12 mg for 3 doses vs clemastine 1.34 mg for 3 doses vs phenyl-propanolamine 50 mg for 3 doses vs placebo Doses were administered at 8:30 AM and 9:00 PM on the first day, and at 8:30 AM on the following day.			assessments, sleep estimates Secondary: Not reported	The reaction times quickened during the study (P<0.01). The reactions of the subjects were slower (P<0.05 vs placebo) two hours after the first dose of carbinoxamine on day one, but reactions returned to normal thereafter. Phenylpropanolamine improved reaction times (P<0.05) compared to placebo, carbinoxamine and brompheniramine. Clemastine and brompheniramine slightly decreased and phenylpropanolamine significantly decreased (P<0.001) reaction mistakes compared to placebo. On both treatment days, phenylpropanolamine enhanced the ability to distinguish between two discrete flashes of light. The effect was significant in comparison with placebo, carbinoxamine and brompheniramine (P<0.01). No treatment significantly affected the subjective feeling of performance. On the first day of treatment, antihistamines were estimated to be a tranquilizer more often than placebo, but only clemastine differed significantly from placebo (P<0.05). On day two, no active treatment differed from placebo. Diurnal variation in the alertness-drowsiness scale was seen during placebo administration. Antihistamines tended to cause drowsiness. Significant differences in drowsiness were seen with brompheniramine (six hours after dose) and clemastine (12 hours after dose) compared to placebo. Drowsiness was felt only on the first day of antihistamine treatment. Phenylpropanolamine increased alertness. Secondary: Not reported
Nicholson et al.[38] (1979) Brompheniramine 4 mg IR as a single dose	DB, PC, RCT, XO Healthy volunteers	N=6 >4 weeks	Primary: Visuomotor coordination and subjective assessments of performance, well-being and sleep	Primary: Brompheniramine IR (4 mg) impaired performance at 1.5 hours and 3.0 hours (P<0.05). Brompheniramine SR (12 mg) impaired performance at 1.5 hours (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs brompheniramine 12 mg SR as a single dose vs triprolidine 2.5 mg IR as a single dose vs triprolidine 10 mg SR as a single dose vs placebo			Secondary: Not reported	Triprolidine IR (2.5 mg) had an immediate effect on performance (P<0.001) which persisted for 3.0 hours (P<0.01). Triprolidine SR (10 mg) impaired performance from 1.5 hours (P<0.001) to 5.0 hours (P<0.01). Performance reached placebo level about seven hours after triprolidine (2.5 and 10 mg), and about five hours after brompheniramine (4 and 12 mg). There were no consistent changes in the assessments of well-being, sleep and performance among any of the antihistamines compared to placebo. Secondary: Not reported
Ng et al.[39] (2004) Chlorpheniramine 4 mg as a single dose vs cetirizine 10 mg as a single dose vs placebo	DB, PC, RCT, XO Children 7 to 14 years of age with allergic rhinitis	N=24 >3 weeks	Primary: P300 event-related potential (objective measure of sedation) and sleepiness or somnolence using a VAS (subjective measure of sedation) Secondary: Not reported	Primary: There was an increase in P300 latency for chlorpheniramine (P=0.04) and cetirizine (P=0.03) compared to baseline, but this was not demonstrated with placebo. However, the mean percentage change in P300 latency for cetirizine and chlorpheniramine did not differ significantly from placebo. There was no significant increase in VAS scores for chlorpheniramine, cetirizine or placebo compared to baseline (P>0.05). The mean percentage change in VAS scores for cetirizine and chlorpheniramine did not differ significantly from placebo. Secondary: Not reported
Kamei et al.[40] (2003) Chlorpheniramine	DB, PC, RCT, XO Healthy volunteers	N=11 4 weeks	Primary: CFF, CRT, CTT, RVIP, LARS, WA	Primary: There was no significant difference in CFF or CRT among the treatment groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
4 mg as a single dose vs fexofenadine 120 mg as a single dose vs olopatadine 10 mg as a single dose vs placebo			Secondary: Not reported	Chlorpheniramine significantly reduced the tracking ability in the CTT compared to placebo (P<0.01). There was no significant difference in RVIP among the treatment groups. There was no significant difference in LARS among the treatment groups. In the WA analysis, chlorpheniramine and olopatadine caused a significant reduction in behavioral activity compared to placebo (P<0.05 and P<0.01, respectively). There was also a significant difference between fexofenadine and olopatadine groups (P<0.01). Secondary: Not reported
Hindmarch et al.[41] (1976) Clemastine 1.34 mg BID for 3 days vs placebo	DB, PC, XO Healthy volunteers	N=21 11 days	Primary: Car driving ability, personality and subjective feeling states Secondary: Not reported	Primary: There was no significant difference in car driving ability (garaging a car, controlled braking ability, estimation of width at a distance, maneuvering ability, reverse parking) with clemastine compared to placebo. There was no significant difference in the Middlesex Hospital Questionnaire between clemastine and placebo, which assessed personality and subjective feeling states. Secondary: Not reported
Cohen et al.[42] (1987) <u>Study 1</u> Diphenhydramine 50 mg vs	DB, PC, XO Healthy volunteers	<u>Study 1</u> N=12 Single dose <u>Study 2</u> N=12 Single dose	Primary: Adaptive tracking test, reaction time, body sway, eye movement tests (Study 1) Secondary: Not reported	Primary: *Study 1* Alcohol alone and acrivastine alone produced no impairment in tracking performance at any time during the study. Diphenhydramine alone (50 mg) reduced tracking performance at 2.5 hours after drug administration compared to placebo. At one hour, the effects of diphenhydramine plus alcohol were significantly different from placebo, but not from alcohol alone. At 2.5 hours, diphenhydramine plus alcohol (50 mg) caused impairment of performance compared to all other treatment groups. Acrivastine plus alcohol (8 mg) impaired tracking at 2.5 hours compared

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
diphenhydramine 50 mg and alcohol 32 mL vs acrivastine 8 mg vs acrivastine 8 mg and alcohol 32 ml vs alcohol 32 ml vs placebo <u>Study 2</u> Acrivastine 4 mg and alcohol 32 mL vs acrivastine 8 mg and alcohol 32 mL vs terfenadine† 60 mg and alcohol 32 mL vs				with placebo and single treatments, but produced significantly less impairment than diphenhydramine plus alcohol (50 mg). No single treatment prolonged reaction time at any time, with the exception of alcohol alone. It significantly increased reaction time compared to placebo at one hour. At one hour, diphenhydramine plus alcohol (50 mg) increased reaction time compared to placebo and all other treatments. At 2.5 hours, diphenhydramine plus alcohol (50 mg) was different from all of the single treatments (including placebo), but did not differ from the acrivastine and alcohol (8 mg) combination. The acrivastine plus alcohol (8 mg) differed from placebo and acrivastine alone at one hour, but not from alcohol alone. At 2.5 hours, acrivastine plus alcohol (8 mg) prolonged reaction time compared with placebo, alcohol and acrivastine alone. With regards to body sway, the main effects occurred at one hour. Impairment after the diphenhydramine plus alcohol (50 mg) combination was significantly different from all single treatments (excluding diphenhydramine alone). The acrivastine plus alcohol (8 mg) combination differed from placebo, alcohol alone and acrivastine alone. The eye movement analyses included smooth pursuit velocity, as well as PSV duration and reaction time. Diphenhydramine plus alcohol (50 mg) impaired PSV compared with placebo and alcohol at 1 and 2.5 hour(s). At 2.5 and 7.5 hours, PSV was also decreased by diphenhydramine alone (50 mg). No significant differences were seen after acrivastine (8 mg) or alcohol, either alone or in combination. The duration of the saccades of 30° showed similar effects to the PSV. Diphenhydramine plus alcohol (50 mg) was different from placebo, alcohol alone, and acrivastine alone (8 mg) at one hour and from all the other treatments at 2.5 hours. At 2.5 hours, diphenhydramine alone (50 mg) was different from placebo. Both acrivastine (8 mg) and alcohol alone produced no effects, but their combination increased the duration of saccade at 1 and 2.5 hour(s) compared with placebo, but not with alcohol alone. Diphenhydramine alone (50 mg) and the combination with alcohol produced prolongation in the duration of saccade at 1 and 2.5 hour(s) compared with placebo. At 2.5 hours, diphenhydramine plus alcohol (50 mg) also produced significant

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
terfenadine† 120 mg and alcohol 32 mL vs alcohol 32 mL vs placebo				impairment compared to alcohol alone. None of the other single treatments produced impairment compared with placebo. Acrivastine plus alcohol (8 mg) impaired reaction time at 1 and 2.5 hour(s) compared with placebo, but not with alcohol. Smooth pursuit velocity was significantly reduced after alcohol and acrivastine plus alcohol (8 mg) compared with placebo, but acrivastine plus alcohol (8 mg) was not different from alcohol alone. There were no differences between placebo and any of the other treatments. *Study 2* At 1 hour, alcohol alone and all drug/alcohol combinations prolonged reaction time and there were no differences between the combination treatments and alcohol alone. At 2.5 hours, the combination treatments had prolonged reaction time compared with placebo, but alcohol did not. There were no differences between alcohol-containing treatments and alcohol alone. With regards to body sway, at 1 and 2.5 hour(s), all drug/alcohol combinations and alcohol alone differed significantly from placebo. However, there was no difference between any of the active treatments. Secondary: Not reported
Ramaekers et al.[43] (1994) Diphenhydramine-50 mg as a single dose vs acrivastine 8 mg as a single dose vs	DB, RCT, XO Healthy female volunteers 21 to 45 years of age	N=18 10 to 11 weeks	Primary: Two repetitions of the highway driving test and car-following test given 1.5 to 2.75 hours (first trial) and 3.25 to 4.50 hours (second trial) post dosing Secondary: Not reported	Primary: *Highway Driving* All acrivastine doses significantly impaired driving (P<0.05) in the first trial. Only the 24 mg dose remained significant in the second trial (P=0.014). The combination of acrivastine (8 mg) with pseudoephedrine (60 mg) had no significant effect on highway driving in either trial. There was no significant effect of any terfenadine dose in either trial. Diphenhydramine significantly impaired driving in both trials (P=0.000 and 0.001, respectively). The effect of diphenhydramine differed from all other treatments in both trials, except acrivastine 16 and 24 mg. In the first trial, the effect of 16 mg acrivastine differed significantly from that of all three terfenadine doses. In the second trial, the effect of 24 mg acrivastine differed

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
acrivastine 16 mg as a single dose vs acrivastine 24 mg as a single dose vs acrivastine 8 mg and pseudoephedrine 60 mg as a single dose vs terfenadine 60 mg as a single dose vs terfenadine 120 mg as a single dose vs terfenadine 180 mg as a single dose vs placebo				significantly from that of terfenadine (120 and 60 mg). No other pair of treatment effects differed significantly. The difference in driving impairment was significant between placebo and diphenhydramine in both trials (P=0.010 and P=0.020, respectively); between placebo and acrivastine (16 mg) and terfenadine (60 mg) in the first trial (P=0.001 and P=0.031, respectively); between placebo and acrivastine (24 mg) in the second trial (P=0.018). The combination of acrivastine and pseudoephedrine had no significant effect on driving impairment compared to placebo. *Car-Following Test* The combined effect of all acrivastine doses on reaction time was significant in the first trial (P=0.046). The effects were also significant specifically for the 16 mg dose (P=0.027) and the 24 mg dose (P=0.04) compared to placebo. The effect of 24 mg dose remained significant in the second trial (P=0.025). The combination of acrivastine with pseudoephedrine had no significant effect on reaction time in either trial compared to placebo. There was no significant effect of any terfenadine dose (or combination of doses) in either trial. Diphenhydramine significantly affected reaction time in both trials (P=0.000 and P=0.042, respectively). Secondary: Not reported
Vuurman et al.[44] (1996)	DB, PG, RCT Atopic subjects 16 to 25 years of age	N=104 14 days	Primary: Symptom scores, memory test, learning test,	Primary: There were significant improvements in symptoms on day 1 with diphenhydramine and acrivastine plus pseudoephedrine compared to placebo (P=0.024 and P=0.029, respectively). There were no significant

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Diphenhydramine 50 mg QD vs acrivastine 8 mg and pseudoephedrine 60 mg QD administered as a fixed-dose combination vs placebo	with seasonal allergic rhinitis requiring antihistamine therapy and matched controls who did not require antihistamine therapy		examination performance Secondary: Not reported	treatment effects on day two or day three. At examination, symptom scores were not significantly different between groups. There was no overall treatment effects regarding the number of words during immediate recall (P=0.761); however, there was a significant increase over time in overall performance (P<0.001). Analysis of the scores for each day showed no significant differences between the groups on any day. There was no overall effect of treatment found on any day, or over all days, in mean delayed recall results; however, there was a significant increase over time (P<0.001). Training and examination scores increased in all groups. Atopic subjects had significantly lower scores than the control group (P=0.043). There was a significant performance deficiency noted after administration of diphenhydramine in atopic subjects compared to controls (P<0.001). Performance after acrivastine plus pseudoephedrine was significantly better than after administration of diphenhydramine (P=0.001). The difference between placebo and diphenhydramine was not significant (P=0.067). Performance after acrivastine plus pseudoephedrine was not significantly different from placebo (P=0.13) or controls (P=0.87). Atopic subjects performed significantly worse than controls in the performance at examination analysis (P=0.012). There was a significant performance deficiency noted after administration of diphenhydramine in atopic subjects compared to controls (P<0.001). The mean performance after acrivastine plus pseudoephedrine was significantly better than after administration of diphenhydramine (P=0.001). Performance after acrivastine plus pseudoephedrine was not significantly different from the control group (P=0.73). Secondary: Not reported
Simons et al.[45] (1996)	DB, PC, RCT, XO Healthy men 18 to 40 years of age	N=15 >7 weeks	Primary: Cognitive function assessed using the P300-event-related	Primary: The percent change in the P300 latency from baseline from least to greatest was: terfenadine, placebo, cetirizine, ketotifen, loratadine, astemizole and diphenhydramine. Diphenhydramine increased the P300 latency significantly compared with baseline and with placebo.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Diphenhydramine 50 mg as a single dose vs astemizole 10 mg as a single dose vs cetirizine 10 mg as a single dose vs ketotifen 2 mg as a single dose vs loratadine 10 mg as a single dose vs terfenadine† 60mg as a single dose vs placebo			potential, and subjective assessment of somnolence using a VAS Secondary: Not reported	The mean change in the visual analogue scale for somnolence from least to greatest was: placebo, astemizole, terfenadine, loratadine, cetirizine, ketotifen and diphenhydramine. Somnolence was significantly greater than baseline after astemizole, terfenadine and loratadine. It was also significantly greater than baseline and placebo after cetirizine, ketotifen and diphenhydramine. The effect of terfenadine, cetirizine, ketotifen, loratadine, and astemizole on the P300 latency and the visual analogue scale did not differ significantly from that of diphenhydramine. Secondary: Not reported
Schweitzer et al.[46] (1994)	DB, RCT, XO Healthy atopic adults	N=12 >28 days	Primary: MSLT, SALT, VAS sleepiness ratings, global sleepiness and	Primary: *MSLT* Mean sleep latencies were 7.5, 5.5, and 7.8 minutes on day one for cetirizine, diphenhydramine, and placebo, respectively, and 8.0, 8.3, and 8.3 minutes on day three.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Diphenhydramine 50 mg TID for 3 consecutive days vs cetirizine 10 mg for 3 consecutive days QD vs placebo			performance ratings Secondary: Not reported	On day one, diphenhydramine produced significant sedation at 1:00 PM and 5:00 PM relative to placebo (P<0.05) and at 11:00 AM (P=0.056) and 1:00 PM (P<0.05) compared with cetirizine. There were no differences between placebo and cetirizine on treatment day 1 and no differences among the three conditions on treatment day three. There was a significant decrease in physiologic sleepiness with diphenhydramine on day three compared with day one (P<0.05). During both treatment days, physiologic sleepiness was maximal at 11:00 AM and generally decreased as the day progressed for all conditions. *SALT* On day 1, subjects made fewer correct responses with diphenhydramine (83.1%) than with cetirizine (87.8%) or placebo (88.9%; P<0.05 for both). On day 3, correct response rate was equivalent among the three treatment groups. Performance improved on day three (compared with day one) in the diphenhydramine group (P<0.05), whereas performance remained stable on day three in the other two treatment groups. Performance was most impaired on day one during the two morning test periods after diphenhydramine administration and was impaired to a lesser extent in the afternoon after the second diphenhydramine dose. On treatment day one, subjects responded twice as quickly to assembly line malfunctions in the cetirizine and placebo groups (1.3 seconds and 1.2 seconds, respectively) compared with diphenhydramine (2.6 seconds, P<0.05 for both). Response time with diphenhydramine improved on day 3 (1.7 seconds, P<0.05 compared with day one). *VAS Sleepiness Ratings* Subjects rated themselves as 20% sleepier with diphenhydramine compared with placebo (P<0.05) and 14% sleepier compared with cetirizine (P=0.08). Subjective ratings of sleepiness did not differ between cetirizine and placebo.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Subjects rated themselves as slightly more alert on day three compared with day one. Subjects judged that they were sleepiest at 11:00 AM and 3:00 PM. On day one, diphenhydramine produced significantly more subjective sleepiness than placebo at 11:00 AM, 1:00 PM, 3:00 PM, and 5:00 PM (P<0.05). *Global Sleepiness and Performance Ratings* Subjects rated themselves as being more sleepy at the end of diphenhydramine treatment on day one compared with cetirizine and placebo (P<0.05 for both), which did not differ from each other. On treatment day three, there were no significant differences among the three groups. Subjects rated themselves as being significantly more alert at the end of day three in the diphenhydramine condition compared with treatment day one (P<0.001), whereas alertness ratings were similar on both treatment days for cetirizine and placebo. Performance was poorer on day one with diphenhydramine compared with cetirizine (P<0.01) and placebo (P=0.083), which did not differ from each other. Performance ratings improved on day 3 with diphenhydramine compared to day one (P<0.01). Performance ratings during the cetirizine and placebo conditions were similar on both treatment days. There were no significant differences among the three groups on day three. Secondary: Not reported
Simons et al.[47] (1999) Diphenhydramine 50 mg as a single dose vs	DB, PC, RCT, XO Healthy subjects >65 years of age	N=15 >5 weeks	Primary: Cognitive function assessed using the P300-event-related potential, and subjective assessment of somnolence using a VAS	Primary: The change in the P300 latency from baseline from least to greatest was: cetirizine, placebo, loratadine, diphenhydramine, and chlorpheniramine. However, there were no significant differences in the in P300 latency measurements at 2 to 2.5 hours after dosing compared to predose values (P>0.05). The change in VAS for somnolence from least to greatest was: placebo, loratadine, cetirizine, chlorpheniramine, and diphenhydramine. There were

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
chlorpheniramine 8 mg as a single dose vs cetirizine 10 mg as a single dose vs loratadine 10 mg as a single dose vs placebo			Secondary: Not reported	no significant differences in the subjective assessment of somnolence 2 to 2.5 hours after dosing compared to predose values (P>0.05). Secondary: Not reported
Vuurman et al.[48] (2004) Diphenhydramine 50 mg as a single dose vs desloratadine 5 mg as a single dose vs placebo	AC, DB, PC, RCT, XO Healthy volunteers	N=18 >3 weeks	Primary: Driving performance (SDLP) and psychomotor performance Secondary: Not reported	Primary: In the highway driving test, significantly more weaving behavior occurred following treatment with diphenhydramine (P<0.001 vs desloratadine or placebo). The mean SDLP was comparable following treatment with desloratadine or placebo. Subjects maintained a more constant speed with desloratadine than with diphenhydramine treatment (P=0.045); there was no significant difference between desloratadine and placebo. In the car-following test, mean brake reaction time was significantly shorter with desloratadine than with placebo (P=0.033) or diphenhydramine (P=0.001). No significant difference was observed between the diphenhydramine and placebo groups. No significant differences were observed among the groups with regard to headway variability. Subjects treated with diphenhydramine demonstrated a significantly greater increase in sleepiness score from baseline compared with desloratadine (P<0.001) or placebo (P<0.001). No difference was observed between the desloratadine and placebo groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Mean tracking error significantly increased from baseline following treatment with diphenhydramine compared with desloratadine and placebo (P=0.002 and P=0.001, respectively). Diphenhydramine significantly increased mean reaction time compared with desloratadine (P=0.014). There was no significant difference between desloratadine and placebo for either of these parameters. Secondary: Not reported
Wilken et al.[49] (2003) Diphenhydramine 50 mg as a single dose vs desloratadine 5 mg as a single dose vs placebo	DB, PC, PG, RCT Healthy adults 18 to 60 years of age with ragweed induced allergic rhinitis	N=248 1 week	Primary: Vigilance and cognitive performance battery; symptom evaluation Secondary: Not reported	Primary: Subjects taking diphenhydramine performed significantly worse on all parameters of vigilance compared with subjects taking either desloratadine or placebo. Subjects taking diphenhydramine performed significantly worse on measures across other cognitive domains (working memory, psychomotor speed, reasoning/computation, divided attention) compared with subjects taking either desloratadine or placebo. There were no statistically significant differences between subjects taking placebo and those taking desloratadine on any of the measures of cognitive functioning. Subjects taking diphenhydramine reported significantly worse functioning on the performance battery (P<0.001) compared with subjects taking desloratadine or placebo. Subjects in the diphenhydramine group reported a significantly greater degree of sedation (P<0.001) following the completion of the Stanford Sleepiness Scale test battery than subjects taking either desloratadine or placebo. Subjects taking diphenhydramine reported being significantly drowsier, more lethargic, and less clear-headed, quick-witted, attentive, coordinated, and proficient than subjects taking desloratadine or placebo. Subjects in the desloratadine group reported being significantly more clear-headed (P=0.05) and less drowsy (P=0.046) than those in the placebo group. Desloratadine and diphenhydramine treatment led to significant reductions in TTSs (P<0.001 and P<0.04, respectively) and TNSSs (P<0.001 and P<0.046, respectively) compared to placebo. There was a significant improvement in nonnasal symptoms for subjects taking diphenhydramine

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				(P<0.001) compared with subjects taking placebo; however, this finding was not significant for desloratadine. Self-reported global therapeutic response was significantly better in subjects taking either desloratadine (P=0.03) or diphenhydramine (P<0.001) compared with placebo. Secondary: Not reported
Mansfield et al.[50] (2003) Diphenhydramine 50 mg as a single dose vs fexofenadine 180 mg as a single dose vs placebo	DB, PC, RCT, XO Healthy volunteers	N=44 <40 days	Primary: Cognitive performance using the Test of Variables of Attention Secondary: Not reported	Primary: Mean response time was significantly longer with diphenhydramine than with placebo (P=0.0230). There was no significant difference between fexofenadine and placebo (P=0.5264), nor was there a significant difference between fexofenadine and diphenhydramine (P=0.1258). There was a significant difference in the average omission error values between diphenhydramine and placebo (P=0.0398). Fexofenadine and placebo were not statistically different (P=0.6389) nor was fexofenadine and diphenhydramine (P=0.1028). The frequency of commission errors was not significantly different for diphenhydramine or fexofenadine compared to placebo (P=0.4975 and P=0.1483, respectively). However, diphenhydramine was associated with significantly more commission errors than fexofenadine (P=0.0354). Diphenhydramine was associated with significantly more drowsiness than placebo (P=0.0004). Fexofenadine was not statistically different from placebo for drowsiness scores (P=0.0810). There was no significant difference in drowsiness with diphenhydramine compared to fexofenadine (P=0.0742). Secondary: Not reported
Weiler et al.[51] (2000) Diphenhydramine 50 mg as a single dose	DB, RCT, XO Licensed drivers with seasonal allergic rhinitis	N=41 4 weeks	Primary: Driving performance (using the Iowa Driving Simulator) and	Primary: *Phase 1* After taking diphenhydramine, participants performed car-following with significantly less coherence than after taking alcohol, fexofenadine, or placebo (95% CI excludes zero).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs fexofenadine 60 mg as a single dose vs alcohol (~0.1% blood alcohol concentration) vs placebo			self-reported drowsiness Secondary: Not reported	Significant differences in minimum following distance were observed among the four treatments. When participants performed car-following after consuming alcohol, they had significantly smaller minimum following distances than they did after taking fexofenadine or placebo. There was no significant difference in car-following after taking diphenhydramine and alcohol. After participants took fexofenadine, they had significantly less steering instability than after taking diphenhydramine or alcohol, but not placebo. After participants took placebo, they had significantly less steering instability than after consuming alcohol or diphenhydramine. *Phase 2* After completing phase 1, participants drove the remaining 30 miles of the course "as you normally would drive." After participants took fexofenadine, they had significantly less steering instability than after taking diphenhydramine or alcohol, but not placebo. After participants took placebo, they had significantly less steering instability than after consuming alcohol or diphenhydramine. After participants consumed alcohol, they had the same or less steering instability than after taking diphenhydramine. No significant differences for lane excursions to the right were noted among the four treatments. Significant differences were noted the four treatments for excursions to the left. After participants took diphenhydramine, they crossed the center line significantly more often than after taking fexofenadine or placebo. After participants took alcohol, they crossed the center line significantly more often than after taking fexofenadine and placebos. Fexofenadine and placebo did not differ significantly. There were no significant differences among the treatment groups on response time to a blocking vehicle. However, after consuming alcohol, participants responded more slowly to the event than after they took fexofenadine. Responses to the blocking vehicle were categorized as clear

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				avoidance, potentially unsafe avoidance, or collision. The overall differences were not significant. Drowsiness scores on the second visual analogue scale (given 1 hour after treatment administration) were not significantly different among the treatment groups. At the time of the third visual analogue scale (just before the drive), participants were significantly more drowsy after taking diphenhydramine and least drowsy after taking fexofenadine or placebo. The differences between diphenhydramine and fexofenadine or placebo were significant. After the drive, participants were most drowsy with diphenhydramine and least drowsy with placebo. The difference between fexofenadine and placebo was not significant. Participants reported significantly higher levels of drowsiness with diphenhydramine than with fexofenadine and placebo. Secondary: Not reported
Gandon et al.[52] (2002) Diphenhydramine 50 mg QD for 5 consecutive days vs levocetirizine 5 mg QD for 5 consecutive days vs placebo	XO Healthy volunteers	N=19 >1 month	Primary: CFF Secondary: CRT, body sway, LMT, and subjective assessments of alertness	Primary: The mean CFF values for levocetirizine and placebo were not significantly different from each other globally across all time points (P=0.292) or at any specific time point. Mean CFF values after diphenhydramine administration was significantly different than placebo across all time points (P=0.019) and at one, two and three hours after dosing (P<0.04). Secondary: Mean CRT scores were comparable over time for the three treatments, with no significant differences for groups on day five. With regards to body sway, results on distance and surface displacement from the center of gravity (measured with eyes open or closed) were similar for levocetirizine and placebo. An increase in total displacement distance was demonstrated up to three hours after dosing with diphenhydramine on day one (eyes closed: 16.35 cm (95% CI, 5.61 to 27.10).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Scores of alertness increased after levocetirizine and placebo. A decrease in alertness was observed after diphenhydramine administration on day one compared with placebo. There was a similar evolution of contentedness in all three treatments on days one and five. There was no consistent decrease in calmness observed with any treatment. There was no significant difference in LMT among the three treatment groups.
Verster et al.[53] (2003) Diphenhydramine 50 mg as a single dose on 4 consecutive days vs levocetirizine 5 mg as a single dose on 4 consecutive days vs placebo	DB, PC, RCT, XO Healthy volunteers	N=48 >3 weeks	Primary: Memory, psychomotor performance, mood Secondary: Not reported	Primary: On the word learning test, learning was not significantly impaired after administration of either levocetirizine or diphenhydramine compared to placebo on day one or day four. On the Sternberg Memory Scanning Test, there were no significant differences in reaction time or percentage of errors made during test performance between the treatments and placebo on day one. On day four, there were no significant differences on memory-scanning parameters between the treatments and placebo. On the tracking test, tracking ability after administration of diphenhydramine was significantly impaired in both the easy and hard versions of the test on day one ($P<0.0001$ for both). Tracking ability after administration of levocetirizine was not significantly impaired compared to placebo. On day four, there were no significant differences between the treatments and placebo. On the divided attention test, tracking ability after administration of diphenhydramine was significantly different from that after placebo on day one ($P<0.0001$). Tracking ability after administration of levocetirizine was not significantly different from that after placebo. Compared to placebo, reaction times after administration of diphenhydramine were significantly increased ($P<0.0001$). Reaction times with levocetirizine did not change. On day four, there were no significant differences between treatments and placebo on divided attention test parameters. After administration of diphenhydramine, scores on the ARCI-49 questionnaire indicated significantly increased sedation on days one and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				four. Euphoria, intellectual efficacy and energy were significantly decreased with diphenhydramine. The effects of levocetirizine on all ARCI-49 scales were not significantly different from the effects of placebo. Secondary: Not reported
Verster et al.[54] (2003) Diphenhydramine 50 mg as a single dose on 4 consecutive days vs levocetirizine 5 mg as a single dose on 4 consecutive days vs placebo	DB, PC, RCT, XO Healthy volunteers	N=48 >3 weeks	Primary: Driving performance (SDLP) and subjective assessments Secondary: Not reported	Primary: When assessing the acute effects of treatment, the majority of individual SDLPs after levocetirizine were similar to placebo (P=not significant). Only 16.7% of subjects drove worse than the acceptance limit. For those receiving diphenhydramine, 43.8% drove worse than the legal limit (for driving in The Netherlands; P<0.0001). The SDLP of diphenhydramine differed significantly from placebo (P<0.0001). No significant effects were found for the other parameters of the driving test. When assessing the sub-chronic effects of treatment, the majority of individual SDLPs after levocetirizine were similar to placebo (P=not significant). Only 16.7% of subjects drove worse than the acceptance limit. For those receiving diphenhydramine, 31.1% of subjects drove worse than the legal limit (for driving in The Netherlands; P<0.001). The SDLP of diphenhydramine differed significantly from placebo (P<0.0003). No significant effects were found for the other parameters of the driving test. In the subjective assessment (acute treatment), diphenhydramine significantly reduced driving quality (P<0.0001), increased mental effort during driving (P<0.0001), and reduced alertness (P<0.0001). There were no significant differences found between levocetirizine and placebo. In the subjective assessment (sub-chronic treatment), driving quality and mental effort during driving did not differ significantly between the treatments. Alertness was significantly reduced after diphenhydramine compared to placebo (P<0.005). The level of alertness did not differ between levocetirizine and placebo. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Not reported
Bender et al.[55] (2001) Diphenhydramine 25 mg twice daily (6 hours apart) on 3 different school days vs loratadine 10 mg QD on 3 different days vs placebo	DB, PC, PG, RCT Children 8 to 10 years of age with allergic rhinitis requiring an antihistamine	N=63 15 days (4 laboratory school days)	Primary: Total Verbal Instruction Score, Total Reading Recall Score, Total Average Reaction Time, and Somnolence Scale using a computer-administered neuropsychologic test battery (administered on four school days) Secondary: Not reported	Primary: In the Verbal Instruction Score, no significant treatment-group differences were found. Errors decreased significantly with age (P<0.0001) and over time (P<0.0001) as familiarity with materials and testing situations increased. In the Reading Test Score, no significant treatment-group differences were found. Both age and baseline reading ability were significant covariates (P<0.0001), and errors decreased markedly over time (P<0.0001). For Average Reaction Time, no treatment-group differences were found for reaction time or performance scores on any of the four visits. Average reaction time to computer tasks decreased over all four visits (P<0.0001). For Somnolence Scale ratings, there was no significant differences between treatment groups (P=0.17). Secondary: Not reported
Kay et al.[56] (1997) Diphenhydramine 50 mg for 1 dose on day 1, then 25 mg QID vs loratadine 10 mg QD vs placebo	DB, RCT Healthy volunteers	N=98 5 days	Primary: Cognitive and psychomotor test performance on day one, day three, and day five, as well as self-reported measures Secondary: Not reported	Primary: *Day 1* Subjects receiving diphenhydramine performed poorly compared with subjects receiving loratadine or placebo on measures of divided attention, working memory, and vigilance. Compared to placebo, loratadine did not adversely affect performance on any of these measures. Subjects receiving diphenhydramine demonstrated poorer performance on a measure of tracking accuracy under divided attention conditions (Cog Screen Dual Task Test) compared with subjects taking loratadine or placebo. Subjects taking loratadine outperformed subjects taking placebo (P=0.02). Subjects taking diphenhydramine were less efficient in their performance on the Complex Cognitive Assessment Battery Mark Numbers Test than subjects taking loratadine (P=0.002).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Subjects taking diphenhydramine obtained lower accuracy scores on the ANAM Running Memory Test compared with subjects taking loratadine (P=0.008). ANAM Math throughput scores were also lower for subjects taking diphenhydramine (P<0.001). The CogScreen Shifting Attention Test-Instruction Condition throughput score was higher for subjects who received loratadine (P<0.05) than for subjects taking diphenhydramine. On the Kay Continuous Performance Test, subjects taking diphenhydramine were more likely to make errors of commission and errors of omission (P=0.05 and P=0.002, respectively). Ratings of sleepiness on the Stanford Sleepiness Scale were higher after diphenhydramine than after administration of loratadine (P=0.02). Subjects receiving diphenhydramine reported higher levels of fatigue than subjects receiving loratadine (P<0.001). Subjects receiving diphenhydramine also had lower levels of motivation (P<0.001) and rated the quality of their test performance as lower (P<0.001), compared with subjects receiving loratadine. *Days three and five* There were no differences among the treatment groups for the cognitive and psychomotor tests performed on days three and five. However, subjects who received diphenhydramine performed less well than subjects who received placebo on days three and five on a test of tracking errors. There were no differences between loratadine and placebo on the cognitive and psychomotor tests on day five. Subjects who received diphenhydramine reported greater fatigue (P=0.001) and rated the quality of their test performance as lower (P=0.007) compared with subjects who received loratadine. Subjects in the diphenhydramine group also reported lower motivation than subjects taking loratadine (P=0.001). Loratadine did not differ significantly from placebo with respect to level of motivation, mood, or self appraised quality of performance on day five.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Vuurman et al.[57] (1993) Diphenhydramine 25 mg BID (4 hours apart) for 2 weeks vs loratadine 10 mg QD for 2 weeks vs placebo	RCT Children 10 to 12 years of age with seasonal allergic rhinitis requiring antihistamine therapy and matched controls who did not require antihistamine therapy	N=52 14 days	Primary: Factual knowledge scores, conceptual knowledge scores, composite learning scores Secondary: Not reported	Primary: For factual knowledge scores, atopic children were significantly less knowledgeable than children in the control group (P<0.01). Paired comparisons of the atopic group with controls showed a significant effect of diphenhydramine (P=0.012). For conceptual knowledge scores, atopic children were significantly less knowledgeable than children in the control group (P=0.001). Paired comparisons of the atopic group with controls showed a significant effect of diphenhydramine (P=0.001). Geometric mean survival years (knowledge application scores) were significantly lower in children receiving antihistamines compared to the control group (P<0.02). The composite learning scores were significantly lower in atopic children compared to the control group (P<0.003). Composite learning scores were also lower in atopic children receiving placebo or diphenhydramine compared to the control group (P=0.007 and P=0.002, respectively). Secondary: Not reported
Roth et al.[58] (1987) Diphenhydramine 50 mg TID for 2 days vs loratadine 10 mg QD for 2 days vs	DB, RCT, XO Healthy adults 19 to 35 years of age	N=16 28 days	Primary: Measures of performance and daytime sleepiness Secondary: Not reported	Primary: The nocturnal polysomnogram did not detect any difference among the treatments on any parameter evaluated, including total sleep time, latency to sleep, number and duration of awakenings after sleep onset, and percentages of various sleep stages. There was a significant reduction (increased sleepiness) in mean latency to sleep (P<0.01) with diphenhydramine compared to placebo (P<.01) and both loratadine doses (P<0.01 and P<0.02). The low loratadine dose did not differ from the placebo dose or from the large loratadine dose. Although the high loratadine dose did not differ from the low loratadine dose, it did differ from the placebo dose (P<0.04).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
loratadine 40 mg QD for 2 days vs placebo				Subjects rated themselves as being sleepier with diphenhydramine. The vigilance and reaction time tasks demonstrated no effect of treatments. On the performance battery at 9:30 A.M., diphenhydramine produced decrements in digit symbol substitution (P<0.05), whereas both loratadine doses had no effects. The afternoon performance battery (1:30 P.M.) demonstrated no effects of the treatments. Secondary: Not reported
Witek et al.[59] (1995) <u>Study1</u> Diphenhydramine 50 mg as a single dose vs terfenadine† 60 mg as a single dose vs placebo <u>Study 2</u> Diphenhydramine 25 mg as a single dose vs diphenhydramine 50 mg as a single dose	DB, PC, RCT, XO Healthy volunteers 18 to 45 years of age	<u>Study1</u> N=18 >1 week <u>Study 2</u> N=20 >1 week	Primary: Subjective assessments and psychomotor performance Secondary: Not reported	Primary: *Study 1* In the subjective assessments, diphenhydramine-induced sleepiness was significantly greater than that reported after terfenadine or placebo (P<0.05). There was no difference in sleepiness between terfenadine and placebo. In the VAS analysis, subjects receiving diphenhydramine reported significantly higher levels of sleepiness at three and five hours after taking the dose than after taking terfenadine or placebo (P<0.05). No significant differences were noted between terfenadine and placebo. Significant reductions in alertness were reported with diphenhydramine compared to terfenadine or placebo at three hours after dosing (P<0.05). The difference between diphenhydramine and terfenadine was still evident five hours after dosing (P<0.05). CRT significantly increased one and three hours after diphenhydramine compared with terfenadine. Diphenhydramine produced significant increases in reaction time relative to placebo three hours after drug. No significant differences between terfenadine and placebo were found. There were significant impairments with diphenhydramine in tracking ability compared to terfenadine or placebo at one and three hours. *Study 2* In the subjective assessments, all antihistamine treatments resulted in significantly higher scores on the Stanford Sleepiness Scale three hours after dosing than those reported after placebo (P<0.05). Sleepiness scores were significantly higher with diphenhydramine 50 mg than diphenhydramine 25 mg three hours after dosing and significantly higher

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs chlorpheniramine 4 mg as a single dose vs placebo				than chlorpheniramine five hours after dosing. In the VAS analysis, all three antihistamines produced significantly higher sleepiness compared to placebo three hours after drug administration (P<0.05). Significant reductions in alertness were reported with diphenhydramine 50 mg. There were no significant differences among treatments in jitteriness self-assessments. All three antihistamines impaired reaction relative to placebo one and three hours after dosing (P<0.05). Chlorpheniramine resulted in prolonged reaction time seven hours after dosing, which was significantly greater than the response following diphenhydramine 25 mg. Tracking was significantly impaired with diphenhydramine (25 and 50 mg) compared to placebo one hour after dosing. At three hours after dosing, diphenhydramine 25 mg significantly impaired tracking relative to placebo and chlorpheniramine. Secondary: Not reported
Cohen et al.[60] (1985) Triprolidine 2.5 mg as a single dose vs triprolidine 5 mg as a single dose vs acrivastine 4 mg as a single dose vs	DB, PC, XO Healthy volunteers	N=12 1 days	Primary: 10-minute tracking test score, reaction time, subjective effects using a VAS Secondary: Not reported	Primary: Triprolidine (2.5 and 5 mg) decreased the time tracking score at 1.5 hours after drug dosing compared with placebo and all the acrivastine treatments. The mean tracking score continued to be impaired three hours after triprolidine (5 mg). None of the acrivastine treatments caused any significant impairment compared to placebo. Reaction time was increased at 1.5 hours after triprolidine (2.5 and 5 mg) compared with placebo, and at three hours (triprolidine 5 mg). None of the treatments were different from placebo 5 hours after drug dosing. None of the acrivastine treatments caused a significant change in reaction time compared with placebo at any time during the study. Triprolidine (2.5 and 5 mg) made subjects feel drowsy, clumsy, lethargic, mentally slow, dreamy, and bored at 1.5 hours after drug dosing compared to placebo. Triprolidine (5 mg) also made them feel muzzier and more incompetent. No effects were noted after any of the acrivastine doses.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
acrivastine 8 mg as a single dose vs acrivastine 16 mg as a single dose vs placebo				Effects were seen 3 hours after triprolidine (5 mg) as the subjects felt clumsy, lethargic, and mentally slow. Secondary: Not reported

†Agent not available in the United States.
Drug regimen abbreviations: BID=twice daily, ER=extended-release, IR=immediate-release, QD=once daily, QID=four times daily, SR=sustained-release, TID=three times daily
Study design abbreviations: AC=active control, DB=double-blind, MC=multicenter, OL=open-label, PC=placebo-controlled, PG=parallel-group, RCT=randomized-controlled trial, XO=cross-over
Miscellaneous abbreviations: ANAM=Automated Neuropsychological Assessment Metrics, ARCI=Addiction Research Center Inventory, CFF=critical flicker fusion, CI=confidence interval, CRT=choice reaction time, CTT=compensatory tracking test, LARS=line analogue rating scale, LMT=learning memory test, MSLT=multiple sleep latency test, NAR=nasal airway resistance, PSV=peak saccade velocity, RVIP=rapid visual information processing, SALT=simulated assembly line task, SDLP=standard deviation of lateral position, TAR=total airflow rates, TNSS=total nasal symptom scores, TSS=total symptom scores, VAS=visual rating scale, WA=wrist actigraphy

Additional Evidence

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

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

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

IX. Cost

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

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

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

Rx=prescription

Table 9. Relative Cost of the First Generation Antihistamines

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Ethanolamine Derivatives				
Carbinoxamine	extended-release suspension, solution*, tablet*	Karbinal ER®, Ryvent®	$	$
Clemastine	syrup, tablet	N/A	N/A	$
Diphenhydramine	elixir, injection	N/A	N/A	$$
Propylamine Derivatives				
Dexchlorpheniramine	solution	Ryclora®	$	N/A
Phenylephrine and chlorpheniramine	drops	N/A	N/A	$

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

X. Conclusions

The first generation antihistamines are approved for the treatment of allergic and non-allergic conditions; however, they are primarily used for the management of allergic rhinitis, urticaria, and angioedema. They are

available as single entity agents, as well as in combination with oral decongestants. Many of the products are available in a generic formulation.

There are several organizations that provide recommendations on the use of first generation antihistamines. There are a variety of effective treatment options for allergic rhinitis, including H_1-antihistamines. The second generation antihistamines are preferred over first generation agents because they have a lower tendency to cause sedation, anticholinergic effects, and performance impairment.[1,10] Due to their pharmacokinetic properties (prolonged half-life and active metabolites), the central nervous system effects cannot be eliminated by administering these agents at bedtime.[1] For the treatment of urticaria, antihistamines are the cornerstone of therapy. Second generation antihistamines are generally preferred; however, first generation agents can also be effective and well-tolerated by patients. The addition of a sedating first generation antihistamine to a second generation antihistamine may help patients sleep better.[2] For the treatment of atopic dermatitis, topical corticosteroids are the standard of care.[5-6] Antihistamines may help relieve pruritic symptoms, especially in those with concomitant urticaria or allergic rhinitis.[6] First generation antihistamines may also be useful in patients with sleep disturbances due to pruritus.[5-7] For the management of allergic/atopic conjunctivitis, topical antihistamines are an effective treatment option; however, oral antihistamines may also be considered.[7] Antihistamines are not recommended for the treatment of acute sinusitis. They may have a role in the management of chronic sinusitis if allergic rhinitis is an underlying risk factor.[9,12-13] The available guidelines do not give preference to one particular first generation antihistamine over another.[1-2,4-14]

There are very few studies that directly compare the first generation antihistamines. Clemastine and chlorpheniramine were found to be equally effective for the treatment of allergic rhinitis.[22-24] The first generation antihistamines have also been shown to be as effective as second generation antihistamines in multiple studies.[18,20-28,30,35] The fixed-dose combination of triprolidine-pseudoephedrine was shown to be more effective than monotherapy with triprolidine or pseudoephedrine.[31-33] However, there were no studies found in the medical literature that directly compared the efficacy of the fixed-dose combination product to the coadministration of each component as separate formulations. Several clinical trials have evaluated the central nervous system effects of antihistamines. The first generation antihistamines have been shown to adversely affect cognitive and psychomotor functions, as well as impair driving performance.[37-60]

Oral decongestants (pseudoephedrine and phenylephrine) help to relieve nasal congestion and are available in combination with some first generation antihistamines. Pseudoephedrine has been used to make methamphetamine and there are restrictions on the sale of this product in the United States. Many over-the-counter products now contain phenylephrine; however, phenylephrine appears to be less effective than pseudoephedrine as it is extensively metabolized in the gut.[1]

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

Therefore, all brand products 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 first generation antihistamine 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 Estrogens
AHFS Class 681604
November 8, 2023

I. Overview

The estrogens are approved for the treatment of vasomotor symptoms associated with menopause, vulvar and vaginal atrophy, abnormal uterine bleeding, hypoestrogenism, prevention of postmenopausal osteoporosis, as well as for the palliative treatment of prostate and breast cancer.[1-3] The menopausal transition period is associated with irregular or heavy bleeding, hot flashes, sleep disturbance, vaginal dryness, sexual dysfunction, incontinence, urinary tract infections, depression, and other clinical manifestations. For most women, these symptoms are usually mild and of short duration. The use of hormone therapy helps to alleviate these symptoms. Estrogen can be used alone in women who have had a hysterectomy; however, a progestin should be added to the regimen for women with an intact uterus as it reduces the risk of endometrial cancer.[4-14]

For over 20 years, studies have examined the role of hormone therapy in the prevention of chronic diseases.[14] Observational studies suggested that there was a lower risk of cardiovascular disease, colorectal cancer, and osteoporotic fractures with the use of hormone therapy.[15] The Women's Health Initiative (WHI) studies were designed to further assess the effects of hormone therapy on these end points. Women with an intact uterus were enrolled in the estrogen-plus-progestin therapy (EPT) trial, whereas women without a uterus were enrolled in the estrogen-alone therapy (ET) study. The EPT substudy was stopped early due to an increased risk for cardiovascular events, stroke, pulmonary emboli, venous thromboembolic events, and invasive breast cancer.[16] The ET substudy was also stopped early due to an increased risk of stroke and no benefit with regards to cardiovascular disease.[17] Two additional long-term trials (HERS and HERS II) also failed to show a benefit with hormone therapy for the primary or secondary prevention of cardiovascular disease.[18] The estrogen products carry boxed warnings based on the information from the WHI studies.[1-3] Many organizations recommend the use of hormone therapy only for the short-term treatment of menopausal symptoms. The long-term use of hormone therapy is no longer recommended for the prevention of chronic diseases.[7,12-14]

The estrogens are available in a variety of dosage forms, including injectable, oral, topical, transdermal, and vaginal preparations. Oral estrogens have a greater effect on the liver than topical formulations due to first-pass metabolism following gastrointestinal absorption. Oral estrogens may increase the production of cholesterol (triglycerides and high density lipoprotein cholesterol) and clotting factors, which is only minimally affected by topical, transdermal, and vaginal preparations.[19]

Conjugated estrogens-bazedoxifene bind to and activate estrogen receptors alpha and beta, which vary in proportion from tissue to tissue. Bazedoxifene is a third generation selective estrogen receptor modulator which acts as an agonist in some tissues and as an antagonist in the uterus. The pairing of conjugated estrogens with bazedoxifene produces a composite effect specific to each tissue. The addition of bazedoxifene reduces the risk of endometrial hyperplasia associated with the conjugated estrogens component.[1-3]

The estrogens that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Estradiol, estradiol valerate, estradiol-norethindrone, and norethindrone-ethinyl estradiol are available in a generic formulation. This class was last reviewed in November 2021.

Table 1. Estrogens Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Estradiol	tablet, topical gel, topical spray, transdermal patch, vaginal cream, vaginal ring, vaginal tablet	Climara®*, Divigel®*, Elestrin®, Estrace®*, Estring®, Evamist®, Menostar®, Minivelle®*, Vagifem®*, Vivelle-Dot®*	estradiol
Estradiol acetate	vaginal ring	Femring®	none

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Estradiol cypionate	injection	Depo-Estradiol®	none
Estradiol valerate	injection	Delestrogen®*	estradiol valerate
Estradiol and drospirenone	tablet	Angeliq®	none
Estradiol and levonorgestrel	transdermal patch	Climara Pro®	none
Estradiol and norethindrone	tablet, transdermal patch	Activella®*, Amabelz®*, Combipatch®, Mimvey®*	estradiol and norethindrone
Estradiol and norgestimate	tablet	Prefest®	none
Estradiol and progesterone	capsule	Bijuva®	none
Estrogens, conjugated	injection, tablet, vaginal cream	Premarin®	Premarin® (tablets only)
Estrogens, conjugated and bazedoxifene	tablet	Duavee®	none
Estrogens, conjugated and medroxyprogesterone	tablet	Premphase®, Prempro®	Prempro®
Estrogens, esterified	tablet	Menest®	none
Norethindrone and ethinyl estradiol	tablet	Jinteli®*	norethindrone and ethinyl estradiol

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

II. Evidence-Based Medicine and Current Treatment Guidelines

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

Table 2. Treatment Guidelines Using the Estrogens

Clinical Guideline	Recommendation(s)
The International Menopause Society, The North American Menopause Society, The Endocrine Society, The European Menopause and Andropause Society, The Asia Pacific Menopause Federation, The International Osteoporosis Foundation, and The Federation of Latin American Menopause Societies: **Revised Global Consensus Statement on Menopausal Hormone Therapy (2016)[4]**	<u>Benefit/risk profile of menopausal hormone therapy (MHT)</u> • MHT (including tibolone and the combination of conjugated equine estrogens and bazedoxifene) is the most effective treatment for vasomotor symptoms associated with menopause at any age, but benefits are more likely to outweigh risks for symptomatic women before the age of 60 years or within 10 years after menopause. • If MHT is contraindicated or not desired for treatment of vasomotor symptoms, selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors such as paroxetine, escitalopram, venlafaxine and desvenlafaxine, which have been shown to be effective in randomized controlled trials (RCTs), may be considered. Gabapentin may also be considered. • Quality of life, sexual function and other menopause-related complaints, such as joint and muscle pains, mood changes and sleep disturbances, may improve during MHT. • MHT is effective in the prevention of bone loss and has been shown to significantly lower the risk of hip, vertebral and other osteoporosis-related fractures in postmenopausal women. • MHT is the only therapy available with RCT-proven efficacy of fracture reduction in a group of postmenopausal women not selected for being at risk of fracture and with mean *T*-scores in the normal to osteopenic range. • MHT, including tibolone, can be initiated in postmenopausal women at risk of fracture or osteoporosis before the age of 60 years or within 10 years after menopause. • Initiation of MHT after the age of 60 years for the indication of fracture prevention is considered second-line therapy and requires individually calculated benefit/risk, compared to other approved drugs. If MHT is elected, the lowest effective dose should be used.

Clinical Guideline	Recommendation(s)
	• MHT, including tibolone, is effective in the treatment of vulvovaginal atrophy (VVA), now also considered as a component of the genitourinary syndrome of menopause (GSM). Local low-dose estrogen therapy is preferred for women whose symptoms are limited to vaginal dryness or associated discomfort with intercourse or for the prevention of recurrent urinary tract infections. Ospemifene, an oral selective estrogen receptor modulator, is also licensed in some countries for the treatment of dyspareunia attributed to VVA. • RCTs and observational data as well as meta-analyses provide evidence that standard-dose estrogen-alone MHT may decrease the risk of myocardial infarction and all-cause mortality when initiated in women younger than 60 years of age and/or within 10 years of menopause. Data on estrogen plus progestogen MHT initiated in women younger than age 60 years or within 10 years of menopause show a less compelling trend for mortality benefit, and evidence on cardioprotection is less robust with inconsistent results compared to the estrogen-alone group. • The risk of venous thromboembolism (VTE) and ischemic stroke increases with oral MHT, although the absolute risk of stroke with initiation of MHT before age 60 years is rare. Observational studies and a meta-analysis point to a probable lower risk of VTE and possibly stroke with transdermal therapy (0.05 mg twice weekly or lower) compared to oral therapy. • The risk of breast cancer in women over 50 years of age associated with MHT is a complex issue with decreased risk reported from RCTs for estrogen alone (conjugated equine estrogens in the Women's Health Initiative (WHI)) in women with hysterectomy and a possible increased risk when combined with a progestin (medroxyprogesterone acetate in the WHI) in women without hysterectomy. The increased risk of breast cancer thus seems to be primarily, but not exclusively, associated with the use of a progestin with estrogen therapy in women without hysterectomy and may be related to the duration of use. • The risk of breast cancer attributable to MHT is rare. It equates to an incidence of <1.0 per 1000 women per year of use. This is similar or lower than the increased risk associated with common factors such as sedentary lifestyle, obesity and alcohol consumption. The risk may decrease after treatment is stopped, but data are inconsistent. • Women experiencing a spontaneous or iatrogenic menopause before the age of 45 years and particularly before 40 years are at a higher risk for cardiovascular disease and osteoporosis and may be at increased risk of affective disorders and dementia. In such women, MHT reduces symptoms and preserves bone density. Observational studies that suggest MHT is associated with reduced risk of heart disease, longer lifespan, and reduced risk of dementia require confirmation in RCTs. MHT is advised at least until the average age of menopause. • MHT initiated in early menopause has no substantial effect on cognition, but, based on observational studies, it may prevent Alzheimer's disease in later life. In RCTs, oral MHT initiated in women aged 65 years or older also has no substantial effect on cognition and increases the risk of dementia. • MHT may be beneficial in improving mood in early postmenopausal women with depressive and/or anxiety symptoms. MHT may also be beneficial for perimenopausal women with major depression but antidepressant therapy remains first-line treatment in this setting. <u>General principles governing the use of MHT</u> • The option of MHT is an individual decision in terms of quality of life and health priorities as well as personal risk factors such as age, time since menopause, and the risk of venous thromboembolism, stroke, ischemic heart disease, and breast cancer. MHT should not be recommended without a clear indication for its use.

Clinical Guideline	Recommendation(s)
	• Consideration of MHT for symptom relief or osteoporosis prevention should be a part of an overall strategy including lifestyle recommendations regarding diet, exercise, smoking cessation and safe levels of alcohol consumption for maintaining the health and quality of life of peri- and postmenopausal women. • MHT includes a wide range of hormonal products and routes of administration, including tibolone (where available) or conjugated equine estrogens/bazedoxifene, with potentially different risks and benefits. However, evidence regarding differences in risks and benefits between different products is limited. • The type and route of administration of MHT should be consistent with treatment goals, patient preference and safety issues and should be individualized. The dosage should be titrated to the lowest appropriate and most effective dose. • Duration of treatment should be consistent with the treatment goals of the individual, and the benefit/risk profile needs to be individually reassessed annually. This is important in view of new data indicating longer duration of vasomotor symptoms in some women. • Estrogen as a single systemic agent is appropriate in women after hysterectomy but concomitant progestogen is required in the presence of a uterus for endometrial protection with the exception that conjugated equine estrogens can be combined with bazedoxifene for uterine protection. • The use of continuous testosterone therapy, either alone or with MHT, is supported in carefully selected postmenopausal women with sexual interest/arousal disorder (in countries with regulatory approval). • The use of custom-compounded hormone therapy is not recommended because of lack of regulation, rigorous safety and efficacy testing, batch standardization, and purity measures. • Current safety data do not support the use of MHT in breast cancer survivors.
The British Menopause Society, International Menopause Society, European Menopause and Andropause Society, Royal College of Obstetricians and Gynaecologists, and Australasian Menopause Society: **Joint Statement on menopausal hormone therapy (MHT) and breast cancer risk (2020)[5]**	<u>Menopausal symptoms</u> • The menopause transition can have a significant impact on many women, with more than 75% experiencing menopausal symptoms, a quarter describing severe symptoms, and a third experiencing long-term symptoms. <u>Treatments</u> • MHT, compared with placebo, has been consistently shown to improve menopausal symptoms and overall quality of life and remains the most effective treatment for menopausal symptoms. For some women, MHT may not be suitable, and alternative treatments are available. <u>MHT and breast cancer risk - The Collaborative Group on Hormonal Factors in Breast Cancer meta-analysis</u> • Duration-dependent increase in the risk of breast cancer diagnosis with both unopposed estrogen and combined MHT. • The risk is higher with continuous combined MHT regimens compared to cyclical. • The risk of breast cancer remains elevated more than 10 years after discontinuing MHT. • No estrogen dosage effect on the risk of breast cancer with MHT. • Vaginal estrogen exposure did not increase the risk of breast cancer diagnosis. • Only a small number of women on micronized progesterone were included. Therefore, conclusions regarding its impact on the risk of breast cancer diagnosis could not be determined from this meta-analysis. • The decision whether to take MHT, the dose of MHT and the duration of its use should be made on an individualized basis after discussing the benefits and risks with women to help them make an informed choice about their health and care.

Clinical Guideline	Recommendation(s)
	Osteoporosis • Evidence from RCTs and meta-analysis shows that women using MHT have a significant reduction in the risk of any fracture compared with women not using MHT. Cardiovascular disease (CVD) • The timing MHT is initiated, referred to as the 'timing hypothesis' and 'the cardiovascular window of opportunity', can have a significant impact on the risk of CVD with MHT intake. • Cochrane data-analysis shows that MHT initiated within 10 years of the menopause is likely to be associated with a reduction in coronary heart disease and cardiovascular mortality. • Evidence from the Cochrane data-analysis and that from the long-term follow-up data of the WHI showed no increase in cardiovascular events, cardiovascular mortality or all-cause mortality in women who initiated MHT more than 10 years after the menopause. Risk of venous thromboembolism • Compared with women not on MHT, the risk of venous thromboembolism is increased by oral intake MHT. • Transdermal administration of estradiol is unlikely to increase the risk of venous thrombosis above that in non-users and is associated with a lower risk compared with oral administration of estradiol.
North American Menopause Society: **Management of Osteoporosis in Postmenopausal Women: 2021 Position Statement (2021)[6]**	• Intervening to prevent rapid bone loss and deterioration of skeletal structure is a unique opportunity to maintain bone health. • Such intervention would be most appropriate in women with low bone mineral density (BMD) who are experiencing relatively rapid bone loss because of acute estrogen deficiency in the perimenopausal and early postmenopausal periods or on discontinuing estrogen-alone therapy. • For younger, healthy postmenopausal women, particularly those with vasomotor symptoms, who are candidates for prevention of bone loss, estrogen alone (if no uterus) or combined with progestogen or bazedoxifene are the most appropriate therapies. o A bisphosphonate could be chosen if estrogen is contraindicated or on stopping estrogen-alone therapy. o Raloxifene is a good option for prevention of bone loss in postmenopausal women with an elevated risk of breast cancer and infrequent vasomotor symptoms. • Bisphosphonates to prevent bone loss can be considered in postmenopausal women with low BMD (T-score <1) and other risk factors for fracture (e.g., family history) who do not meet criteria for osteoporosis treatment. • The choice of the initial treatment for osteoporosis is based on the patient's current BMD and fracture risk. • Raloxifene is an option for the treatment of postmenopausal osteoporosis in women with a low risk of hip fracture, an elevated risk of breast cancer, and low risk of stroke and venous thromboembolism. • Bisphosphonates are appropriate to reduce fracture risk in women with postmenopausal osteoporosis. o Use with caution in patients with significantly impaired renal function. o Consider a bisphosphonate holiday only in women at low fracture risk who no longer meet criteria for therapy. Restart therapy if bone loss or fractures occur or when patient again meets criteria for treatment.

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	○ For patients remaining at high fracture risk after three to five years of bisphosphonate therapy, continue treatment or switch to another drug. • Denosumab is appropriate for women with postmenopausal osteoporosis, including those at high risk of fracture. ○ There is no limit to the duration of denosumab therapy. ○ Administration of denosumab should not be delayed or stopped beyond seven months without subsequent therapy to prevent bone loss and vertebral fractures. • Osteoanabolic therapies are most appropriately used in women at very high risk of fracture, including those with prior and especially recent fractures, very low BMD (T-score below 3.0), and those who sustain fractures or lose BMD while taking antiremodeling therapy. ○ Osteoanabolic therapies increase bone mass more rapidly and reduce fracture risk more effectively than do bisphosphonates. ○ Anabolic therapy should be followed by an antiremodeling agent to maintain bone density gains. ○ Bone mineral density gains, particularly in the hip, are greater when an anabolic drug is administered before an antiremodeling drug, compared with the opposite sequence. • Bone mineral density measured while on therapy correlates with current fracture risk. • If the response to the initial treatment does not achieve preventing bone loss or reducing the risk of fracture, a change in treatment should be considered. • If drug-related adverse events occur, appropriate management strategies should be instituted. If adverse events persist, switching to another agent may be required. • Identify barriers to nonadherence to therapy and encourage adherence to the treatment plan. Providing clear information to women regarding their risk for fracture and the purpose of osteoporosis therapy may be an optimal way to improve adherence. • Depending on the treatment, an appropriate interval for repeat BMD testing is one to two years after beginning treatment or when a change in therapy is considered. • Initial dual-energy X-ray absorptiometry (DXA) and follow-up scans should ideally be performed on the same instrument, using the same procedure. Interpretation of BMD changes requires careful attention to DXA quality control. • If progressive loss of BMD or fractures occurs while on therapy, evaluate for reasons for suboptimal response to therapy, including poor adherence and underlying medical conditions or medications. • Even when treatment increases T-score values above 2.5, the patient still has the diagnosis and risks of osteoporosis. • Referral to bone specialists is recommended for women with very low T-scores, inadequate treatment response, including progressive decline in BMD or fractures while on therapy, or additional factors (e.g., renal failure, hyperparathyroidism) requiring special management.
North American Menopause Society: **The 2022 Hormone Therapy Position Statement (2022)**[7]	<u>Formulation, dosing, routes of administration, and safety</u> • The appropriate, often lowest, effective dose of systemic estrogen therapy consistent with treatment goals that provides benefits and minimizes risks for the individual woman should be the therapeutic goal. • The various formulations, doses, and routes of prescription hormone therapy preparations have comparable high efficacy for relieving vasomotor symptoms.

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	• Formulation, dose, and route of administration for hormone therapy should be determined individually and reassessed periodically. • Different hormone therapy doses, formulations, and routes of administration may have different effects on target organs, potentially allowing options to minimize risk. • The appropriate formulation, dose, and route of administration of progestogen is needed to counter the proliferative effects of systemic estrogen on the endometrium. • Overall, the increased absolute risks associated with estrogen plus progestogen therapy (EPT) and estrogen therapy are rare (<10/10,000/y) and include increased risk for venous thromboembolism (VTE) and gallbladder disease. In addition, EPT carries a rare increased risk for stroke and breast cancer, and if estrogen is inadequately opposed, an increased risk of endometrial hyperplasia and endometrial cancer. • The absolute risks are reduced for all-cause mortality, fracture, diabetes mellitus (EPT and estrogen therapy), and breast cancer (estrogen therapy) in women aged younger than 60 years. <u>Compounded bioidentical hormones</u> • Compounded bioidentical hormone therapy presents safety concerns, such as minimal government regulation and monitoring, overdosing and underdosing, presence of impurities and lack of sterility, lack of scientific efficacy and safety data, and lack of a label outlining risks. • Salivary and urine hormone testing to determine dosing are unreliable and not recommended. Serum hormone testing is rarely needed. • Shared decision-making is important, but patient preference alone should not be used to justify the use of compounded bioidentical hormone preparations, particularly when government-regulated bioidentical hormone preparations are available. • Situations in which compounded bioidentical hormones could be considered include allergies to ingredients in a government-approved formulation or dosages not available in government-approved products. <u>Vasomotor symptoms</u> • Vasomotor symptoms may begin during perimenopause, and frequent vasomotor symptoms may persist on average 7.4 years or longer. They affect quality of life and may be associated with cardiovascular (CV), bone, and brain health. • Hormone therapy remains the gold standard for relief of vasomotor symptoms. • Estrogen-alone therapy can be used for symptomatic women without a uterus. • For symptomatic women with a uterus, EPT or a tissue-selective estrogen complex protects against endometrial neoplasia. • Shared decision-making should be used when considering formulation, route of administration, and dose of hormone therapy for menopause symptom management, with adjustment tailored to symptom relief, adverse events, and patient preferences. • Periodic assessment of the need for ongoing use of hormone therapy should be individualized on the basis of a woman's menopause symptoms, general health and underlying medical conditions, risks, treatment goals, and personal preferences. • Micronized progesterone 300 mg nightly significantly decreases vasomotor symptoms (hot flashes and night sweats) compared with placebo and improves sleep. Synthetic progestins have also shown benefit for vasomotor symptoms in some studies. No long-term study results are available, and use of progestogens without estrogen for either indication is off-label.

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	Sleep disturbances • During the menopause transition, women with vasomotor symptoms are more likely to report disrupted sleep. • Hormone therapy improves sleep in women with bothersome nighttime vasomotor symptoms by reducing nighttime awakenings. Estrogen may have some effect on sleep, independent of vasomotor symptoms. Genitourinary symptoms • Low-dose vaginal estrogen therapy preparations are effective and generally safe for the treatment of genitourinary syndrome of menopause, with minimal systemic absorption, and are preferred over systemic therapies when estrogen therapy is used only for genitourinary symptoms. • For women with breast cancer, low-dose vaginal estrogen therapy should be prescribed in consultation with their oncologists. • Progestogen therapy is not required with low-dose vaginal estrogen, but RCT data are lacking beyond one year. • Nonestrogen prescription FDA-approved therapies that improve vulvovaginal atrophy in postmenopausal women include ospemifene and intravaginal DHEA. • Vaginal bleeding in a postmenopausal woman requires thorough evaluation. Urinary tract symptoms (including pelvic floor disorders) • Systemic hormone therapy does not improve urinary incontinence and may increase the incidence of stress urinary incontinence. • Low-dose vaginal estrogen therapy may provide benefit for urinary symptoms, including prevention of recurrent UTIs, overactive bladder, and urge incontinence. • Hormone therapy does not have FDA approval for any urinary health indication. Sexual function • Both systemic hormone therapy and low-dose vaginal estrogen therapy increase lubrication, blood flow, and sensation of vaginal tissues. • Systemic hormone therapy generally does not improve sexual function, sexual interest, arousal, or orgasmic response independent of its effect on genitourinary syndrome of menopause. • If sexual function or libido are concerns in women with menopause symptoms, transdermal estrogen therapy may be preferable over oral estrogen therapy because of minimal effect on sex hormone-binding globulin and free testosterone levels. • Low-dose vaginal estrogen therapy improves sexual function in postmenopausal women with genitourinary syndrome of menopause. • Nonestrogen alternatives FDA approved for dyspareunia include ospemifene and intravaginal DHEA. Primary ovarian insufficiency • Women with primary ovarian insufficiency and premature or early menopause may be at increased risk for fracture, CVD, heart failure, DM, overall mortality, persistent vasomotor symptoms, loss of fertility, bone loss, genitourinary symptoms, sexual dysfunction, cognitive and mood changes, increased risk of dementia, open-angle glaucoma, depression, and poor quality of life. • In the absence of contraindications, hormone therapy is recommended at least until the average age of menopause (approximately age 52 y), with an option for use of oral contraceptives in healthy younger women. • Results of the Women's Health Initiative trials in older women do not apply to women with primary ovarian insufficiency or premature or early menopause.

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	• In women with BO before the average age of menopause, early initiation of estrogen therapy, with endometrial protection if the uterus is preserved, reduces vasomotor symptoms, genitourinary symptoms, risk for osteoporosis and related fractures, and likely CVD and overall mortality, with benefit seen in observational studies for CV mortality and cognitive impairment or dementia. • Fertility preservation and counseling should be explored for young women at risk for primary ovarian insufficiency. • Ovarian conservation is recommended when hysterectomy is performed for benign indications in premenopausal women at average risk for ovarian cancer. Osteoporosis • Hormone therapy prevents bone loss in healthy postmenopausal women, with dose-related effects on bone density. • Hormone therapy reduces fracture risk in healthy postmenopausal women. • Discontinuing hormone therapy results in rapid bone loss; however, no excess in fractures was seen in the Women's Health Initiative after discontinuation. • Hormone therapy is FDA approved for prevention of bone loss, but not for treatment of osteoporosis. • In the absence of contraindications, in women aged younger than 60 years or within 10 years of menopause onset, systemic hormone therapy is an appropriate therapy to protect against bone loss. • Unless contraindicated, women with premature menopause without prior fragility fracture or osteoporosis are best served with hormone therapy or oral contraceptives to prevent bone density loss and reduce fracture risk, rather than other bone-specific treatments, until the average age of menopause, when treatment may be reassessed. • Decisions regarding initiation and discontinuation of hormone therapy should be made primarily on the basis of extraskeletal benefits (i.e., reduction of vasomotor symptoms) and risks. Cardiovascular disease and all-cause mortality • For healthy symptomatic women aged younger than 60 years or within 10 years of menopause onset, the favorable effects of hormone therapy on CHD and all-cause mortality should be considered against potential rare increases in risks of breast cancer, VTE, and stroke. • Hormone therapy is not government approved for primary or secondary cardioprotection. (Level I) • Personal and familial risk of CVD, stroke, VTE, and breast cancer should be considered when initiating hormone therapy. • The effects of hormone therapy on CHD may vary depending on when hormone therapy is initiated in relation to a woman's age or time since menopause onset. • Initiation of hormone therapy in recently postmenopausal women reduced or had no effect on subclinical atherosclerosis progression and coronary artery calcification in randomized, controlled trials. • Observational data and meta-analyses show reduced risk of CHD in women who initiate hormone therapy when aged younger than 60 years or within 10 years of menopause onset. Meta-analyses show a null effect of hormone therapy on CHD after excluding open-label trials. • Women who initiate hormone therapy aged older than 60 years or more than 10 or 20 years from menopause onset are at higher absolute risks of CHD, VTE, and stroke than women initiating hormone therapy in early menopause. Breast cancer • The risk of breast cancer related to hormone therapy use is low, with estimates indicating a rare occurrence (less than one additional case per 1,000 women per

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	year of hormone therapy use or three additional cases per 1,000 women when used for 5 years with conjugated equine estrogens [CEE] plus medroxyprogesterone acetate). • Women should be counseled about the risk of breast cancer with hormone therapy, putting the data into perspective, with risk similar to that of modifiable risk factors such as two daily alcoholic beverages, obesity, and low physical activity. • The effect of hormone therapy on breast cancer risk may depend on the type of hormone therapy, duration of use, regimen, prior exposure, and individual characteristics. • Different hormone therapy regimens may be associated with increased breast density, which may obscure mammographic interpretation, leading to more mammograms or more breast biopsies and a potential delay in breast cancer diagnosis. • A preponderance of data does not show an additive effect of underlying breast cancer risk (age, family history of breast cancer, genetic risk of breast cancer, benign breast disease, personal breast cancer risk factors) and hormone therapy use on breast cancer incidence. • Insufficient data are available to assess the risk of breast cancer with newer therapies such as tissue-selective estrogen complexes, including bazedoxifene plus CEE. • Observational evidence suggests that hormone therapy use does not further increase risk of breast cancer in women at high risk because of a family history of breast cancer or after bilateral salpingo-oophorectomy (BSO) for BRCA 1 or 2 genetic variants. • Systemic hormone therapy is generally not advised for survivors of breast cancer, although hormone therapy use may be considered in women with severe vasomotor symptoms unresponsive to nonhormone options, with shared decision-making in conjunction with their oncologists. • For survivors of breast cancer with genitourinary syndrome of menopause, low-dose vaginal estrogen therapy or DHEA may be considered in consultation with their oncologists if bothersome symptoms persist after a trial of nonhormone therapy. There is increased concern with low-dose vaginal estrogen therapy for women on AIs. • Regular breast cancer surveillance is advised for all postmenopausal women per current breast cancer screening guidelines, including those who use hormone therapy. <u>Endometrial cancer</u> • Unopposed systemic estrogen therapy in a postmenopausal woman with an intact uterus increases the risk of endometrial cancer, so adequate progestogen is recommended. • Low-dose vaginal estrogen therapy does not appear to increase endometrial cancer risk, although trials with endometrial biopsy end points are limited to 1 year in duration. • Use of hormone therapy is an option for the treatment of bothersome menopause symptoms in women with surgically treated, early stage, low-grade endometrial cancer in consultation with a woman's oncologist if nonhormone therapies are ineffective. • Systemic hormone therapy is not advised with high-grade, advanced-stage endometrial cancers or with endometrial stromal sarcomas or leiomyosarcomas. <u>Ovarian cancer</u> • Use of oral contraceptives is associated with a significant reduction in ovarian cancer risk.

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	• Current and recent use of hormone therapy is associated with a small but statistically significant risk of ovarian cancer in observational studies, principally for serous type, although there was no increase in ovarian cancer risk in women randomized to EPT in the Women's Health Initiative. • In women with a history of ovarian cancer, benefits of hormone therapy use generally outweighs risks, especially with bothersome vasomotor symptoms or early menopause; use of hormone therapy is not advised in women with hormone-dependent ovarian cancers, including granulosa-cell tumors and low-grade serous carcinoma. • Short-term hormone therapy use appears safe in women with BRCA1 and BRCA2 genetic variants who undergo risk-reducing BSO before the average age of menopause. <u>Colorectal cancer</u> • Observational studies suggest a reduced incidence of colorectal cancer in current hormone therapy users, with reduced mortality. • In the Women's Health Initiative, EPT, but not estrogen therapy alone, reduced colorectal cancer risk, although cancers diagnosed in EPT users were diagnosed at a more advanced stage. There was no difference in colorectal cancer mortality with either EPT or estrogen therapy. <u>Duration of use, initiation after age 60 years, and discontinuation of hormone therapy</u> • The safety profile of hormone therapy is most favorable when initiated in healthy women aged younger than 60 years or within 10 years of menopause onset, so initiation of hormone therapy by menopausal women aged older than 60 years requires careful consideration of individual benefits and risks. • Long-term use of hormone therapy, including for women aged older than 60 years, may be considered in healthy women at low risk of CVD and breast cancer with persistent vasomotor symptoms or at elevated risk of fracture for whom other therapies are not appropriate. • Factors that should be considered include severity of symptoms, effectiveness of alternative nonhormone interventions, and underlying risk for osteoporosis, CHD, cerebrovascular accident, VTE, and breast cancer. • Hormone therapy does not need to be routinely discontinued in women aged older than 60 or 65 years. • Mitigation of risk through use of the lowest effective dose and potentially with a nonoral route of administration becomes increasingly important as women age and with longer duration of therapy. • Longer durations or extended use beyond age 65 should include periodic reevaluation of comorbidities with consideration of periodic trials of lowering or discontinuing hormone therapy. • For women with genitourinary syndrome of menopause, low-dose vaginal estrogen therapy may be considered for use at any age and for extended duration, if needed. • In the absence of contraindications, a woman should determine her preferred hormone therapy formulation, dose, and duration of use, with ongoing assessment and shared decision-making with her healthcare professional.
European Menopause and Andropause Society: **Maintaining post-reproductive health: A care pathway (2016)[8]**	<u>Menopausal hormone therapy (MHT) general considerations</u> • Administration of systemic MHT has a favorable risk–benefit profile for women under the age of 60 years or within 10 years after menopause for menopausal symptoms and osteoporosis. • MHT at very low doses or non-estrogen-based therapies should be considered for older women.

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	• Symptoms due to the genitourinary syndrome of the menopause can be managed with low-dose topical estrogens or non-hormonal therapies. • Prevention and management of cardiovascular disease should be undertaken in accordance with international and national guidelines. • MHT should not be used primarily for the primary or secondary prevention of cognitive decline or dementia. • Estrogen alone is given to hysterectomized women. Progestogens and the selective estrogen receptor modulator bazedoxifene are added in regimens for non-hysterectomized women to reduce the increased risk of endometrial hyperplasia and carcinoma which occurs with unopposed estrogen. Tibolone is a synthetic steroid compound that is in itself inert, but whose metabolites have estrogenic, progestogenic and androgenic actions. It is classified as MHT. The main benefits of MHT • MHT is the most effective treatment for vasomotor symptoms. • Systemically administered MHT and topical estrogens are effective in the management of symptoms of vulvar and vaginal atrophy. • MHT prevents postmenopausal bone loss. • MHT may aid in the management of low mood that results from menopause. • Standard-dose estrogen-alone MHT may decrease coronary heart disease and all-cause mortality in women younger than 60 years of age and within 10 years of menopause. The main risks of MHT • Estrogen-alone MHT increases the risk of endometrial cancer. • Oral, but not transdermal, estrogens increase the risk of venous thromboembolism. • Combined MHT, but not estrogen-alone MHT, may be associated with an increased risk of breast cancer; this risk seems to be lost when MHT is discontinued. • MHT may confer a small increased risk of stroke: there is a suggestion that transdermal preparations have less impact on the risk of stroke than oral preparations • MHT use over the age of 65 years may cause deterioration in cognitive function. • Initiation of standard-dose oral MHT in women over the age of 60 years who have established atherosclerosis may not result in a decreased risk of coronary heart events.
Bone Health and Osteoporosis Foundation: **Clinician's Guide to Prevention and Treatment of Osteoporosis (2022)**[9]	Universal recommendations for all patients • Counsel individual patients on their risk for osteoporosis, fractures, and potential consequences of fractures (functional deterioration, loss of independence, increased mortality). • Recommend a diet with adequate total calcium intake (1000 mg/day for men aged 50 to 70 years; 1200 mg/day for women ≥ 51 years and men ≥ 71 years), incorporating calcium supplements if intake is insufficient. • Monitor serum 25-hydroxyvitamin D levels. • Maintain serum vitamin D sufficiency (≥ 30 ng/mL but below ≤ 50 ng/mL). Prescribe supplemental vitamin D (800 to 1000 units/day) as needed for individuals aged 50 years and older to achieve a sufficient vitamin D level. Higher doses may be necessary in some adults, especially those with malabsorption. (Note: in healthy individuals a serum 25(OH) vitamin D level ≥ 20 ng/mL may be sufficient, but in the setting of known or suspected metabolic bone disease ≥ 30 ng/mL is appropriate.) • Identify and address modifiable risk factors associated with falls, such as sedating medications, polypharmacy, hypotension, gait or vision disorders, and out-of-date prescription glasses.

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	• Provide guidance for smoking cessation, and avoidance of excessive alcohol intake; refer for care as appropriate.
	• Counsel or refer patients for instruction on balance training, muscle-strengthening exercise, and safe movement strategies to prevent fracture(s) in activities of daily life.
	• In community-dwelling patients, refer for at-home fall hazard evaluation and remediation.
	• In post-fracture patients who are experiencing pain, prescribe over-the-counter analgesia, heat/ice home care, limited bed rest, physical therapy, and alternative non-pharmacologic therapies when appropriate. In cases of intractable or chronic pain, refer to a pain specialist or physiatrist.
	• Coordinate post-fracture patient care via fracture liaison service (FLS) and multidisciplinary programs in which patients with recent fractures are referred for osteoporosis evaluation and treatment, rehabilitation, and transition management.
	
	<u>Pharmacologic treatment recommendations</u>
	• No uniform recommendation applies to all patients. Management plans must be individualized.
	• Current FDA-approved pharmacologic options for osteoporosis are as follows:
	  ○ Bisphosphonates (alendronate, ibandronate, risedronate, zoledronic acid)
	  ○ Estrogen-related therapy (ET/HT, raloxifene conjugated estrogens/ bazedoxifene)
	  ○ Parathyroid hormone analogs (teriparatide, abaloparatide)
	  ○ RANK-ligand inhibitor (denosumab)
	  ○ Sclerostin inhibitor (romosozumab)
	  ○ Calcitonin salmon
	• Consider initiating pharmacologic treatment in postmenopausal women and men ≥ 50 years of age who have the following:
	  ○ Primary fracture prevention:
	  ▪ T-score ≤ − 2.5 at the femoral neck, total hip, lumbar spine, 33% radius (some uncertainty with existing data) by DXA.
	  ▪ Low bone mass (osteopenia: T-score between − 1.0 and − 2.5) at the femoral neck or total hip by DXA with a 10-year hip fracture risk ≥ 3% or a 10-year major osteoporosis-related fracture risk ≥ 20% (i.e., clinical vertebral, hip, forearm, or proximal humerus) based on the US-adapted FRAX® model.
	  ○ Secondary fracture prevention:
	  ▪ Fracture of the hip or vertebra regardless of BMD.
	  ▪ Fracture of proximal humerus, pelvis, or distal forearm in persons with low bone mass (osteopenia: T-score between − 1.0 and − 2.5). The decision to treat should be individualized in persons with a fracture of the proximal humerus, pelvis, or distal forearm who do not have osteopenia or low BMD.
	• Initiate antiresorptive therapy following discontinuation of denosumab, teriparatide, abaloparatide, or romosozumab.

North American Menopause Society: **The 2020 Genitourinary Syndrome of Menopause Position Statement (2020)[10]**	• Education about and screening for genitourinary syndrome of menopause (GSM) is recommended for perimenopausal and postmenopausal women. • GSM describes the symptoms and signs resulting from the effect of estrogen deficiency on the female genitourinary tract, including the vagina, labia, urethra, and bladder. This syndrome includes genital symptoms of dryness, burning, and irritation; urinary symptoms and conditions of dysuria, urgency, and recurrent urinary tract infections (UTIs); and sexual symptoms of pain and dryness. • First-line therapies for women with GSM include nonhormone lubricants with sexual activity and regular use of long-acting vaginal moisturizers.

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	• For women with moderate to severe GSM and those who do not respond to lubricants and moisturizers, several safe and effective options are available:
	  ○ Low-dose vaginal estrogen therapy (ET)
	  ○ Vaginal dehydroepiandrosterone (DHEA)
	  ○ Ospemifene
	  ○ Systemic ET (when vasomotor symptoms (VMS) are also present)
	• For women with a history of breast or endometrial cancer, management depends on a woman's preferences, symptom severity, and understanding of potential risks after consultation with her oncologist.
	• Although product labeling for low-dose vaginal ET notes risks associated with systemic hormone therapy (including CHD, stroke, VTE, breast and endometrial cancer), these risks are highly unlikely given minimal systemic absorption and reassuring findings from clinical trials and observational studies.
	• Use of a progestogen is not recommended with low-dose vaginal ET, although women at increased risk of endometrial cancer may warrant endometrial surveillance. Endometrial safety clinical trial data are not available for use longer than 1 year, although observational studies are reassuring regarding longer-term use.
	• Routine endometrial surveillance is not recommended for asymptomatic women using low dose vaginal ET. Transvaginal ultrasound or intermittent progestogen therapy may be considered for women at increased risk of endometrial cancer.
	• Spotting or bleeding in a postmenopausal woman requires a thorough evaluation that may include transvaginal ultrasound (TVU) and/or endometrial biopsy.
	• Energy-based therapies, including vaginal laser and radiofrequency devices, require long-term, sham-controlled safety and efficacy studies before their routine use can be recommended.
	• Therapy for GSM should be continued, with appropriate clinical follow up, for as long as bothersome symptoms are present.

American College of Cardiology: **Updated Recommendations for Primary Prevention of CVD in Women (2020)**[11]	• CVD continues to be the leading cause of morbidity and mortality among women. • Unique risk factors related to female sex include pregnancy-associated conditions such as hypertensive disorders of pregnancy, gestational diabetes mellitus, preterm birth, and pregnancy loss. Intrauterine growth restriction has also been associated with increased risk for dyslipidemia, insulin resistance, and diastolic dysfunction. • When added to current risk prediction models, pregnancy-related conditions (such as gestational diabetes) do not increase the accuracy of such models. This may be due to the association of pregnancy-related risk factors associated with traditional risk factors, which are incorporated into current prediction models. However, identification of such pregnancy-related conditions may help identify younger women (with low risk scores) to allow for earlier monitoring of cardiometabolic factors and management as needed earlier in a woman's life. • Premature menopause, defined as menopause before the age of 40 years, is associated with increased risk for CVD. In the 2018 cholesterol guidelines, premature menopause was included as a risk-enhancing factor. • Polycystic ovarian syndrome (POS) is associated with cardiometabolic factors, which, in turn, are associated with increased CVD risk. These POS factors include abdominal obesity, abnormal glucose control and diabetes, elevated blood pressure, and dyslipidemia. • Sex-related differences in traditional risk factors are prevalent. Hypertension is highly prevalent among women, in particular non-Hispanic black women, compared to other groups. Obesity is a strong risk factor for hypertension among women. Sodium restriction among postmenopausal women with hypertension may be particularly beneficial. Diabetes is also a particularly strong risk factor for CVD and heart failure among women.

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	• Sex-related differences in CV medications exist. For women of childbearing years, modification of medications typically used for management of CVD and related risk factors may be needed. This includes the use of angiotensin-converting enzyme inhibitors/angiotensin-receptor blockers or statins, which are not recommended if pregnancy is planned or occurs. For many women with CV risk factors or CVD, receipt of evidence-based medications is often less likely to occur compared to men with similar risk factors or CV conditions. Last, differences in the efficacy of medications may differ by sex. • Women are at greater risk for stroke in the setting of atrial fibrillation compared to men. Guidelines also recommend novel anticoagulants for women as the first choice for anticoagulation, given the evidence of lower risk of bleeding in women taking a novel agent as compared to vitamin K antagonists. The 2019 guidelines were revised to recommend anticoagulation for women with a CHA2DS2-VASc score of ≥3 (prior recommendations were for ≥2). • There are no recommendations for the use of menopausal hormonal therapy for CV prevention at this time. Long-standing evidence suggests either no benefit or increased risk for women when hormonal therapy is used. However, researchers have and continue to investigate the potential for a "timing hypothesis" where hormonal therapy may be of benefit (related to CV risk) among women closer to the time of menopausal onset. Providers are recommended to review each woman's risk factor profile and provide a tailored and shared decision-making discussion when menopausal hormonal therapy is considered, even among younger perimenopausal women. • Psychosocial factors such as depression, anxiety, and acute or chronic emotional stress are often observed to be more prevalent among women compared to men. Given the association between these factors and CVD risk, providers are recommended to identify and assist in the management of such factors as part of CVD prevention.
International Menopause Society: **Updated 2013 Recommendations on women's midlife health and menopause hormone therapy (2016)[12]**	• MHT remains the most effective therapy for vasomotor symptoms and urogenital atrophy. • Other menopause-related complaints, such as joint and muscle pains, mood swings, sleep disturbances and sexual dysfunction (including reduced libido) may improve during MHT. Quality of life and sexual function may also improve. • The administration of individualized MHT (including androgenic preparations when appropriate) may improve both sexuality and overall quality of life. • Consideration of MHT should be part of an overall strategy including lifestyle recommendations regarding diet, exercise, smoking cessation and safe levels of alcohol consumption for maintaining the health of peri- and postmenopausal women. • MHT must be individualized and tailored according to symptoms and the need for prevention, as well as personal and family history, results of relevant investigations, the woman's preferences and expectations. • The risks and benefits of MHT differ for women during the menopause transition compared to those for older women. • MHT includes a wide range of hormonal products and routes of administration, with potentially different risks and benefits. Thus, the term 'class effect' is confusing and inappropriate. However, evidence regarding differences in risks and benefits between different products is limited. • Women experiencing a spontaneous or iatrogenic menopause before the age of 45 years and particularly before 40 years are at higher risk for cardiovascular disease and osteoporosis and may be at increased risk of affective disorders and dementia. MHT may reduce symptoms and preserve bone density and is advised at least until the average age of menopause.

Clinical Guideline	Recommendation(s)
	• Counselling should convey the benefits and risks of MHT in clear and comprehensible terms, e.g., as absolute numbers rather than, or in addition to, percentage changes from baseline expressed as a relative risk. This allows a woman and her physician to make a well-informed decision about MHT. Written information about risks and benefits as well as decision aids may be useful. • MHT should not be recommended without a clear indication for its use, i.e., significant symptoms or physical effects of estrogen deficiency. • Women taking MHT should have at least an annual consultation to include a physical examination, update of medical and family history, relevant laboratory and imaging investigations, a discussion on lifestyle, and strategies to prevent or reduce chronic disease. There is currently no indication for increased mammographic or cervical smear screening. • There are no reasons to place mandatory limitations on the duration of MHT. Data from the WHI trial and other studies support safe use for at least five years in healthy women initiating treatment before age 60 years. • Whether or not to continue therapy should be decided at the discretion of the well-informed woman and her health professional, dependent upon the specific goals and an objective estimation of ongoing individual benefits and risks. • The dosage should be titrated to the lowest effective dose. • Lower doses of MHT than previously used may reduce symptoms sufficiently and maintain quality of life for many women. However, long-term data on lower doses regarding fracture or cancer risks and cardiovascular implications are still lacking.
American Association of Clinical Endocrinologists: **Clinical Practice Guideline for the Diagnosis and Treatment of Postmenopausal Osteoporosis (2020)**[13]	Who Needs Pharmacologic Therapy? • Pharmacologic therapy is strongly recommended for patients with osteopenia or low bone mass and a history of fragility fracture of the hip or spine. • Pharmacologic therapy is strongly recommended for patients with a T-score of − 2.5 or lower in the spine, femoral neck, total hip, or 1/3 radius. • Pharmacologic therapy is strongly recommended for patients with a T-score between − 1.0 and − 2.5 if the FRAX® (fracture risk assessment tool) (or if available, trabecular bone score [TBS]-adjusted FRAX®) 10-year probability for major osteoporotic fracture is ≥ 20% or the 10-year probability of hip fracture is ≥ 3% in the U.S. or above the country-specific threshold in other countries or regions. • Consider patients with a recent fracture (e.g., within the past 12 months), fractures while on approved osteoporosis therapy, multiple fractures, fractures while on drugs causing skeletal harm (e.g., long-term glucocorticoids), very low T-score (e.g., less than − 3.0), high risk for falls or history of injurious falls, and very high fracture probability by FRAX® (fracture risk assessment tool) (e.g., major osteoporosis fracture > 30%, hip fracture > 4.5%) or other validated fracture risk algorithm to be at very high fracture risk. Consider patients who have been diagnosed with osteoporosis but are not at very high fracture risk, as defined above, to be high risk. What Medication Should Be Used to Treat Osteoporosis? • Approved agents with efficacy to reduce hip, nonvertebral, and spine fractures including alendronate, denosumab, risedronate, and zoledronate are appropriate as initial therapy for most osteoporotic patients with high fracture risk. • Abaloparatide, denosumab, romosozumab, teriparatide, and zoledronate should be considered for patients unable to use oral therapy and as initial therapy for patients at very high fracture risk. • Ibandronate or raloxifene may be appropriate initial therapy in some cases for patients requiring drugs with spine-specific efficacy.

Clinical Guideline	Recommendation(s)
	How Long Should Patients Be Treated? • Limit treatment with abaloparatide and teriparatide to two years and follow abaloparatide or teriparatide therapy with a bisphosphonate or denosumab. • Limit treatment with romosozumab to one year and follow with a drug intended for long-term use, such as a bisphosphonate or denosumab). • For oral bisphosphonates, consider a bisphosphonate holiday after five years of treatment if fracture risk is no longer high (such as when the T score is greater than -2.5, or the patient has remained fracture free), but continue treatment up to an additional five years if fracture risk remains high. • For oral bisphosphonates, consider a bisphosphonate holiday after six to 10 years of stability in patients with very high fracture risk. • For zoledronate, consider a bisphosphonate holiday after three years in high-risk patients or until fracture risk is no longer high, and continue for up to six years in very-high-risk patients. • The ending of a bisphosphonate holiday should be based on individual patient circumstances such as an increase in fracture risk, a decrease in bone mineral density beyond the least significant change (LSC) of the dual-energy X-ray absorptiometry (DXA) machine, or an increase in bone turnover markers. • A holiday is not recommended for non-bisphosphonate antiresorptive drugs, and treatment with such agents should be continued for as long as clinically appropriate. • If denosumab therapy is discontinued, patients should be transitioned to another antiresorptive. What Is the Role of Concomitant Use of Therapeutic Agents? • Until the effect of combination therapy on fracture risk is better understood, AACE does not recommend concomitant use of these agents for prevention or treatment of postmenopausal osteoporosis. What Is the Role of Sequential Use of Therapeutic Agents? • Follow treatment with an anabolic agent (e.g., abaloparatide, romosozumab, teriparatide) with a bisphosphonate or denosumab to prevent bone density decline and loss of fracture efficacy.

United States Preventive Services Task Force: **Hormone Therapy for the Primary Prevention of Chronic Conditions in Postmenopausal Persons (2022)**[14]	• This recommendation statement applies to asymptomatic, postmenopausal persons who are considering hormone therapy for the primary prevention of chronic medical conditions. It does not apply to persons who are considering hormone therapy for the management of perimenopausal symptoms, such as hot flashes or vaginal dryness. It also does not apply to persons who have had premature menopause (primary ovarian insufficiency) or surgical menopause.
	• The use of combined estrogen and progestin has no net benefit for the primary prevention of chronic conditions in most postmenopausal persons with an intact uterus.
	• The use of estrogen alone has no net benefit for the primary prevention of chronic conditions in most postmenopausal persons who have had a hysterectomy.
	• Benefits of preventative medicine
	  ○ Use of combined estrogen and progestin has a moderate benefit in reducing the risk of fractures in postmenopausal persons, adequate evidence that it has a small benefit in reducing the risk of diabetes and colorectal cancer, and adequate evidence that it does not have a beneficial effect on risk of coronary heart disease.
	  ○ The use of estrogen without progestin has generally been restricted to persons who have had a hysterectomy, because unopposed estrogen use increases the risk of endometrial cancer in persons with an intact uterus.

Clinical Guideline	Recommendation(s)
	○ Use of estrogen alone has a moderate benefit in reducing the incidence of fractures in postmenopausal persons. There is adequate evidence that the use of estrogen alone has a moderate benefit in reducing the risk of developing or dying of invasive breast cancer and a small benefit in reducing the risk of diabetes. There is adequate evidence that estrogen use does not have a beneficial effect on risk of coronary heart disease. • Harms of preventative medicine ○ Use of combined estrogen and progestin is associated with moderate harms, including increased risk of invasive breast cancer, stroke, venous thromboembolism, dementia, gallbladder disease, and urinary incontinence. ○ There is adequate evidence that use of estrogen alone is associated with moderate harms, including increased risk of stroke, venous thromboembolism, gallbladder disease, and urinary incontinence.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the estrogens 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 Estrogens-Single Entity Products[1-3]

Indications	Estradiol	Estradiol Acetate	Estradiol Cypionate	Estradiol Valerate	Estrogens, Conjugated Equine	Estrogens, Esterified
Palliative treatment of advanced prostate cancer	✔ (Estrace®*)			✔	✔ *	✔
Palliative treatment of metastatic breast cancer	✔ (Estrace®*)				✔ *	✔
Prevention of postmenopausal osteoporosis	✔ (Alora®, Climara®, Estrace®*, Menostar®, Vivelle-Dot®)				✔ *	
Treatment of abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology					✔ †	
Treatment of atrophic vaginitis and kraurosis vulvae					✔ ‡	
Treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure	✔ (Alora®, Climara®, Estrace®*, Vivelle-Dot®)		✔	✔	✔ *	✔
Treatment of vasomotor symptoms associated with menopause	✔ (Alora®, Climara®, Divigel®, Elestrin®, Estrace®*, Estrasorb®, Evamist®, Vivelle-Dot®)	✔	✔	✔	✔ *	✔
Treatment of vulvar and vaginal atrophy associated with menopause	✔ (Alora®, Climara®, Estrace®*, Estring®, Vagifem®, Vivelle-Dot®)	✔ §		✔	✔	✔
Treatment of vulvar and vaginal atrophy	✔ (Estrace®‡)					

*Tablet formulation.
†Injection formulation.
‡Cream formulation.
§Vaginal ring formulation

Table 4. FDA-Approved Indications for the Estrogens-Combination Products[1-3]

Indications	Estradiol and Drospirenone	Estradiol and Levonorgestrel	Estradiol and Norethindrone	Estradiol and Norgestimate	Estradiol and Progesterone	Estrogens, Conjugated and Bazedoxifene	Estrogens, Conjugated Equine and Medroxyprogesterone	Ethinyl Estradiol and Norethindrone
Prevention of postmenopausal osteoporosis		✔	✔ (Activella®, Amabelz®, Mimvey®)	✔		✔	✔	✔
Treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure			✔ (Combipatch®)					
Treatment of moderate to severe symptoms of vulvar and vaginal atrophy due to menopause	✔ (1/0.5 mg)		✔	✔			✔	
Treatment of moderate to severe vasomotor symptoms due to menopause	✔	✔	✔	✔	✔	✔	✔	✔

IV. Pharmacokinetics

The pharmacokinetic parameters of the estrogens are listed in Table 5.

Table 5. Pharmacokinetic Parameters of the Estrogens[1]

Generic Name(s)	Bioavailability	Protein Binding	Metabolism	Excretion	Half-Life
Single Entity Agents					
Estradiol	Transdermal: 20 times higher bioavailability compared to oral dosage forms Vaginal ring: 8%	Primarily bound to SHBG and to albumin	Liver (primary) and skin (minimal). Estradiol, estrone, and estriol are all active metabolites	Urine (estradiol, estrone, and estriol along with glucuronide and sulfate conjugates) and bile (biliary secretion of conjugates into the intestine)	Transdermal (gel): Divigel®: 10 hours Estrogel®: 36 hours Transdermal (patch): Alora®:1.75 hours Vivelle®: 4.4 hours Vivelle-Dot®: 5.9 to 7.7 hours

Generic Name(s)	Bioavailability	Protein Binding	Metabolism	Excretion	Half-Life
Estradiol acetate	Vaginal: rapidly absorbed for the first hour, followed by a decline to constant rate for the remaining three months	Primarily bound to SHBG and to albumin	Liver (primary). Estradiol, estrone, and estriol are all active metabolites	Urine (estradiol, estrone, and estriol along with glucuronide and sulfate conjugates) and bile (biliary secretion of conjugates into the intestine)	Not reported
Estradiol cypionate	Intramuscular: absorbed over several weeks	Primarily bound to SHBG and to albumin	Liver (primary). Estrone and estriol are both active metabolites	Urine (estradiol, estrone, and estriol along with glucuronide and sulfate conjugates) and bile (biliary secretion of conjugates into the intestine, hydrolyzed, and reabsorbed)	Not reported
Estradiol valerate	Intramuscular: absorbed over several weeks	Primarily bound to SHBG and to albumin	Liver (primary). Estrone and estriol are both active metabolites	Urine (estradiol, estrone, and estriol along with glucuronide and sulfate conjugates) and bile (biliary secretion of conjugates into the intestine, hydrolyzed, and reabsorbed)	Not reported
Estrogens, conjugated Equine	Oral: well absorbed	Bound to albumin, SHBG, cortisol binding globulin, and α-1-glycoproteins	Liver (primary). Estradiol, estrone, and estriol are all active metabolites	Urine (estradiol, estrone, and estriol along with glucuronide and sulfate conjugates) and bile (biliary secretion of conjugates into the intestine)	Oral (estrone): 26.5 to 26.7 hours
Estrogens, esterified	Not reported	Primarily bound to SHBG and to albumin	Liver (primary). Estradiol, estrone, and estriol are all active metabolites	Urine (estradiol, estrone, and estriol along with glucuronide and sulfate conjugates) and bile (biliary secretion of conjugates into the intestine)	Not reported

Generic Name(s)	Bioavailability	Protein Binding	Metabolism	Excretion	Half-Life
Combination Products					
Estradiol and drospirenone	Drospirenone: 76 to 85% Estradiol: 53%	Drospirenone: 97% bound to serum proteins Estradiol: primarily bound to SHBG and to albumin	Drospirenone: liver (extensive) and cytochrome P450 3A4 isoenzyme (minor). No active metabolites Estradiol: liver (primary) and skin (minimal). Estradiol, estrone, and estriol are all active metabolite	Drospirenone: urine (38 to 47% as glucuronide and sulfate conjugates) and feces (17 to 20% as glucuronide and sulfate conjugates) Estradiol: urine (estradiol, estrone, and estriol along with glucuronide and sulfate conjugates) and bile (biliary secretion of conjugates into the intestine)	Drospirenone: 36 to 42 hours Estradiol: not reported
Estradiol and levonorgestrel	Estradiol (transdermal): 20 times higher bioavailability compared to oral dosage forms Levonorgestrel: not reported	Estradiol: primarily bound to SHBG and to albumin Levonorgestrel: bound to SHBG and to albumin (97.5 to 99%)	Estradiol: liver (primary) and skin (minimal). Estradiol, estrone, and estriol are all active metabolites Levonorgestrel: blood (extent unspecified). Activity of three metabolites not specified	Estradiol: urine (estradiol, estrone, and estriol along with glucuronide and sulfate conjugates) and bile (biliary secretion of conjugates into the intestine) Levonorgestrel: urine (45% of levonorgestrel and metabolites are excreted in the urine, mostly as glucuronide conjugates) and feces (32% of levonorgestrel and metabolites are excreted in the urine, mostly as glucuronide conjugates)	Estradiol: 1.75 to 77 hours Levonorgestrel: Not reported

Generic Name(s)	Bioavailability	Protein Binding	Metabolism	Excretion	Half-Life
Estradiol and norethindrone	Estradiol (oral): 53% Norethindrone (oral): 100%	Estradiol (oral): SHBG (37%), albumin (61%), and unbound (1 to 2 %) Norethindrone: SHBG (36%) and albumin (61%)	Estradiol (oral): liver (primary) Norethindrone: liver (primary)	Estradiol (oral): urine (metabolites as glucuronide and sulfate conjugates Norethindrone (oral): liver (primary).	Estradiol (oral): 12 to 14 Estradiol (transdermal): 2 to 3 hours Norethindrone (oral): 8 to 11 hours Norethindrone (transdermal): 6 to 8 hours
Estradiol and norgestimate	Not reported	Estradiol: primarily bound to SHBG and to albumin Norgestimate (17-deacetyl-norgestimate): primarily bound to serum proteins (99%)	Estradiol: liver (primary). Estradiol, estrone, and estriol are all active metabolites Norgestimate: liver (extensive) and gastrointestinal tract (extensive). 17-deacetylnoregestimate is an active metabolite	Estradiol: urine (estradiol, estrone, estriol, and glucuronide and sulfate conjugates) Norgestimate: urine and feces	Estradiol: 16 hours Norgestimate (17-deacetyl-norgestimate): 37 hours
Estradiol and progesterone	Not reported	Estradiol: primarily bound to SHBG and to albumin Progesterone: albumin (50 to 54%), transcortin (43 to 48%)	Estradiol: liver (primary). Estradiol, estrone, and estriol are all active metabolites Progesterone: liver (extensive)	Estradiol: urine (estradiol, estrone, estriol, and glucuronide and sulfate conjugates) Progesterone: urine, feces, bile	Estradiol: 26 hours Progesterone: 10 hours
Estrogens, conjugated and bazedoxifene	Bazedoxifene: 6% Estrogens, conjugated: Well absorbed	Bazedoxifene: 98 to 99% bound to plasma proteins Estrogens, conjugated: Primarily bound to SHBG and to albumin	Bazedoxifene: liver (extensive) via glucuronidation Estrogens, conjugated: liver (primary). Estradiol, estrone, and estriol are all active metabolites	Bazedoxifene: urine (<1%), feces (85%), and bile (major) Estrogens, conjugated: urine (estradiol, estrone, estriol, and glucuronide and sulfate conjugates)	Bazedoxifene: 30 hours Estrogens, conjugated: 17 hours

Generic Name(s)	Bioavailability	Protein Binding	Metabolism	Excretion	Half-Life
Estrogens, conjugated equine and medroxyprogesterone	Well absorbed	Estrogens, conjugated: largely bound to SHBG and albumin Medroxyprogesterone: primarily bound to plasma proteins (99%)	Estrogens, conjugated: liver (primary). Estradiol, estrone, and estriol are all active metabolites Medroxyprogesterone: liver (primary)	Estrogens, conjugated: urine (estradiol, estrone, estriol, and glucuronide and sulfate conjugates) Medroxyprogesterone: urine (most metabolites excreted as glucuronide conjugates with only minor amounts excreted as sulfates)	Estrogens, conjugated: (estrone): 20.7 to 23.6 hours Medroxyprogesterone: 26.2 to 46.3 hours
Ethinyl estradiol and norethindrone	Ethinyl estradiol: 55% Norethindrone: 64%	Ethinyl estradiol: largely bound to albumin (>95%) Norethindrone: largely bound to albumin and SHBG (>95%)	Ethinyl estradiol: liver (primary) Norethindrone acetate: liver (primary)	Ethinyl estradiol: urine and feces (primarily as metabolites) Norethindrone: urine and feces (primarily as metabolites)	Ethinyl estradiol: 24 hours Norethindrone: 13 hours

SHBG=sex hormone binding globulin

V. Drug Interactions

Major drug interactions with the estrogens are listed in Table 6.

Table 6. Major Drug Interactions with the Estrogens[1-3]

Generic Name(s)	Interaction	Mechanism
Estrogens	CYP3A4 inducers or inhibitors	Inducers or inhibitors of CYP3A4 may affect estrogen drug metabolism. Inducers of CYP3A4 such as St. John's wort (Hypericum perforatum) preparations, phenobarbital, carbamazepine, and rifampin may reduce plasma concentrations of estrogens, possibly resulting in a decrease in therapeutic effects and/or changes in the uterine bleeding profile. Inhibitors of CYP3A4 such as erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir and grapefruit juice may increase plasma concentrations of estrogens and result in side effects.

VI. Adverse Drug Events

The most common adverse drug events reported with the estrogens are listed in Tables 7 and 8. The boxed warning for the estrogens is listed in Table 9.

Table 7. Adverse Drug Events (%) Reported with the Estrogens-Single Entity Agents[1,2]

Adverse Event	Estradiol	Estradiol Acetate	Estradiol Cypionate*	Estradiol Valerate*	Estrogens, Conjugated Equine*	Estrogens, Esterified*
Breasts						
Breast cancer	-	-	✔	✔	✔ (injection)	✔
Enlargement	1.1 to 6.7 (Alora®)	-	✔	✔	✔ (injection)	✔
Fibrocystic breast changes	-	-	✔	✔	✔ (injection)	✔
Galactorrhea	-	-	✔	✔	✔ (injection)	✔
Neoplasm	1.1 to 5.6 (Alora®)	-	-	-	-	-
Nipple discharge	-	-	✔	✔	✔ (injection)	✔
Nipple pain	1 to 7 (Evamist®)	-	-	-	-	-
Pain	6.9 to 34.8 (Alora®)/5.0 to 29.0 (Climara®)/1.0 (Estring®)/5.0 (Menostar®)	-	✔	✔	✔ (injection)/ 7.0 to 11.0 (tablet)/ 2.1 to 4.9 (vaginal cream)	✔
Tenderness	2.5 to 8.8 (Divigel®)/5.0 to 7.0 (Evamist®)/6.5 to 12.9 (Minivelle®/Vivelle®)/6.5 to 17.0 (Vivelle-Dot®)	6.2 to 10.7 (vaginal ring)	✔	✔	✔ (injection)	✔
Cardiovascular						
Cardiovascular	10 (Menostar®)	-	-	-	-	-
Chest pain	1.1 to 4.5 (Alora®)/1.0 to 3.0 (Estring®)	-	-	-	-	-
Deep and superficial venous thrombosis	-	-	✔	✔	✔ (injection)	✔
Increase in blood pressure	0.0 to 6.7 (Alora®)/0.0 to 2.9 (Minivelle®/Vivelle®)/0.0 to 4.3 (Vivelle-Dot®)	-	✔	✔	✔ (injection)	✔
Myocardial infarction	-	-	✔	✔	✔ (injection)	✔
Pulmonary embolism	-	-	✔	✔	✔ (injection)	✔
Stroke	-	-	✔	✔	✔ (injection)	✔
Syncope	1 to 3 (Estring®)	-	-	-	-	-
Thrombophlebitis	-	-	✔	✔	✔ (injection)	✔
Vasodilation	0 to 6.7 (Alora®)	-	-	-	2.8 to 2.9 (vaginal cream)	-
Central Nervous System						
Anxiety	0 to 10.0 (Alora®)/1.0 to 3.0 (Estring®)/0.0 to 3.8 (Minivelle®/Vivelle®)/1.5 to 6.4 (Vivelle-Dot®)	-	-	-	-	-
Asthenia	0 to 7.9 (Alora®)	-	-	-	7 to 8 (tablet)	-
Chorea	-	-	✔	✔	-	✔
Dementia	-	-	✔	✔	✔ (injection)	✔
Depression	1.1 to 3.4 (Alora®)/1.0 to 8.0 (Climara®)/0.0 to 6.8 (Minivelle®/Vivelle®)/3.0 to 10.6 (Vivelle-Dot®)	-	✔	✔	✔ (injection)/ 5 to 8 (tablet)	✔
Dizziness	0.6 to 7.8 (Alora®)/5.0 (Menostar®)	-	✔	✔	✔ (injection)/ 4 to 6 (tablet)	✔
Exacerbation of chorea	-	-	-	-	✔ (injection)	-
Exacerbation of epilepsy	-	-	✔	✔	✔ (injection)	✔

Adverse Event	Estradiol	Estradiol Acetate	Estradiol Cypionate*	Estradiol Valerate*	Estrogens, Conjugated Equine*	Estrogens, Esterified*
Headache	5.6 to 21.3 (Alora®)/15.0 to 18.0 (Climara®)/13.0 (Estring®)/1.0 to 12.0 (Evamist®)/25.8 to 50.0 (Minivelle®/Vivelle®)/9.0 (Vagifem®)/14.9 to 50.0 (Vivelle-Dot®)	7.1 to 9.8 (vaginal ring)	✔	✔	✔ (injection)/ 26 to 32 (tablet)/ 2.1 to 3.5 (vaginal cream)	✔
Hypesthesia	0 to 3.4 (Alora®)	-	-	-	-	-
Insomnia	1.1 to 4.6 (Alora®)/4.0 (Estring®)/1.5 to 4.6 (Minivelle®/Vivelle®)/1.5 to 6.4 (Vivelle-Dot®)	-	-	-	6 to 7 (tablet)	-
Irritability	-	-	✔	✔	-	✔
Migraine	0 to 6.7 (Alora®)/1.0 to 3.0 (Estring®)	-	✔	✔	✔ (injection)	✔
Mood disturbances	-	-	✔	✔	-	✔
Nervousness	-	-	✔	✔	✔ (injection)/ 2 to 5 (tablet)	✔
Possible growth potentiation of benign meningioma			-	-	✔ (injection)	
Eyes						
Conjunctivitis	0 to 3.3 (Alora®)	-	-	-	-	-
Intolerance to contact lenses	-	-	✔	✔	✔ (injection)	✔
Retinal vascular thrombosis	-	-	✔	✔	✔ (injection)	✔
Steepening of corneal curvature	-	-	✔	-	-	✔
Gastrointestinal						
Abdominal cramps	-	-	✔	✔	✔ (injection)	✔
Abdominal distention	-	2.7 to 7.1 (vaginal ring)	-	-	-	-
Abdominal pain	1.1 to 7.9 (Alora®)/0 to 16.0 (Climara®)/4.0 (Estring®)/8.0 (Menostar®)/7.0 (Vagifem®)	-	-	-	15 to 17 (tablet)	-
Bloating	-	-	✔	✔	✔ (injection)	✔
Cholestatic jaundice	-	-	✔	✔	✔ (injection)	✔
Constipation	1.1 to 6.7 (Alora®)/5.0 (Menostar®)/1.5 to 6.5 (Minivelle®/Vivelle®)/1.5 to 6.5 (Vivelle-Dot®)	-	-	-	-	-
Diarrhea	1.1 to 3.3 (Alora®)/1 to 3 (Estring®)/5 (Vagifem®)	-	-	-	6 to 7 (tablet)	-
Dyspepsia	1.1 to 9.0 (Alora®)/1.0 to 3.0 (Estring®)/5.0 (Menostar®)/0.0 to 9.2 (Minivelle®/Vivelle®)/2.9 to 9.2 (Vivelle-Dot®)	-	-	-	9 to 11 (tablet)	-
Enlargement of hepatic hemangiomas	-	-	✔	✔	✔ (injection)	✔
Flatulence	1.1 to 4.6 (Alora®)/1 to 7 (Climara®)/1 to 3 (Estring®)	-	-	-	6 to 7 (tablet)	-
Gastritis	1 to 3 (Estring®)	-	-	-	-	-
Gastroenteritis	0 to 4.4 (Alora®)	-	-	-	-	-
Increased incidence of gallbladder disease	-	-	✔	✔	✔ (injection)	✔
Ischemic colitis	-	-	-	-	✔ (injection)	-
Nausea	3.4 to 6.7 (Alora®)/1.0 to 6.0 (Climara®)/3.0 (Estring®)/1.0 to 3.0 (Evamist®)/0.0 to 6.2 (Minivelle®/Vivelle®)/3.9 to 6.2 (Vivelle-Dot®)	1.8 to 2.7 (vaginal ring)	✔	✔	✔ (injection)/ 6 to 9 (tablet)	✔
Pancreatitis	-	-	✔	✔	✔ (injection)	✔
Vomiting	-	-	-	-	✔ (injection)	✔

Adverse Event	Estradiol	Estradiol Acetate	Estradiol Cypionate*	Estradiol Valerate*	Estrogens, Conjugated Equine*	Estrogens, Esterified*
Genitourinary System						
Asymptomatic genital bacterial growth	4 (Estring®)	-	-	-	-	-
Breakthrough bleeding	-	-	✔	✔	-	-
Cervical polyps	6 (Menostar®)	-	-	-	-	-
Change in amount of cervical secretion	-	-	✔	✔	-	-
Changes in cervical ectropion			✔	✔		
Changes in vaginal bleeding pattern and abnormal withdrawal bleeding or flow	-	-	✔	✔	-	-
Cystitis	1 to 3 (Estring®)	-	-	-	-	-
Dysmenorrhea	0.0 to 6.5 (Minivelle®/Vivelle®)/0 to 6.5 (Vivelle-Dot®)	-	✔	✔	-	-
Dysuria	1 to 3 (Estring®)	-	-	-	1.4 (vaginal cream)	-
Endometrial cancer			✔	✔		
Endometrial hyperplasia			✔	✔		
Genital eruption	1 to 3 (Estring®)	-	-	-	-	-
Increase in size of uterine leiomyomata	-	-	✔	✔	-	-
Intermenstrual bleeding	0.0 to 10.6 (Minivelle®/Vivelle®)/0 to 10.6 (Vivelle-Dot®)	8.0 to 9.8 (vaginal ring)	-	-	-	-
Leukorrhea	1.7 to 4.5 (Alora®)/1.0 to 7.0 (Climara®)/7.0 (Estring®)/11.0 (Menostar®)	-	-	-	4.0 to 7.0 (tablet)/2.1 to 2.9 (vaginal cream)	-
Metrorrhagia	4.1 to 9.6 (Divigel®)	-	-	-	-	-
Ovarian cancer			✔	✔		
Spotting	-	-	✔	✔	-	-
Urinary incontinence	1 to 3 (Estring®)	-	-	-	-	-
Urinary tract infection	1.7 to 5.6 (Alora®)/2.0 (Estring®)	0.9 to 3.6 (vaginal ring)	-	-	-	-
Urogenital pruritus	1 to 3 (Estring®)	-	-	-	-	-
Uterine pain	-	1.8 to 4.5 (vaginal ring)	-	-	-	-
Vaginal bleeding	8.7 to 33.3 (Alora®)	-	-	-	-	-
Vaginal candidiasis	-	6.2 to 10.7 (vaginal ring)	-	-	-	-
Vaginal discharge	-	(vaginal ring)	-	-	-	-
Vaginal hemorrhage	4 (Estring®)	-	-	-	2.0 to 14.0 (tablet)/0.7 to 1.4 (vaginal cream)	-
Vaginal irritation	-	0.9 to 1.8 (vaginal ring)	-	-	-	-
Vaginal moniliasis	-	-	-	-	5.0 to 6.0 (tablet)/1.4 (vaginal cream)	-
Vaginal mycosis	2.4 to 6.4 (Divigel®)	-	-	-	-	-
Vaginal pain/discomfort	5 (Estring®)	-	-	-	-	-
Vaginitis	0 to 8.0 (Alora®)/5.0 (Estring®)	-	-	-	5.0 to 7.0 (tablet)/1.4 to 2.1 (vaginal cream)	-

Adverse Event	Estradiol	Estradiol Acetate	Estradiol Cypionate*	Estradiol Valerate*	Estrogens, Conjugated Equine*	Estrogens, Esterified*
Vulvovaginal disorder	-	-	-	-	2.1 to 2.8 (vaginal cream)	-
Vulvovaginal mycotic infection	8 (Vagifem®)	-	-	-	-	-
Vulvovaginal pruritus	8 (Vagifem®)	-	-	-	-	-
Vulvovaginitis	-	0.9 to 5.3 (vaginal ring)	-	-	-	-
Respiratory						
Asthma	1.1 to 3.4 (Alora®)	-	-	-	-	-
Bronchitis	3.4 to 7.9 (Alora®)/1.0 to 3.0 (Estring®)/6.0 (Menostar®)	-	-	-	-	-
Cough increased	1.1 to 4.4 (Alora®)	-	-	-	4 to 7 (tablet)	-
Nasopharyngitis	4.1 to 5.7 (Divigel®)/1.0 to 5.0 (Evamist®)/8.3 to 19.6 (Minivelle®/Vivelle®)/6.4 to 19.6 (Vivelle-Dot®)	1.8 (vaginal ring)	-	-	-	-
Pharyngitis	2.2 to 4.5 (Alora®)/0.5 to 7.0 (Climara®)/1.0 (Estring®)	-	-	-	10 to 12 (tablet)	-
Pneumonia	0.6 to 4.5 (Alora®)	-	-	-	-	-
Respiratory infection	16.1 to 24.7 (Alora®)	-	-	-	-	-
Rhinitis	2 to 6 (Climara®)	-	-	-	6 to 10 (tablet)	-
Sinus congestion	2.9 to 6.5 (Minivelle®/Vivelle®)/0 to 6.5 (Vivelle-Dot®)	-	-	-	-	-
Sinusitis	6.7 to 12.2 (Alora®)/4.0 to 5.0 (Climara®)/4.0 (Estring®)/5.3 to 13.1 (Minivelle®/Vivelle®)/5.3 to 13.1 (Vivelle-Dot®)	1.8 to 3.6 (vaginal ring)	-	-	6 to 11 (tablet)	-
Upper respiratory tract infection	6.0 to 17.0 (Climara®)/1.6 to 5.7 (Divigel®)/5.0 (Estring®)/16.0 (Menostar®)/5.0 (Vagifem®)/4.5 to 10.7 (Minivelle®/Vivelle®)/4.5 to 10.7 (Vivelle-Dot®)	3.6 to 4.4 (vaginal ring)	-	-	9 to 12 (tablet)	-
Skin						
Acne	-	-	-	-	1.4 (vaginal cream)	-
Application site reaction	5.7 to 56.7 (Alora®)/9.0 (Menostar®)	-	-	-	-	-
Chloasma or melasma that may persist when drug is discontinued	-	-	✔	✔	✔ (injection)	✔
Cyst	0 to 6.7 (Alora®)	-	-	-	-	-
Dermatitis	1 to 3 (Estring®)	-	-	-	-	-
Erythema multiforme	-	-	✔	✔	✔ (injection)	✔
Erythema nodosum	-	-	✔	✔	✔ (injection)	✔
Hemorrhagic eruption	-	-	✔	✔	✔ (injection)	✔
Hemorrhoids	1 to 3 (Estring®)	-	-	-	-	-
Hirsutism	0.6 to 4.5 (Alora®)	-	✔	✔	✔ (injection)	✔
Loss of scalp hair	-	-	✔	✔	✔ (injection)	✔
Pruritus	1.1 to 6.7 (Alora®)/0.5 to 6.0 (Climara®)	-	✔	✔	✔ (injection)/ 4.0 to 5.0 (tablet)/ 0.7 to 1.4 (vaginal cream)	✔
Rash	2.9 to 8.9 (Alora®)	-	✔	✔	✔ (injection)	✔
Skin hypertrophy	1 to 3 (Estring®)	-	-	-	-	-

Adverse Event	Estradiol	Estradiol Acetate	Estradiol Cypionate*	Estradiol Valerate*	Estrogens, Conjugated Equine*	Estrogens, Esterified*
Other						
Accidental injury	4.5 to 8.9 (Alora®)/14.0 (Menostar®)	-	-	-	6 to 12 (tablet)	-
Aggravation of porphyria	-	-	✔	✔	✔ (injection)	✔
Allergy	1 (Estring®)	-	-	-	-	-
Allergic reaction	0.6 to 4.5 (Alora®)	-	-	-	-	-
Anaphylactoid/ anaphylactic reactions	-	-	✔	✔	✔ (injection)	✔
Angioedema	-	-	✔	✔	✔ (injection)	✔
Arthralgia	1.1 to 12.4 (Alora®)/1.0 to 5.0 (Climara®)/3.0 (Estring®)/1.0 to 4.0 (Evamist®)/12.0 (Menostar®)/3.8 to 8.5 (Minivelle®/Vivelle®)/3.8 to 8.5 (Vivelle-Dot®)	1.8 (vaginal ring)	✔	✔	✔ (injection)/ 7 to 14 (tablet)	✔
Arthritis	4 (Estring®)/5 (Menostar®)	-	-	-	-	-
Back pain	3.3 to 7.9 (Alora®)/4.0 to 9.0 (Climara®)/6.0 (Estring®)/3.0 to 5.0 (Evamist®)/7.7 to 10.6 (Minivelle®/Vivelle®)/7.0 (Vagifem®)/7.7 to 10.6 (Vivelle-Dot®)	3.6 to 6.2 (vaginal ring)	-	-	13 to 14 (tablet)	-
Bone fracture spontaneous	0 to 3.3 (Alora®)	-	-	-	-	-
Changes in libido	-	-	✔	✔	✔ (injection)	✔
Changes in weight	-	-	✔	✔	✔ (injection)	✔
Edema	0.5 to 13.0 (Climara®)	-	✔	✔	✔ (injection)	✔
Exacerbation of asthma	-	-	✔	✔	✔ (injection)	✔
Family stress	2 (Estring®)	-	-	-	-	-
Flu syndrome	3.4 to 13.3 (Alora®)/3.0 (Estring®)/0.0 to 7.8 (Minivelle®/Vivelle®)	-	-	-	10 to 11 (tablet)	-
Fungal infection	0 to 10.0 (Alora®)	-	-	-	-	-
Genital disorder	-	2.7 (vaginal ring)	-	-	-	-
Glucose intolerance	-	-	-	-	✔ (injection)	-
Hot flashes	2 (Estring®)/0.0 to 2.9 (Minivelle®/Vivelle®)/0 to 6.4 (Vivelle-Dot®)	-	-	-	-	-
Hypocalcemia	-	-	✔	✔	✔ (injection)	✔
Increased triglycerides	-	-	✔	✔	✔ (injection)	✔
Increased weight	0.6 to 4.5 (Alora®)/0.0 to 4.3 (Minivelle®/Vivelle®)/1.9 to 8.5 (Vivelle-Dot®)	-	-	-	-	-
Infection	1.1 to 3.4 (Alora®)/5.0 (Menostar®)	-	-	-	18 to 23 (tablet)	-
Influenza	0.0 to 7.6 (Minivelle®/Vivelle®)/2.3 to 8.5 (Vivelle-Dot®)	-	-	-	-	-
Injection site edema	-	-	-	-	✔ (injection)	-
Injection site pain	-	-	-	-	✔ (injection)	-
Injection site phlebitis	-	-	-	-	✔ (injection)	-
Joint disorder	1.1 to 4.5 (Alora®)	-	-	-	-	-
Leg cramps	-	-	✔	✔	✔ (injection)/ 3 to 7 (tablet)	✔
Leg edema	1 to 3 (Estring®)	-	-	-	-	-
Metabolic and nutritional disorders	12 (Menostar®)	-	-	-	-	-
Moniliasis	6 (Estring®)/5 (Vagifem®)	-	-	-	0.7 to 1.4 (vaginal cream)	-

Adverse Event	Estradiol	Estradiol Acetate	Estradiol Cypionate*	Estradiol Valerate*	Estrogens, Conjugated Equine*	Estrogens, Esterified*
Muscle cramp	-	-	-	-	1.4 (vaginal cream)	-
Myalgia	1.7 to 5.6 (Alora®)/5.0 (Menostar®)	-	-	-	5 to 9 (tablet)	-
Neck pain	0.0 to 4.5 (Minivelle®/Vivelle®)/3.1 to 6.4 (Vivelle-Dot®)	-	-	-	-	-
Otitis media	0 to 3.4 (Alora®)/1.0 to 3.0 (Estring®)	-	-	-	-	-
Pain	5.6 to 10.1 (Alora®)/1.0 to 11.0 (Climara®)/13.0(Menostar®)/0.0 to 6.2 (Minivelle®/Vivelle®)/4.3 to 6.2 (Vivelle-Dot®)	-	-	-	17.0 to 20.0 (tablet)/0.7 to 1.4 (vaginal cream)	-
Pain in limb	4.3 to 7.7 (Minivelle®/Vivelle®)/4.3 to 7.7 (Vivelle-Dot®)	0.9 to 2.7 (vaginal ring)	-	-	-	-
Pelvic pain	-	-	-	-	2.8 to 2.9 (vaginal cream)	-
Peripheral edema	1.7 to 4.4 (Alora®)	-	-	-	-	-
Reduced carbohydrate tolerance	-	-	✔	✔	-	✔
Sinus headache	1.5 to 10.9 (Minivelle®/Vivelle®)/1.5 to 10.9 (Vivelle-Dot®)	-	-	-	-	-
Skeletal pain	2 (Estring®)	-	-	-	-	-
Tooth disorder	1 to 3 (Estring®)	-	-	-	-	-
Toothache	1 to 3 (Estring®)	-	-	-	-	-
Urticaria	-	-	✔	✔	✔ (injection)	✔

*Adverse events have been reported with estrogen and/or progestin therapy (estrogens, conjugated equine injection formulation only).
-Incidence not reported or <1%
✔ Incidence not specified.

Table 8. Adverse Drug Events (%) for the Estrogens-Combination Products[1-3]

Adverse Event	Estradiol and Drospirenone	Estradiol and Levonorgestrel	Estradiol and Norethindrone	Estradiol and Norgestimate	Estradiol and Progesterone	Estrogens, Conjugated and Bazedoxifene	Estrogens, Conjugated Equine and Medroxyprogesterone	Ethinyl Estradiol and Norethindrone
Abdominal pain	-	4.2	6 to 14*	-	-	7	13 to 23	5.3 to 10.2
Accidental injury	-	3.3	3 to 17	-	-	-	4 to 10	-
Acne	-	-	4 to 5*	-	-	-	-	-
Anxiety	-	-	-	-	-	-	2 to 5	-
Application site reaction	-	40.6	2 to 23*	-	-	-	-	-
Arthralgia	-	4.2	6*	9	-	-	7 to 13	2.9 to 5.8
Asthenia	-	-	8 to 13*	-	-	-	6 to 10	-
Back pain	-	6.1	3 to 15	12	-	-	13 to 16	4.7 to 5.3
Breast enlargement	-	-	2 to 7*	-	-	-	2 to 5	-
Breast pain or discomfort	3.3 to 17.9	18.9	17 to 48	16	10	-	12 to 38	5.3 to 9.0
Bronchitis	-	4.2	3 to 5*	-	-	-	-	-
Cervical polyp	1.2	-	-	-	-	-	-	-
Cervix disorder	-	-	-	-	-	-	4 to 5	-
Constipation	-	-	2 to 5*	-	-	-	-	-
Cough	-	-	-	5	-	-	5 to 8	-
Depression	-	5.7	3 to 9*	5	-	-	5 to 11	3.7 to 5.8

Adverse Event	Estradiol and Drospirenone	Estradiol and Levonorgestrel	Estradiol and Norethindrone	Estradiol and Norgestimate	Estradiol and Progesterone	Estrogens, Conjugated and Bazedoxifene	Estrogens, Conjugated Equine and Medroxyprogesterone	Ethinyl Estradiol and Norethindrone
Diarrhea	2.2	-	4 to 14	-	-	8	5 to 7	3.9 to 5.7
Dizziness	-	-	6 to 7*	5	-	5	3 to 5	-
Dysmenorrhea	-	-	20 to 31*	8	-	-	3 to 13	-
Dyspepsia	-	-	1 to 8*	-	-	7	5 to 8	3.1 to 5.3
Edema	-	3.8	-	-	-	-	-	15.7 to 16.9
Emotional lability	1.2	-	0 to 6†	-	-	-	-	-
Endometrial thickening	-	-	10†	-	-	-	-	-
Fatigue	-	-	-	6	-	-	-	-
Female genital tract bleeding	14	-	-	-	-	-	-	-
Flatulence	-	3.8	4 to 7*	5	-	-	5 to 9	-
Gastroenteritis	-	-	0 to 6†	-	-	-	-	-
Gastrointestinal and abdominal pains	6.0 to 6.5	-	-	12	-	-	-	-
Headache	6	5.2	11 to 25	23	3	-	28 to 37	5.7 to 18.2
Hypertension	-	3.3	-	-	-	-	-	-
Hypertonia	-	-	-	-	-	-	3 to 4	-
Infection	-	3.3	3 to 5*	-	-	-	16 to 21	-
Influenza-like symptoms	-	4.7	5 to 9*	11	-	-	8 to 12	-
Insomnia	-	-	0 to 8	-	-	-	6 to 7	-
Leg cramps	-	-	-	-	-	-	3 to 7	-
Leukorrhea	-	-	5 to 10*	-	-	-	3 to 9	-
Menorrhagia	-	-	2 to 5*	-	-	-	-	-
Menstrual disorder	-	-	6 to 19*	-	-	-	-	-
Migraine	1	-	-	-	-	-	-	-
Moniliasis, genital	-	-	0 to 6†	-	-	-	4 to 8	-
Muscle spasms	-	-	-	-	-	9	-	-
Myalgia	-	-	-	5	-	-	4 to 5	7.8 to 8.6
Nasopharyngitis	-	-	21†	-	-	-	-	-
Nausea	3.3	-	3 to 12	6	-	8	7 to 11	5.3 to 33.0
Neck pain	-	-	-	-	-	5	-	-
Nervousness	-	-	3 to 6*	-	-	-	2 to 3	1.6 to 5.4
Oropharyngeal pain	-	-	-	-	-	7	-	-
Ovarian cyst	-	-	0 to 7†	-	-	-	-	-
Pain	-	5.2	4 to 19*	6	-	-	11 to 20	-
Pain in extremity	-	-	5†	-	-	-	-	-
Papanicolaou smear suspicious	-	-	4 to 8*	-	-	-	-	-
Pelvic pain	-	-	-	-	3	-	4 to 5	-
Peripheral edema	2.2	-	6*	-	-	-	3 to 4	-
Pharyngitis	-	-	4 to 10*	7	-	-	8 to 13	-
Post-menopausal bleeding	-	-	5 to 11†	-	-	-	-	-
Pruritus	-	-	-	-	-	-	4 to 10	-
Rash	-	2.4	5 to 6*	-	-	-	4 to 6	-
Respiratory disorder	-	-	7 to 13*	-	-	-	-	-
Rhinitis	-	-	7 to 22*	-	-	-	6 to 10	12.7 to 15.1

Adverse Event	Estradiol and Drospirenone	Estradiol and Levonorgestrel	Estradiol and Norethindrone	Estradiol and Norgestimate	Estradiol and Progesterone	Estrogens, Conjugated and Bazedoxifene	Estrogens, Conjugated Equine and Medroxyprogesterone	Ethinyl Estradiol and Norethindrone
Sinusitis	-	3.8	4 to 15	8	-	-	7 to 10	8.1 to 9.4
Tooth disorder	-	-	4 to 6*	5	-	-	-	-
Upper respiratory tract infection	-	13.2	10 to 18†	21	-	-	9 to 11	-
Urinary tract infection	-	3.3	-	-	-	-	-	3.7 to 6.2
Uterine fibroid	-	-	0 to 5†	-	-	-	-	-
Vaginal bleeding	9	36.8	-	-	-	-	-	-
Vaginal discharge	-	-	-	-	3	-	-	-
Vaginal hemorrhage	-	-	3 to 26	-	3	-	1 to 6	-
Vaginitis	-	1.9	6 to 13*	7	-	-	4 to 7	5.4 to 4.5
Viral infection	-	-	0 to 6†	6	-	-	-	7.0 to 8.6
Vomiting	-	-	-	-	-	-	-	5.3 to 33.0
Vulvovaginal fungal infections	5.5	-	-	-	-	-	-	-
Weight increase	-	2.8	0 to 9†	-	-	-	-	-

*Transdermal patch only.
†Oral therapy only.
-Incidence not reported or <1.0%
✔ Incidence not specified.

Table 9. Boxed Warning for the Estrogens[2]

WARNING
Estrogen-alone therapy: Endometrial cancer: There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens. Adding a progestin to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer. Adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding. Cardiovascular disorders and probable dementia: Estrogen-alone therapy should not be used for the prevention of cardiovascular disease or dementia. The Women's Health Initiative (WHI) estrogen-alone substudy reported increased risks of stroke and deep vein thrombosis in postmenopausal women (50 to 79 years of age) during 7.1 years of treatment with daily oral conjugated estrogens 0.625 mg alone, relative to placebo. The WHI Memory Study (WHIMS) estrogen-alone ancillary study of WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years or older during 5.2 years of treatment with daily CE 0.625 mg alone, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women. Only daily oral 0.625 mg CE was studied in the estrogen-alone substudy of WHI. Therefore, the relevance of the WHI findings regarding adverse cardiovascular events and dementia to lower conjugated estrogens doses, other routes of administration, or other estrogen-alone products is not known. Without such data, it is not possible to definitively exclude these risks or determine the extent of these risks for other products. Discuss with your patient the benefits and risks of estrogen-alone therapy, taking into account her individual risk profile. Prescribe estrogens with or without progestins at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman. Estrogen plus progestin therapy: Cardiovascular disorders and probable dementia: Estrogen plus progestin therapy should not be used for the prevention of cardiovascular disease or dementia. The WHI estrogen plus progestin substudy reported increased risks of DVT, pulmonary embolism, stroke and myocardial infarction in postmenopausal women (50 to 79 years of age) during 5.6 years of treatment with daily oral conjugated estrogen 0.625 mg combined with medroxyprogesterone 2.5 mg, relative to placebo. The WHIMS estrogen plus progestin ancillary study of the WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years or older during 4 years of treatment with daily conjugated estrogen 0.625 mg combined with medroxyprogesterone 2.5 mg, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women. Breast cancer: The WHI estrogen plus progestin substudy also demonstrated an increased risk of invasive breast cancer. Only daily oral 0.625 mg conjugated estrogens and 2.5 mg MPA were studied in the estrogen plus progestin substudy of WHI. Therefore, the relevance of the WHI findings regarding adverse cardiovascular events, dementia and breast cancer to lower conjugated estrogens plus other MPA doses, other routes of administration, or other estrogen plus progestin products is not known. Without such data, it is not possible to definitively exclude these risks or determine the extent of these risks for other products. Discuss with your patient the benefits and risks of estrogen plus progestin therapy, taking into account her individual risk profile. Prescribe estrogens with or without progestins at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman..

VII. Dosing and Administration

The usual dosing regimens for the estrogens are listed in Table 10.

Table 10. Usual Dosing Regimens for the Estrogens[1-3]

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
Single Entity Agents			
Estradiol	Palliative treatment of advanced androgen-dependent carcinoma of the prostate: Tablet (Estrace®): 1 to 2 mg TID Palliative treatment of breast cancer in appropriately selected women and men with metastatic breast cancer: Tablet (Estrace®): 10 mg TID for ≥3 months Prevention of postmenopausal osteoporosis: Tablet (Estrace®): initial, 0.5 mg/day; maintenance, adjust dose as necessary Transdermal patch (Alora®): initial, 0.025 mg/day applied twice weekly; maintenance, adjust dose as necessary Transdermal patch (Climara®): initial, 0.025 mg/day applied once weekly; maintenance, adjust dose as necessary Transdermal patch (Menostar®): 14 µg/day applied once weekly Transdermal patch (Vivelle-Dot®, Minivelle®): initial, 0.025 mg/day applied twice weekly; maintenance, adjust dose as necessary Treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure: Tablet (Estrace®): initial, 1 to 2 mg/day; maintenance, adjust dose as necessary Transdermal patch (Alora®): initial, 0.05 mg/day applied twice weekly; maintenance, adjust dose as necessary Transdermal patch (Climara®): initial, 0.025 mg/day applied once weekly; maintenance, adjust dose as necessary Transdermal patch (Vivelle-Dot®, Minivelle®): initial, 0.025 mg/day applied twice weekly; maintenance, adjust dose as necessary Treatment of moderate to severe vasomotor symptoms associated with menopause: Tablet (Estrace®): initial, 1 to 2 mg/day administered cyclically (three weeks on and one week off); maintenance, adjust dose as necessary Transdermal gel (Divigel®): initial, 0.25 g/day; maintenance, adjust dose as necessary	Safety and efficacy in children have not been established.	Tablet (Estrace®): 0.5 mg 1 mg 2 mg Transdermal gel (Divigel®): 0.25 mg (0.1%) 0.5 mg (0.1%) 0.75 mg (0.1%) 1 mg (0.1%) Transdermal gel (Elestrin®): 0.87 gm/pump (0.06%) Transdermal patch (Alora®): 0.025 mg/day 0.05 mg/day 0.075 mg/day 0.1 mg/day Transdermal patch (Climara®): 0.025 mg/day 0.0375 mg/day 0.05 mg/day 0.06 mg/day 0.075 mg/day 0.1 mg/day Transdermal patch (Menostar®): 14 µg/day Transdermal patch (Minivelle®): 0.025 mg/day 0.0375 mg/day 0.05 mg/day 0.075 mg/day 0.1 mg/day Transdermal patch (Vivelle-Dot®): 0.025 mg/day

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
	Transdermal gel (Elestrin®): initial, 0.87 g/day (one pump); maintenance, adjust dose as necessary Transdermal patch (Alora®): initial, 0.05 mg/day applied twice weekly; maintenance, adjust dose as necessary Transdermal patch (Climara®): initial, 0.025 mg/day applied once weekly; maintenance, adjust dose as necessary Transdermal patch (Vivelle-Dot®, Minivelle®): initial, 0.0375 mg/day applied twice weekly; maintenance, adjust dose as necessary Transdermal spray (Evamist®): initial, one spray daily; maintenance, adjust dose as necessary <u>Treatment of moderate to severe vulvar and vaginal atrophy associated with menopause:</u> Tablet (Estrace®): initial, 1 to 2 mg/day administered cyclically (three weeks on and one week off); maintenance, adjust dose as necessary Transdermal patch (Alora®): initial, 0.05 mg/day applied twice weekly; maintenance, adjust dose as necessary Transdermal patch (Climara®): initial, 0.025 mg/day applied once weekly; maintenance, adjust dose as necessary Transdermal patch (Vivelle-Dot®, Minivelle®): initial, 0.0375 mg/day applied twice weekly; maintenance, adjust dose as necessary <u>Treatment of atrophic vaginitis due to menopause:</u> Vaginal tablet (Vagifem®): one tablet administered intravaginally for two weeks, followed by one tablet intravaginally twice weekly; in general start treatment with 10 µg <u>Treatment of moderate to severe urogenital symptoms due to postmenopausal atrophy of the vagina and/or the lower urinary tract:</u> Vaginal ring (Estring®): 2 mg vaginal ring inserted as deeply as possible into the upper one-third of the vaginal vault; the ring is to remain in place continuously for three months <u>Treatment of vulvar and vaginal atrophy:</u> Vaginal cream (Estrace®): 2 to 4 g/day administered intravaginally for one to two weeks, followed by ½ the initial dose for a similar period; maintenance, 1 g administered intravaginally one to three times per week		0.0375 mg/day 0.05 mg/day 0.075 mg/day 0.1 mg/day Transdermal spray (Evamist®): 1.53 mg/spray (1.7%) Vaginal cream (Estrace®): 0.1 mg/g (0.01%) Vaginal ring (Estring®): 2 mg (7.5 µg/day) Vaginal tablet (Vagifem®): 10 µg

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
	(may be used after restoration of the vaginal mucosa has been achieved)		
Estradiol acetate	Treatment of moderate to severe vasomotor symptoms associated with menopause: Vaginal ring: initial, 0.05 mg/day; maintenance, 0.05 to 0.1 mg/day (as one ring inserted into the vagina for three months) Treatment of moderate to severe vulvar and vaginal atrophy associated with menopause: Vaginal ring: initial, 0.05 mg/day; maintenance, 0.05 to 0.1 mg/day (as one ring inserted into the vagina for three months)	Safety and efficacy in children have not been established.	Vaginal ring (Femring®): 0.05 mg/day 0.1 mg/day
Estradiol cypionate	Treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure: Injection: 1.5 to 2 mg intramuscularly at monthly intervals Treatment of vasomotor symptoms associated with menopause: Injection: 1 to 5 mg intramuscularly every three to four weeks	Safety and efficacy in children have not been established.	Injection (intramuscular): 5 mg/mL
Estradiol valerate	Palliative treatment of advanced prostate cancer: Injection: 30 mg or more intramuscularly every one to two weeks Treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure: Injection: 10 to 20 mg intramuscularly every four weeks Treatment of vasomotor symptoms associated with menopause: Injection: 10 to 20 mg intramuscularly every four weeks Treatment of vulvar and vaginal atrophy associated with menopause: Injection: 10 to 20 mg intramuscularly every four weeks	Safety and efficacy in children have not been established.	Injection (intramuscular): 10 mg/mL 20 mg/mL 40 mg/mL
Estrogens, conjugated equine	Palliative treatment of advanced androgen-dependent carcinoma of the prostate: Tablet: 1.25 to 2.5 mg TID Palliative treatment of breast cancer in appropriately selected women and men with metastatic disease: Tablet: 10 mg TID for ≥3 months Prevention of postmenopausal osteoporosis: Tablet: initial, 0.3 mg/day; maintenance, subsequent dosage adjustment may be made based upon the individual clinical and bone mineral density responses	Safety and efficacy in children have not been established.	Injection (intramuscular and intravenous): 25 mg Tablet: 0.3 mg 0.45 mg 0.625 mg 0.9 mg 1.25 mg Vaginal cream:

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
	Treatment of abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology: Injection: 25 mg intramuscularly or intravenously once; repeat in six to 12 hours if necessary Treatment of atrophic vaginitis and kraurosis vulvae: Vaginal cream: initial, 0.5 g/day intravaginally administered cyclically (three weeks on and one week off); maintenance, 0.5 to 2 g Treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure: Tablet: 0.3 or 0.625 mg/day administered cyclically (three weeks on and one week off); maintenance, doses are adjusted depending on the severity of symptoms and responsiveness of the endometrium Treatment of moderate to severe vasomotor symptoms associated with menopause: Tablet: initial, 0.3 mg/day; maintenance, subsequent dosage adjustment may be made based upon the individual patient response Treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause: Vaginal cream: 0.5 mg/day intravaginally in a twice-weekly continuous regimen or in a cyclic regimen of 21 days of therapy followed by seven days off of therapy Treatment of moderate to severe vaginal dryness symptoms of vulvar and vaginal atrophy associated with menopause: Tablet: initial, 0.3 mg/day; maintenance, subsequent dosage adjustment may be made based upon the individual patient response		0.625 mg/g (30 or 42.5 g)
Estrogens, esterified	Palliative treatment of breast cancer in appropriately selected women and men with metastatic disease: Tablet: 10 mg TID for ≥3 months Palliative therapy of advanced prostatic carcinoma: Tablet: 1.25 to 2.5 mg TID Treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure: Tablet (hypogonadism): 2.5 to 7.5 mg/day, in divided doses for 20 days, followed by a rest period of 10 days' duration Tablet (female castration, primary ovarian failure): 1.25 mg/day administered cyclically (three weeks on and one week off)	Safety and efficacy in children have not been established.	Tablet: 0.3 mg 0.625 mg 1.25 mg

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
	Treatment of moderate to severe vasomotor symptoms associated with menopause: Tablet: 1.25 mg/day administered cyclically (three weeks on and one week off) Treatment of vulval and vaginal atrophy associated with menopause: Tablet: 0.3 to 1.25 mg or more daily administered cyclically (three weeks on and one week off)		
Combination Products			
Estradiol and drospirenone	Treatment of moderate to severe symptoms of vulvar and vaginal atrophy due to menopause: Tablet: 0.5-0.25 mg or 1-0.5 mg QD Treatment of moderate to severe vasomotor symptoms due to menopause: Tablet: 1-0.5 mg QD	Safety and efficacy in children have not been established.	Tablet*: 0.5-0.25 mg 1.0-0.5 mg
Estradiol and levo-norgestrel	Prevention of postmenopausal osteoporosis and treatment of moderate to severe vasomotor symptoms due to menopause: Transdermal patch: 0.045-0.015 mg transdermal patch worn continuously for seven days; maintenance, a new 0.045-0.015 mg transdermal patch should be applied weekly during a 28-day cycle	Safety and efficacy in children have not been established.	Transdermal patch: 0.045-0.015 mg/day
Estradiol and norethindrone	Prevention of postmenopausal osteoporosis: Tablet: 0.5-0.1 or 1-0.5 mg QD Treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure: Transdermal patch: 0.05-0.014 or 0.05-0.25 mg transdermal patch worn continuously; maintenance, a new 0.05-0.014 or 0.05-0.25 mg transdermal system should be applied twice weekly during a 28-day cycle† Treatment of moderate to severe symptoms of vulvar and vaginal atrophy due to menopause: Tablet: 1-0.5 mg QD Transdermal patch: 0.05-0.014 or 0.05-0.25 mg transdermal patch worn continuously; maintenance, a new 0.05-0.014 or 0.05-0.25 mg transdermal system should be applied twice weekly during a 28-day cycle† Treatment of moderate to severe vasomotor symptoms due to menopause: Tablet: 0.5-0.1 or 1-0.5 mg QD Transdermal patch: 0.05-0.014 or 0.05-0.25 mg transdermal patch worn continuously; maintenance, a new 0.05-0.014 or 0.05-0.25 mg transdermal system should be applied twice weekly during a 28-day cycle†	Safety and efficacy in children have not been established.	Tablet‡: 0.5-0.1 mg 1.0-0.5 mg Transdermal patch: 0.05-0.14 mg 0.05-0.25 mg
Estradiol and norgestimate	Prevention of postmenopausal osteoporosis, treatment of moderate to severe symptoms of vulvar and vaginal	Safety and efficacy in children have	Tablet§:

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
	atrophy due to menopause, and treatment of moderate to severe vasomotor symptoms due to menopause: Tablet: one tablet QD	not been established.	1 mg (estradiol) and 1-0.09 mg (estradiol/ norgestimate)
Estradiol and progesterone	Treatment of moderate to severe vasomotor symptoms due to menopause: Capsule: one tablet orally each evening with food	Safety and efficacy in children have not been established.	Capsule: 1-100 mg
Estrogens, conjugated and bazedoxifene	Prevention of postmenopausal osteoporosis and treatment of moderate to severe vasomotor symptoms due to menopause: Tablet: one tablet QD	Safety and efficacy in children have not been established.	Tablet: 0.45-20 mg
Estrogens, conjugated equine and medroxy-progesterone	Prevention of postmenopausal osteoporosis, treatment of moderate to severe symptoms of vulvar and vaginal atrophy due to menopause, and treatment of moderate to severe vasomotor symptoms due to menopause: Tablet: one tablet QD	Safety and efficacy in children have not been established.	Tablet‖: 0.3-1.5 mg (Prempro®) 0.45-1.5 mg (Prempro®) 0.625-2.5 mg (Prempro®) 0.625-5 mg (Prempro®) 0.625 mg (estrogen, conjugated equine) and 0.625-5 mg (estrogen, conjugated equine/ medroxy-progesterone) (Premphase®)
Ethinyl estradiol and norethindrone	Prevention of postmenopausal osteoporosis and treatment of moderate to severe vasomotor symptoms due to menopause: Tablet: one tablet QD	Safety and efficacy in children have not been established.	Tablet: 2.5 µg-0.5 mg 5 µg-1 mg

QD=once daily, TID=three times daily
*Available in three blisters of 28 tablets.
†Can also be administered in combination with an estradiol transdermal patch. With this regimen, estradiol transdermal patch (0.05 mg) is administered for the first 14 days of a 28-day cycle, followed by estradiol/norethindrone 0.05/0.14 or 0.05/0.25 mg transdermal patch for the remaining 14 days of the 28-day cycle.
‡Activella®: available as 28 tablets in a calendar dial pack dispenser.
§Available in cartons of six pouches. Each pouch consists of a blister card containing three 1 mg estradiol tablets followed by three 1.0/0.9 mg estradiol/norgestimate tablets. The pattern of three estradiol tablets and three combination tablets repeats for a total of 30 tablets per blister card. Each blister card contains 15 tablets of each of the two tablets. The three day phases are alternated continuously during treatment.
‖Prempro®: available as one or three blisters of 28 tablets. Premphase®: available as one blister of 28 tablets.

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the estrogens are summarized in Table 11.

Table 11. Comparative Clinical Trials with the Estrogens

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Comparative Trials of Estrogens				
WHI Steering Committee[17] (2004) WHI CEE 0.625 mg once daily vs placebo	DB, MC, PC, RCT Postmenopausal women, 50 to 79 years of age, with prior hysterectomy	N=10,739 6.8 years (mean duration of follow-up)	Primary: Rate of CHD (nonfatal MI or CHD death), invasive breast cancer Secondary: Stroke, PE, colorectal cancer, hip fracture, and deaths from other causes	Primary: Treatment with CEE did not significantly affect the incidence of CHD or overall mortality. The estimated HR for CHD was 0.91 (95% CI, 0.75 to 1.12), breast cancer was 0.77 (95% CI, 0.59 to 1.01), and death was 1.04 (95% CI, 0.88 to 1.22). There were an estimated seven fewer cases of breast cancer among the women treated with CEE compared to the women taking placebo, but that did not reach statistical significance. Secondary: Treatment with CEE increased the risk of stroke and reduced the risk of hip and other fractures. The estimated HR for breast cancer was 0.77 (95% CI, 0.59 to 1.01), stroke was 1.39 (95% CI, 1.10 to 1.77), PE was 1.34 (95% CI, 0.87 to 2.06), colorectal cancer was 1.08 (95% CI, 0.75 to 1.55), hip fracture was 0.61 (95% CI, 0.41 to 0.91), and global index was 1.01 (95% CI, 0.91 to 1.12). Thus, there was an absolute excess risk of 12 additional strokes per 10,000 person-years and an absolute risk reduction of 6 fewer hip fractures per 10,000 person-years.
Stefanick et al.[20] (2006) WHI CEE 0.625 mg vs placebo	DB, MC, PC, RCT Postmenopausal women, 50 to 79 years of age, with prior hysterectomy	N=10,739 7.1 years (mean duration of follow-up)	Primary: Breast cancer incidence, tumor characteristics, mammogram findings Secondary: Not reported	Primary: Treatment with CEE did not increase the risk of breast cancer compared to placebo. The HR for invasive breast cancer was 0.80 (95% CI, 0.62 to 1.04; P=0.09) and 0.82 (95% CI, 0.65 to 1.04; P=0.10) for total breast cancer. However, breast cancer that developed in patients who had received CEE was associated with larger tumor size (P=0.03) and higher percentage of positive nodes (P=0.07) compared to placebo. The risk of invasive breast cancer was significantly lower in women who had no prior hormone use. The HR was 0.65 (95% CI, 0.46 to 0.92) for women with no prior hormone use and 1.02 (95% CI, 0.70 to 1.50) for women with prior hormone use (P=0.09).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				There were larger numbers of mammograms with abnormalities that required primarily short interval follow-ups in the CEE group compared to placebo (P<0.001). Secondary: Not reported
Hsia et al.[21] (2006) WHI CEE 0.625 mg once daily vs placebo	DB, MC, PC, RCT Postmenopausal women 50 to 79 years of age at baseline, who had undergone prior hysterectomy	N=10,739 7.1 years (mean duration of follow-up)	Primary: CHD events (MI or coronary death) Secondary: CABG or PCI, angina, hospitalized CHF, acute coronary syndrome	Primary: There were 201 CHD events reported among the women assigned to estrogen treatment compared to 217 events in the placebo group (HR, 0.95; 95% CI, 0.79 to 1.16). The HR was 0.61 (95% CI, 0.25 to 1.50) for the 50 to 59 years age group, 0.86 (95% CI, 0.60 to 1.25) for the 60 to 69 years age group, and 1.10 (95% CI, 0.69 to 1.73) for the 70 to 79 years of age group; P=0.35. There was no significant trend in risk of primary outcome over time (P=0.14). Secondary: Coronary revascularization was less frequent among the 50 to 59 years age group that was assigned to estrogen treatment (HR, 0.55; 95% CI, 0.35 to 0.86). Composite outcomes were less frequent with estrogen treatment in this age group (HR, 0.66; 95% CI, 0.45 to 0.96). There were no differences in secondary coronary outcomes between treatment groups in the women 60 to 69 years of age or women 70 to 79 years of age.
Chlebowski et al.[22] (2016) WHI CEE 0.625 mg once daily plus medroxyprogeste-rone acetate 2.5mg once daily (as a	DB, MC, PC, RCT Postmenopausal women 50 to 79 years of age at baseline, with an intact uterus	N=16,608 5.6 years (mean duration of follow-up) Extension phase:	Primary: Endometrial cancer incidence Secondary: Not reported	Primary: Over cumulative follow-up, continuous combined estrogen plus progestin use decreased endometrial cancer incidence (66 case patients, 0.06% per year) compared with placebo (95 case patients, 0.10% per year; HR, 0.65; 95% CI, 0.48 to 0.89; P=0.007). While there were somewhat fewer endometrial cancers during intervention (25 vs 30, respectively; HR, 0.77; 95% CI, 0.45 to 1.31), the difference became statistically significant postintervention (41 vs 65, respectively; HR, 0.59; 95% CI, 0.40 to 0.88; P=0.008), but hazard ratios did not differ between phases ($P_{difference}$=0.46).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
single pill: Prempro®) vs placebo		N=12,788 13.2 years (mean duration of follow-up)		There was a statistically nonsignificant reduction in deaths from endometrial cancer in the estrogen plus progestin group (5 vs 11 deaths, HR, 0.42; 95% CI, 0.15 to 1.22). Secondary: Not reported
Manson et al.[23] (2017) WHI CEE 0.625 mg once daily or CEE 0.625 mg once daily plus medroxyprogeste-rone acetate 2.5mg once daily (as a single pill: Prempro®) vs placebo	OBS follow-up US multiethnic postmenopausal women aged 50 to 79 years enrolled in two randomized clinical trials between 1993 and 1998 and followed up through 2014	N=27,347 Cumulative 18-year follow-up	Primary: All-cause mortality Secondary: Cause-specific mortality (cardiovascular disease mortality, cancer mortality, and other major causes of mortality)	Primary: During cumulative 18-year follow-up, all-cause mortality in the overall pooled cohort was 27.1% with hormone therapy vs 27.6% with placebo (HR, 0.99; 95% CI, 0.94 to 1.03; P=0.60). For the individual trials, all-cause mortality was 26.4% for CEE plus MPA vs 26.0% for placebo (HR, 1.02; 95% CI, 0.96 to 1.08; P=0.51), and for CEE alone it was 28.3% vs 30.0% for placebo (HR, 0.94; 95% CI, 0.88 to 1.01; P=0.11). Secondary: In the pooled cohort for cardiovascular mortality, the HR was 1.00 (95% CI, 0.92 to 1.08 [8.9 % with hormone therapy vs 9.0% with placebo]); for total cancer mortality, the HR was 1.03 (95% CI, 0.95 to 1.12 [8.2 % with hormone therapy vs 8.0% with placebo]); and for other causes, the HR was 0.95 (95% CI, 0.88 to 1.02 [10.0% with hormone therapy vs 10.7% with placebo]), and results did not differ significantly between trials.
LaCroix et al.[24] (2011) CEE 0.0625 mg once daily vs placebo	DB, MC, PC, RCT Postmenopausal women 50 to 79 years of age with prior hysterectomy	N=7,645 10.7 years (mean duration of follow-up)	Primary: CHD, invasive breast cancer Secondary: Stroke, PE, colorectal cancer, hip fracture, death	Primary: The post-intervention risk (annualized risk) for CHD among patients receiving CEE was 0.64% compared to 0.67% with patients receiving placebo (HR, 0.97; 95% CI, 0.75 to 1.25) and 0.26 vs 0.34%, respectively, for breast cancer (HR, 0.75; 95% CI, 0.51 to 1.09). Over the entire follow-up, lower breast cancer incidence with CEE persisted and was 0.27% compared to 0.35% with placebo (HR, 0.77; 95% CI, 0.62 to 0.92). Health outcomes were more favorable for younger compared to older women for CHD (P=0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: The risk of stroke was no longer evaluated during the post-intervention follow-up period and was 0.36 and 0.41% among patients receiving CEE and placebo (HR, 0.89; 95% CI, 0.64 to 1.24). The risk of deep vein thrombosis was 0.17 and 0.27%, respectively, among patients receiving CEE and patients receiving placebo (HR, 0.63; 95% CI, 0.41 to 0.98) and the risk of hip fracture did not differ significantly between the two treatments (0.36 vs 0.28%; HR, 1.27; 95% CI, 0.88 to 1.28). The post-intervention risk (annualized risk) for total mortality among patients receiving CEE was 1.47% compared to 1.48% with placebo (HR, 1.00; 95% CI, 0.84 to 1.18). Health outcomes were more favorable for younger compared to older patients for total MI (P=0.007), colorectal cancer (P=0.04), total mortality (P=0.04), and global index of chronic disease (P=0.009).
Espeland et al.[25] (2004) WHIMS CEE 0.625 mg once daily vs placebo	DB, MC, PC, RCT Postmenopausal women, 65 to 79 years of age, with prior hysterectomy	N=2,808 5.4 years (mean follow-up duration)	Primary: Global cognitive function as measured by 3MSE Secondary: Not reported	Primary: The mean 3MSE scores were 0.26 units lower in the estrogen treatment group compared to placebo group (P=0.04). In the group of women with lower cognitive function at baseline, there were significant decreases in 3MSE scores in the estrogen group compared with placebo (P<0.01). The RR of having a 10-unit decrease in 3MSE scores, or greater than 2 standard deviations below the mean, was estimated to be 1.47 (95% CI, 1.04 to 2.07). Secondary: Not reported
Chen et al.[26] (2006) Nurses' Health Study	PRO Postmenopausal women who had a hysterectomy	N=28,835 20 years (mean	Primary: Diagnosis of invasive breast cancer	Primary: The risk of invasive breast cancer was significantly elevated with longer durations of use (P<0.001). The RRs for invasive breast cancer with unopposed estrogen use is 0.96 (95% CI, 0.75 to 1.22) with less than 5 years of use, 0.90 (95% CI, 0.73 to 1.12) with 5 to 9.9 years of use, 1.06

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Conjugated estrogens, with various doses but mostly 0.625 mg once daily vs placebo		duration not specified)	Secondary: Not reported	(95% CI, 0.87 to 1.30) with 10 to 14.9 years of use, 1.18 (95% CI, 0.95 to 1.48) with 15.0 to 19.9 years of use, and 1.42 (95% CI, 1.13 to 1.77) with ≥20 years of use. The risk of estrogen receptor and progesterone receptor positive breast cancer was significantly higher after 15 or more years of unopposed estrogen use (P<0.001). Secondary: Not reported
Jackson et al.[27] (2006) CEE 0.625 mg daily vs placebo	RCT Postmenopausal women 50 to 79 years of age with hysterectomy	N=10,739 7.1 years	Primary: Hip fractures and all other fractures Secondary: Not reported	Primary: CEE reduced the risk of hip (HR, 0.65; 95% CI, 0.45 to 0.94), clinical vertebral (HR, 0.64; 95% CI, 0.44 to 0.93), wrist/lower arm (HR, 0.58; 95% CI, 0.47 to 0.72), and total fracture (HR, 0.71; 95% CI, 0.64 to 0.80). This reduction did not differ among strata according to age, oophorectomy status, past hormone use, race/ethnicity, fall frequency, physical activity, or fracture history. Total fracture reduction was lower in women at the lowest predicted fracture risk in both absolute and relative terms (HR, 0.86; 95% CI, 0.68 to 1.08). The HRs of the global index for CEE were relatively balanced. The summary of fracture is as follows: lowest risk: HR, 0.81; 95% CI, 0.62 to 1.05; midrisk: HR, 1.09; 95% CI, 0.92 to 1.30; highest risk: HR, 1.04; 95% CI, 0.88 to 1.23 (P=0.42). Secondary: Not reported
Schaefers et al.[28] (2009) Transdermal 17β-estradiol 0.014 mg/day (Menostar®) vs	AC, DB, MC, RCT Osteopenic postmenopausal women	N=500 2 years	Primary: Percent change from baseline in bone mineral density at the lumbar spine Secondary: Proportion of women with no	Primary: Lumbar spine bone mineral density increased by 2.4% (95% CI, 1.9 to 2.9) with transdermal 17β-estradiol versus 3.0% (95% CI, 2.5 to 3.5) with raloxifene after two years. Secondary: Of those patients taking transdermal 17β-estradiol, 77.3% had no bone loss in the lumbar spine compared to 80.5% of those taking raloxifene.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
raloxifene 60 mg/day			loss of bone mineral density in lumbar spine, change in bone mineral density at hip, biochemical markers of bone turnover, and safety parameters.	Both treatments were well tolerated. Most women (99% in the transdermal 17β-estradiol group and 100% in the raloxifene group) showed no histological evidence of endometrial stimulation after two years. Mean dense area in breast mammograms was 19.8% in the transdermal 17β-estradiol group vs 19.0% in the raloxifene group after two years.
Haines et al.[29] (2009) Transdermal estradiol patch (0.014 mg/day) vs placebo	DB, MC, PC, RCT Symptomatic postmenopausal Asian women 40 to 65 years of age, had undergone natural menopause, and had ≥24 hot flushes	N=165 12 weeks	Primary: Relative change in the frequency of all hot flushes from baseline to week 12 Secondary: Relative changes in frequency of all hot flushes from baseline to weeks four and eight and frequency of moderate to severe hot flushes from baseline to weeks four, eight, and 12; absolute changes in vaginal pH; vaginal maturation value; Menopause QOL scores; occurrence of urogenital symptoms; vaginal bleeding profiles; safety	Primary: There was a greater relative reduction in the mean weekly number of all hot flushes at week 12 with estradiol transdermal patch (55%) compared to placebo (40%; P<0.01), as well as at weeks four and eight. Secondary: The relative change in the number of moderate and severe hot flushes per week at week 12 was greater with estradiol transdermal patch compared to placebo (-58 vs -39%). The reductions of moderate and severe hot flushes and in any hot flushes were significant (P<0.05) at weeks four, eight, and 12. Vaginal pH had fallen significantly with estradiol transdermal patch by week four (5.60±0.76 to 5.10±0.72) and then remained stable throughout the trial. There were no significant changes with placebo. Vaginal pH decreased significantly more with estradiol transdermal patch compared to placebo (P<0.001). The vaginal maturation value had increased significantly more with estradiol transdermal patch compared to placebo (absolute change at week 12: 17.40±21.85 vs 5.00±17.04; P<0.001). Of the patients with an intact uterus (53 and 46), few had vaginal bleeding or spotting. Any bleeding/spotting was reported by three patients receiving estradiol transdermal patch and four patients receiving placebo in cycle 1, by two and two in cycle 2, by five and two in cycle 3.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The absolute mean change in the Menopause QOL scores from baseline to week 12 were not difference between the treatments (-1.00±1.25 and -1.00±1.06, respectively; P value not reported). All subscores improved with both treatments; vasomotor and sexual subscores improved more with estradiol transdermal patch compared to placebo, while the physical subscore improved more with placebo. There was considerable improvement from baseline in certain urogenital symptoms with both treatments; however, there were no differences between the two treatments for any symptoms assessed. Of the 55 patients who experienced an adverse event, 41.3 and 27.5% received estradiol transdermal patch and placebo. Most events were mild to moderate. The most frequent primary system organ classes with adverse events were the same with both treatments: infections and infestations reproductive system and breast disorders.
Buster et al.[30] (2008) Transdermal estradiol spray vs placebo	DB, MC, PG, RCT Postmenopausal women with at least eight moderate-to-severe hot flushes per day	N=454 12 weeks	Primary: Mean change from baseline in frequency and severity of moderate-to-severe hot flushes at weeks four and 12 Secondary: Safety	Primary: All three dosing regimen groups (one, two or three sprays daily) of the estradiol group showed a significant decrease in hot flushes at weeks four and 12 compared with their placebo groups (P<0.010). The mean change in frequency at week 12 was eight fewer flushes per day for women in the estrogen groups and between four and six fewer flushes for women in the placebo groups. Women in the three- and two-estrogen spray groups demonstrated significant (P<0.050) reductions in severity score at weeks four and 12; women in the one-spray group showed significant reductions at week five. At week 12, the majority (74 to 85%) of women on estrogen showed at least a 50% hot flush frequency reduction as compared with 46% in the placebo group. The systemic estrogen delivery rates at week 12 were approximately 0.021, 0.029, and 0.040 mg/d for the one-, two-, and three-spray doses, respectively. Secondary: Common adverse events were similar to those previously reported with other transdermal products. Treatment-related application site reaction rate was similar to placebo (1.3 compared to 1.8%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Hodis et al.[31] (2016) ELITE Oral 17β-estradiol (1 mg per day, plus progesterone [45 mg] vaginal gel administered sequentially [i.e., once daily for 10 days of each 30-day cycle] for women with a uterus) vs placebo (plus sequential placebo vaginal gel for women with a uterus)	DB, PC, RCT Healthy postmenopausal women, stratified according to time since menopause (<6 years [early postmenopause] or ≥10 years [late postmenopause])	N=643 Median of 5 years	Primary: Rate of change in carotid-artery intima-media thickness (CIMT) Secondary: Coronary atherosclerosis by cardiac computed tomography (CT)	Primary: After a median 5-year intervention, the effect of hormone therapy on CIMT progression differed between the early and late postmenopause strata (P=0.007 for the interaction). In the early-postmenopause stratum, the rate of CIMT progression was significantly lower in the estradiol group than in the placebo group; the absolute difference between the estradiol and placebo groups in the mean progression rate was −0.0034 mm per year (95% CI, −0.0062 to −0.0008; P=0.008). In the late-postmenopause stratum, the rates of CIMT progression were similar in the estradiol and placebo groups (difference, 0.0012 mm per year; 95% CI, −0.0009 to 0.0032; P=0.29). The effect of hormone therapy on the absolute value of CIMT at five years also differed significantly between the early and late postmenopause strata (P=0.03 for the interaction). Secondary: Although the measures of coronary atherosclerosis were significantly greater among women in the late-postmenopause stratum than among those in the early-postmenopause stratum, the CT measures did not differ significantly between the placebo and estradiol groups within either postmenopause stratum.
Comparative Trials of Estrogens with Same Delivery Route				
Mizunuma et al.[32] (2010) Estradiol 0.5 mg/day vs estradiol 1 mg/day vs placebo	DB, MC, PC, RCT Japanese women 45 to 75 years of age who had experienced natural menopause or undergone bilateral oophorectomy ≥1 year prior to trial enrollment with osteoporosis; patients with an intact uterus had a	N=309 2 years	Primary: Percentage change in lumbar BMD at 52 weeks, serial percentage change in lumbar BMD during 104 weeks Secondary: Change in amenorrhea rate; incidence of endometrial hyperplasia at 52	Primary: A total of 241 patients completed all assessments. Combined data of patients receiving monotherapy and combination therapy revealed that the percentage change in lumbar BMD at 52 weeks was significantly greater with estradiol 1 (P<0.001) and 0.5 mg (P<0.001) compared to placebo. The increase in BMD was nonsignificantly greater with estradiol 1 mg compared to estradiol 0.5 mg (P value not reported). Lumbar BMD did not change with placebo. Mean percentage changes in lumbar BMD continued to increase for 104 weeks, reaching 8.0 and 10.2% at 104 weeks with estradiol 0.5 and 1 mg, respectively. At this point, the difference between estradiol 0.5 and 1 mg was significant (P=0.008). There was a greater percentage change in BMD with estradiol 1 mg compared to estradiol 0.5 mg, both overall and in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Patients originally randomized to placebo were switched to estradiol 1 mg/day after 52 weeks for ethical reasons. Patients with an intact uterus, received estradiol/ levonorgestrel 0.5 mg/40 µg or 1 mg/40 µg daily. All patients received daily calcium and vitamin D supplementation.	diagnostically valid negative endometrial biopsy or, for those from whom no tissue was obtained or tissue was insufficient for diagnosis, an endometrial thickness ≤4 mm on transvaginal ultrasound		and 104 weeks; percentage change in bone turnover markers; changes in calcium, inorganic phosphate, and creatinine levels; fractures	patients receiving combination therapy. In repeated measurement analysis, neither the estradiol dose nor the presence or absence of levonorgestrel had a significant effect (P=0.058 and P=0.192, respectively). The osteoporosis cure rate (percentage of patients with BMD >-2.5 SD of young adult mean) was greater with estradiol 1 mg (44, 50, and 60% of patients at 28, 52, and 104 weeks, respectively) compared to estradiol 0.5 mg (35, 44, and 50%, respectively). Secondary: The amenorrhea rate was greater with estradiol/levonorgestrel 0.5 mg/40 µg compared to estradiol/levonorgestrel 1 mg/40 µg at both 52 and 104 weeks. Levonorgestrel effectively suppressed possible endometrial proliferation due to estradiol administration. Neither endometrial hyperplasia nor cancer was observed at 52 and 104 weeks among patients who received estradiol/levonorgestrel 1 mg/40 µg. There was no clear difference in the incidence rates of atrophic/inactive endometrium between placebo and combination therapy. Endometrial thickness increased slightly over time with combination therapy without clinical significance. Intact osteocalcin, bone alkaline phosphatase, type 1 collagen cross-linked N-telopeptide, and deoxypyridinoline all decreased with estradiol treatment to within the reference range, and changes were consistent with the change in BMD. Bone resorption markers decreased first, followed by bone formation markers. Urine type 1 collagen cross-linked N-telopeptide, urine deoxypyridinoline, and serum bone alkaline phosphatase achieved the minimum significant change. Changes in bone formation markers were greater with estradiol 1 mg compared to estradiol 0.5 mg at 52 and 104 weeks, but this was not significant. There was no difference between active treatments in changes in bone resorption markers. There was no excessive suppression of bone turnover markers with active treatment. Six patients experienced new fractures in the 104 weeks; four patients receiving placebo, one patient receiving estradiol 0.5 mg, and one patient receiving estradiol 1 mg. Levonorgestrel had no effect on the fracture rate.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Good et al.[33] (1996) Transdermal estradiol patch (Alora®) 50 µg/day vs transdermal estradiol patch (Alora®) 100 µg/day vs placebo	DB, DD, PG, RCT Postmenopausal women ≥21 years of age if surgically menopausal or ≥45 years of age if naturally menopausal, amenorrheic for ≥6 months, experiencing ≥60 moderate or severe hot flashes weekly	N=273 12 weeks	Primary: Reduction in the frequency and severity of hot flashes Secondary: Changes in serum concentrations of estradiol, estrone, estrone sulfate, and FSH; improvements in vaginal cytology; global impressions; adverse events	Primary: There was a significant reduction in the frequency of moderate-to-severe hot flashes by week three of treatment with the 50 µg/day dose (P<0.02) and by week two of treatment with the 100 µg/day dose (P<0.001) compared with placebo. At the end of the study, there was a reduction in frequency of moderate-to-severe hot flashes by 86.6% with the 50 µg/day dose and by 92.5% with the 100 µg/day dose. Forty eight percent of the 50 µg/day group and 68% of the 100 µg/day group did not experience any hot flashes by week 12. Secondary: The changes in estradiol, estrone, and estrone sulfate were increased in a dose-dependent manner. Serum FSH levels were reduced in a dose-dependent manner. Both treatment groups showed improvement in vaginal cytology. Both treatment groups reported improvement in vaginal dryness, itching and dyspareunia. Greater improvement was reported with the 100 µg/day group. The median assessment scores showed patients and investigators rated active treatment as good or excellent and placebo treatment as fair. The number of systemic adverse experiences was similar (71.4% of patients on active treatment and 73.6% of patients on placebo).
Bowen et al.[34] (1998) Transdermal estradiol patch (Alora®) 0.1 mg/day	OL, RCT, XO Postmenopausal women between 35 to 65 years of age	N=24 30 days (11 days of treatment with first drug, then 7 days of	Primary: Serum estradiol concentrations; FI defined as $[C_{max} - C_{min}]/C_{av}$ Secondary:	Primary: Peak estradiol levels were similar (127.1 for Alora® vs 128.6 for Estraderm®; P=0.5228). However, Alora® had fewer fluctuations in steady-state levels. Alora® had an FI of 0.970±0.226, while Estraderm® had an FI of 1.684±0.452 (P=0.0001). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs transdermal estradiol patch (Estraderm®) 0.1 mg/day		washout interval, then crossover to second drug for 11 days of treatment)	Monitoring metabolism of estradiol to estrone and estrone sulphate, local skin tolerability defined as application site reactions such as erythema and pruritus	The peak estrone levels (47.7 vs 36.4) and estrone sulphate levels (1,383.7 vs 1,085.9) were higher with Alora® than Estraderm®. There were fewer fluctuations in steady-state levels of estrone (FI of 0.955±0.338 vs 1.351±0.467) and estrone sulphate (FI of 1.031±0.386 vs 1.483±0.366) with Alora® than Estraderm®. The incidences of erythema (45.8 vs 25%) and pruritus (45.8 vs 29%) were higher in the Estraderm® group than in the Alora® group. There were no severe adverse events reported for either treatment.
Ibarra de Palacios et al.[35] (2002) Transdermal estradiol patch (Estradot®*) 50 µg/day vs transdermal estradiol patch (Climara®) 50 µg/day	OL, RCT Healthy postmenopausal women	N=100 7 days	Primary: Skin irritation and adhesion, estradiol delivery Secondary: Not reported	Primary: The Estradot® group had lower erythema scores and lower incidences of very slight erythema (P=0.0028) than the Climara® group. There was more adherence and fewer incidences of detachment with the Estradot® than with Climara® (not statistically significant). Both transdermal patches had similar delivery of estradiol. Secondary: Not reported
Archer et al.[36] (1994) CEE 0.625 mg once daily plus MPA 2.5 mg (Group A) or 5 mg (Group B) once daily vs	DB, MC, RCT Postmenopausal women	N=1,724 1 year	Primary: Bleeding patterns Secondary: Not reported	Primary: Amenorrhea occurred in 40% of the patients in Group A, 50% of the patients in Group B, 5% of the patients in Group C or D, and 50% of the patients in Group E. Regular withdrawal bleeding or spotting occurred in 81.3% of Group C and 77.0% of Group D. There was no bleeding or spotting in 75.5% of Group E. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
CEE 0.625 mg once daily plus MPA 5 mg (Group C) or 10 mg (Group D) once daily on the last 14 days of each 28 day cycle vs placebo once daily (Group E)				
Archer et al.[37] (1999) Transdermal estradiol 50 µg/day (Vivelle®) vs transdermal estradiol 50 µg plus norethindrone acetate 140, 250, or 400 µg/day (Combipatch®)	DB, MC, RCT Postmenopausal women, 40 to 70 years of age, with an intact uterus	N=625 1 year	Primary: Incidences of endometrial hyperplasia, bleeding and/or spotting, vasomotor events Secondary: Not reported	Primary: There were significantly fewer cases of endometrial hyperplasia in the estradiol/norethindrone acetate group than in the estradiol group (P<0.001). There was a longer mean duration of irregular bleeding or spotting in the estradiol group compared to the estradiol/norethindrone acetate group. There was a higher incidence of no uterine bleeding in the estradiol/norethindrone acetate group than in the estradiol group. Similar reductions in mean number of hot flashes and intensity of sweating were observed with all treatment groups. Secondary: Not reported
Harrison et al.[38] (2002) Transdermal estradiol patch (generic) 0.1 mg/24 hours once weekly, applied to buttocks	OL, RCT, XO Postmenopausal women, 45 to 70 years of age	N=42 7 days	Primary: Estradiol, estrone, and estrone sulfate levels, application site irritation, patch adhesion Secondary: Not reported	Primary: The C_{max} levels for the two treatments were outside the interval of 0.80 and 1.25, suggesting non-bioequivalence when the patches are applied to the buttocks. Treatment with the generic estradiol patch vs Climara® resulted in more application site reactions (19.5 vs 2.4%) and skin irritations (three incidences of moderate erythema with generic patch vs 1 incidence of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs transdermal estradiol patch (Climara®) 0.1 mg/24 hours once weekly, applied to buttocks				intense erythema with Climara®; P=0.039). Both patches resulted in a score of 0 or no visible reaction by day 5 of treatment. Higher incidences of detachment (3 vs 1) and patch lifting (22 vs 6) were reported with the generic patch vs Climara®. Thus, the OR for detachment or lifting of the patch was 6.95 (P<0.001) for the generic estradiol patch compared to Climara®. Secondary: Not reported
Pornel et al.[39] (1995) Transdermal estradiol patch (Menorest®†) 50 µg/24 hours twice weekly vs transdermal estradiol patch (Estraderm®) 50 µg /24 hours twice weekly	MC, OL, PG, RCT Postmenopausal women with moderate-to-severe vasomotor symptoms, 39 to 64 years of age	N=205 12 weeks	Primary: Mean number of hot flashes per day, severity of menopausal symptoms, erythema and pruritus at application sites Secondary: Not reported	Primary: Both treatments resulted in significant improvement in number of hot flashes per day at week 12 (P=0.005). There was no statistically significant difference in mean number of hot flashes between treatment groups at week 12. Both treatments showed improvement in the severity of sweats, sleep disturbances, urogenital symptoms, and depression. There were less topical adverse events, such as erythema and pruritus, in the Menorest® group compared with the Estraderm® group, which did not reach statistical significance (P=0.15). Secondary: Not reported
Toole et al.[40] (2002) Transdermal estradiol patch (Estradot®*) 50 µg/24 hours vs	OL, RCT Healthy postmenopausal women, 40 to 70 years of age	N=208 5 weeks	Primary: Skin irritation as measured by erythema Secondary: Skin reaction, patch adherence, adhesive residue and sensitization	Primary: There was significantly less skin irritation with Estradot® than Menorest® (P=0.0001). Secondary: There were more skin reactions with Menorest® than Estradot® (2.40 vs 0.48%). There was a higher number of patches that detached in the Menorest® group compared to Estradot® group (P=0.0253).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
transdermal estradiol patch (Menorest®†) 50 µg/24 hours				There was a significantly higher percentage of patients with residue in the Menorest® than Estradot® group (10.10 vs 1.92%; P<0.0001). There were no differences between groups in sensitization.
Erianne et al.[41] (1997) Menorest®† matrix (without drug) twice weekly vs Estraderm® matrix (without drug) twice weekly	MC, OL Normal healthy females over 40 years of age	N=275 21 days	Primary: Skin irritation, pruritus (by direct questioning), and adhesion Secondary: Not reported	Primary: There were fewer incidences of skin irritation with Estraderm® compared with Menorest® (11.9 vs 15.9% on the buttocks and 13.7 vs 18.6% on the abdomen). There were fewer incidences of pruritus with Estraderm® compared with Menorest® (92.5 vs 95.9% on the buttocks and 88.7 vs 96.3% on the abdomen). There were similar percentages of patches that were fully adhered to the buttocks application sites during treatment for both groups. There were more patches fully adhered to the abdomen application sites with the Menorest® group compared to the Estraderm® group (88.7 vs 75.8%). Secondary: Not reported
Andersson et al.[42] (2000) Transdermal estradiol patch (Menorest®†) 50 µg/24 hours twice weekly vs transdermal estradiol (Climara®) 50 µg/24 hours once weekly	OL, RCT, XO Healthy postmenopausal women	N=20 8 weeks	Primary: Bioavailability, pharmacokinetics, tolerability Secondary: Not reported	Primary: There were no differences between the groups in AUC, C_{max}, C_{min}, average concentrations, or fluctuations. There were three cases of erythema with Menorest® and 21 cases of skin reactions in 15 subjects treated with Climara®. There were eight systemic adverse events in 8 subjects treated with Menorest® and 13 systemic adverse events in 10 subjects treated with Climara®. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Suckling et al.[43] (2006) Intravaginal estrogens (creams, tablets, pessaries, and an estradiol-releasing ring)	MA Postmenopausal women with vaginitis or vaginal atrophy	N=4,162 (19 trials) ≥3 months	Primary: Efficacy (improvement in vaginal atrophy measured both objectively and subjectively), safety (assessment of endometrial stimulations, breast pain) and acceptability (measures of withdrawal, adherence, acceptability of treatment to women) Secondary: Not reported	Primary: The estradiol ring showed an improvement of pruritus (two RCTs: OR, 2.71; 95% CI, 1.66 to 4.43) when compared to estrogen cream. In the ring versus tablets trials, there were significant improvements in the tablet group for vaginal dryness (two RCTs: OR, 0.40; 95% CI, 0.24 to 0.64), dyspareunia (two RCTs: OR, 0.53; 95% CI, 0.36 to 0.78), and frequency (two RCTs: OR, 0.63; 95% CI, 0.41 to 0.95). Compared to the cream group, the tablet group showed an improvement for vaginal dryness (one RCT: OR, 7.00; 95% CI, 1.64 to 29.85). The estradiol ring versus placebo ring showed an improvement for freedom of symptoms of dyspareunia (one RCT: OR, 12.67; 95% CI, 3.23 to 49.67). The estrogen tablets versus placebo showed an improvement for burning and itching symptoms (two RCTs: OR, 0.15; 95% CI, 0.10 to 0.20) and dyspareunia (two RCTs: OR, 0.17; 95% CI, 0.12 to 0.23). An improvement in vaginal dryness was seen in the vaginal tablet group when compared to placebo (three RCTs: OR, 0.08; 95% CI, 0.06 to 0.10). There were no significant differences between groups (estradiol ring versus estrogen cream, estradiol ring versus estrogen tablets, estriol tablets versus placebo) for the following outcomes: dysuria, nocturia, urgency, urge incontinence, participant symptom improvement in dryness, urge incontinence, soreness and irritation, loss of sexual desire and vaginitis. Significant findings for the relief of vaginal atrophy favored the cream, ring, and tablets when compared to placebo. One trial showed significant adverse effects (including uterine bleeding, breast pain and perineal pain) of CEE cream compared to estradiol tablets (OR, 0.18; 95% CI, 0.07 to 0.50). Two trials showed endometrial overstimulation with CEE cream compared to the ring (OR, 0.29; 95% CI, 0.11 to 0.78). Secondary: Not reported
Comparative Trials of Estrogens with Different Delivery Routes				
Yang et al.[44]	PRO	N=82	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2007) Oestrogel® gel (1.25 g daily; 2.5 g daily; 5.0 g daily) vs control (Estriol [Ovestin®] 2 mg/day) All women received calcium carbonate, 500 mg/day of elemental calcium.	Postmenopausal women	1 year	BMD evaluated by 1 QCT at baseline (before treatment), then at six-month intervals Secondary: Not reported	At 12-month posttreatment of Oestrogel® versus estriol 2 mg/day, Oestrogel® showed the following BMD changes at the respected doses: 1.25 g/day showed BMD change of 4.82%; P=0.017; 2.5 g/day BMD change of 2.72%; P=0.226; and 5.0 g/day BMD change of 8.69%; P=0.051). At 6 months, all Oestrogel® groups showed significant increases in lumbar spine BMD after treatment (P<0.05), except for the Oestrogel® gel 1.25 g/day group (P=0.232). Secondary: Not reported
Polvani et al.[45] (1991) Oral CEE, dose not specified vs transdermal estradiol, dose not specified	MC, RCT Postmenopausal women	N=460 6 months	Primary: Menopausal symptoms, bleeding Secondary: Not reported	Primary: There were similar improvements in menopausal symptoms and similar effects on the endometrium with both treatments. The quality and duration of bleeding were considered more physiological in the transdermal group than in the oral group. The transdermal estradiol group showed better compliance and fewer dropouts. Secondary: Not reported
Cortellaro et al.[46] (1991) Transdermal estradiol 0.05 mg/day vs	OL, RCT Postmenopausal women	N=45 4 months	Primary: Menopausal symptoms, lipid profile, serum estradiol levels Secondary: Not reported	Primary: Both treatments provided similar relief in postmenopausal symptoms. Both treatments resulted in similar reductions in serum TC and LDL-C. There was a significant decrease in serum TG levels with the transdermal estradiol treatment only. There were no differences between treatment groups in plasma calcium and phosphorus levels or clotting factors.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
CEE 0.625 mg orally once daily Both groups in combination with MPA 10 mg once daily on the last 8 days of each cycle				Only transdermal estradiol resulted in early follicular-phase plasma estradiol levels. Secondary: Not reported
Pattison et al.[47] (1989) Transdermal estradiol patch 50 µg/24 hours vs ethinyl estradiol 20 µg orally once daily	DB, XO Postmenopausal women	N=25 Duration not specified	Primary: Menopausal symptoms, vaginal cytology, gonadotropin levels, urinary calcium levels, menstrual pattern, hepatic proteins Secondary: Not reported	Primary: Both treatments improved menopausal symptoms and vaginal cytology. Both treatments lowered gonadotrophin levels and urinary calcium loss. Transdermal estradiol did not have an effect on hepatic function, while oral ethinyl estradiol had adverse effects on hepatic proteins (sex-hormone-binding globulin, plasma renin substrate, and lipoproteins). Secondary: Not reported
Hirvonen et al.[48] (1987) Estradiol plus MPA, dose not specified vs estradiol plus levonorgestrel, dose not specified vs estradiol valerate 2 mg daily	DB, XO Postmenopausal women	N=36 Duration not specified	Primary: Menopausal symptoms, lipid profile, bleeding episodes Secondary: Not reported	Primary: There were no differences in relief of menopausal symptoms between treatment groups. Women on the estradiol/MPA treatment significantly improved the atherogenic index, which is the LDL-C:HDL-C. Women on the estradiol/levonorgestrel treatment showed deterioration in the atherogenic index. There was more withdrawal bleeding in the estrogen plus progestin group than in the unopposed estrogen group (78 vs 22%). Secondary: Not reported
Place et al.[49]	DB, MC, PG, RCT	N=124	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(1985) Oral CEE (Premarin®) 0.625 mg or 1.25 mg once daily vs transdermal 17β-estradiol (Estraderm®) 0.1 mg/day	Postmenopausal women whose symptoms were satisfactorily controlled with CEE	Duration not specified	Menopausal symptoms, adverse effects Secondary: Not reported	There were no significant differences between the treatment groups in hot flashes, other postmenopausal symptoms such as sweating, insomnia, headache, vaginal symptoms, urinary urgency, global assessment scores or estrogen-related side effects. There were minor topical reactions reported with the transdermal estradiol for about 20% of the study period. Secondary: Not reported
Al-Azzawi et al.[50] (2003) Estradiol acetate vaginal ring (Menoring®‡) that releases 50 µg/day of estradiol plus placebo oral tablet once daily vs oral estradiol 1 mg once daily plus placebo vaginal ring	DB, MC, PG, PRO, RCT Healthy postmenopausal women, <65 years, with moderate-to-severe vasomotor symptoms (defined as ≥20 hot flashes/night sweats per week)	N=159 24 weeks	Primary: Hot flashes, night sweats, urogenital symptoms, adverse events Secondary: Not reported	Primary: Both treatments resulted in significant improvement in hot flashes and night sweats at 12 and 24 weeks from baseline. Reduction in urogenital symptoms was seen with both treatments. Both groups reported similar incidences of adverse events, including local effects. Secondary: Not reported
Nachtigall.[51] (1995) Estradiol vaginal ring that releases 7.5 µg/24 hours of estradiol	MC, OL, PG, RCT Postmenopausal women with estrogen-deficiency-derived atrophic vaginitis	N=196 15 weeks	Primary: Urogenital atrophy/ symptoms, physicians' and patients' assessment of symptoms	Primary: The vaginal ring and creams produced similar improvements in vaginal dryness, vaginal burning, dyspareunia, and vaginal pH. Physicians' and patients' assessment of both treatments were similar. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs conjugated estrogen vaginal cream, 2 g three times a week			Secondary: Frequency of endometrial over stimulation as determined by progestogen challenge test after treatment period	More patients treated with the cream demonstrated signs of endometrial proliferation or hyperplasia than with the ring (10 vs 5%). There were more episodes of bleeding with the progestogen challenge test in the vaginal cream group than the vaginal ring group.
Hilditch et al.[52] (1996) Oral CEE (Premarin®) 0.625 mg once daily vs transdermal estradiol-17β (Estraderm®) 50 µg twice weekly Both groups in combination with oral MPA (Provera®) 10 mg once daily for the last 12 days of each cycle	DB, RCT Women 2 to 7 years after menopause, with intact uterus and ovaries, not currently on hormone therapy, and on average severely symptomatic	N=74 112 days (four 28-day cycles)	Primary: QOL, determined using the Menopause-Specific QOL Questionnaire Secondary: Not reported	Primary: There were significant improvements in QOL scores, but no differences between treatment groups were observed in scores for vasomotor, physical, psychosocial, or sexual domains (P>0.05). There was a significant improvement from baseline to 10 weeks in scores for vasomotor and physical domains (P<0.001), while changes from 10 weeks to 14 weeks were not statistically significant. There was significant improvement from baseline to six weeks in scores for psychosocial and sexual domains (P<0.01), while changes from six weeks to the end of study were not statistically significant. Secondary: Not reported
Blanc et al.[53] (1998) Percutaneous 17β-estradiol gel 1.5 mg/day (Group A)	MC, OL, PRO, RCT Postmenopausal women, mean, 54.9±0.6 years of age	N=54 168 days (six 28-day cycles)	Primary: Rate of amenorrhea Secondary: Climacteric symptoms	Primary: The amenorrhea rates after one month of treatment were 67 to 83% for Group A, 25 to 56% for Group B, and 53 to 61% for Group C, which were significantly different between groups for the fourth (P=0.008) and fifth (P=0.003) treatment cycles.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs transdermal 17β-estradiol patch 50 µg/day (Group B) vs oral estradiol valerate 2 mg once daily (Group C) All groups in combination with a progestin, nomegestrol acetate 2.5 mg once daily				The overall rate of cycles with no bleeding was 78% for Group A, 48% for Group B, and 60% for Group C (P=0.001). Secondary: There were no significant differences between groups in relief of climacteric symptoms by the end of the third cycle.
Polatti et al.[54] (2000) Oral estradiol valerate 2 mg once daily for 21 days plus cyproterone acetate 1 mg once daily for 21 days of each 28-day cycle vs transdermal estradiol 50 µg for 21 days plus MPA 10 mg orally once daily for 10 days of each 28-day cycle	PRO, RCT Postmenopausal women with and without uterine myomas	N=240 2 years	Primary: Risk of uterine myoma onset or progression Secondary: Not reported	Primary: Among the patients without uterine myomas at baseline, 5% of the transdermal estradiol/MPA group developed new onset of myomas while no new cases of uterine myomas were reported in the oral estradiol valerate/cyproterone acetate group (P<0.01). Among the patients with uterine myomas at baseline, treatment with transdermal estradiol/MPA resulted in a mean increase in myoma volumes of 25.3% compared with initial volume of myoma (P<0.01). On the contrary, treatment with oral estradiol valerate/cyproterone acetate resulted in no significant changes in myoma volumes. Secondary: Not reported
Jarvinen et al.[55]	OL, RCT, XO	N=24	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2001) Transdermal estradiol patch (Evorel®‡) 50 µg/24 hours vs transdermal estradiol gel (Divigel®) 1.0 mg	Healthy postmenopausal women	18 days	Estradiol levels Secondary: Not reported	There were no significant differences in peak estradiol levels (C_{max}) or area under the time-concentration curve (AUC) between groups. Estradiol levels fluctuated more with the patch. The total coefficient of variability for AUC was 39% for the patch versus 35% for the gel. Secondary: Not reported
Nelson et al.[56] (2004) Oral CEE vs oral 17β-estradiol vs transdermal 17β-estradiol	MA Postmenopausal women with hot flashes	N=32 trials Duration varied	Primary: Efficacy as measured by relief of hot flashes, adverse effects Secondary: Not reported	Primary: The numbers of hot flashes per week were significantly reduced with all forms of estrogen compared with placebo. Treatment with oral CEE resulted in a mean change in the number of hot flashes per week of -19.1 (95% CI, -33.0 to -5.1). Treatment with oral 17β-estradiol group resulted in a mean change of -16.8 (95% CI, -23.4 to -10.2). Treatment with transdermal 17β-estradiol group resulted in a mean change of -22.4 (95% CI, -35.9 to -10.4). There was no significant difference between the agents in treatment of menopausal hot flashes. The estrogen agents showed similar short-term adverse effects. Breast tenderness and atypical vaginal bleeding were the most frequently reported adverse effects. Secondary: Not reported
Studd et al.[57] (1995) Transdermal estradiol patch (Menorest®†) 50 µg/24 hours twice weekly plus dydrogesterone 20	DB, DD, MC, PG, RCT Postmenopausal women 40 to 65 years of age, with moderate-to-severe vasomotor symptoms (defined	N=214 12 weeks	Primary: Number of hot flashes per day Secondary: Other menopausal symptoms, severity of hot flashes,	Primary: The number of daily hot flashes decreased significantly in both treatment groups compared with baseline (7.14 to 0.92 in the Menorest® group and 6.66 to 0.54 in the Premarin® group). No statistically significant difference was observed between the two treatment groups at 12 weeks (P=0.36). Secondary: Menopausal symptoms significantly improved in both treatment groups, with 98% of the patients reporting no severe vasomotor symptoms at 12

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg for 12 days of every 28-day cycle vs CEE (Premarin®) 0.625 mg orally once daily plus dydrogesterone 20 mg for 12 days of every 28-day cycle	as ≥21 hot flashes per week)		global assessment, and hormone levels	weeks. There was no statistically significant difference in menopausal symptoms improvements between the groups. There was no statistically significant difference in global assessment scores between groups as reported by the investigator (P=0.63) or the patient (P=0.71). There was no significant difference between the groups in mean plasma estradiol (P=0.37) or estrone (P=0.56) levels at posttreatment. The mean estradiol to estrone ratio was similar in both groups (0.72 for Menorest® and 0.70 for Premarin®). The number of severe adverse events was similar in both groups (7% for Menorest® and 9% for Premarin®).
Good et al.[58] (1999) Transdermal estradiol patch (Alora®) 0.05 mg/day administered twice weekly vs transdermal estradiol patch (Alora®) 0.1 mg/day administered twice weekly vs CEE 0.625 mg once daily	DB, DD, PG, RCT Highly symptomatic postmenopausal women	N=321 12 weeks	Primary: Frequency and severity of hot flashes Secondary: Not reported	Primary: There were no significant differences in the frequency of hot flashes or the frequency of moderate-to-severe hot flashes between the Alora® 0.05 mg/day and CEE 0.625 mg groups or Alora® 0.1 mg/day and CEE 1.25 mg groups at week 12. There were no significant differences in vaginal cytology, breast tenderness, and unexpected vaginal bleeding between the transdermal and oral estrogen groups. However, there was a lower incidence of bleeding in the Alora® 0.05 mg/day group. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs CEE 1.25 mg once daily				
Chetkowski et al.[59] (1986) Transdermal estradiol 25, 50, 100, or 200 µg per 24 hours vs oral conjugated estrogens 0.625 or 1.25 mg once daily	Dose-response study Postmenopausal women	N=23 Duration not specified	Primary: Levels of estradiol and estrone, renin substrate, SHBG, TBG, CBG, lipoproteins Secondary: Not reported	Primary: Transdermal estradiol increased levels of circulating estradiol and estrone, while oral estrogens increased levels of estrone. There were significant increases in circulating levels of renin substrate, SHBG, TBG, and CBG with the oral estrogens, but there was no effect with transdermal estradiol. The oral estrogens at higher doses showed significant improvement in the concentrations of LDL-C and HDL-C, while transdermal estradiol did not. Secondary: Not reported
Manonai et al.[60] (2001) Estradiol vaginal tablet 25 µg vs conjugated estrogen cream 1 g	RCT Postmenopausal women	N=53 12 weeks	Primary: Urogenital symptoms, vaginal health index, vaginal cytology, endometrial thickness, estradiol level Secondary: Not reported	Primary: There was improvement from baseline to four weeks of treatment with both groups in urogenital symptoms, vaginal health index, and vaginal cytology. There were significant improvements in vaginal dryness and dyspareunia with the conjugated estrogen cream compared to vaginal tablet. Secondary: Not reported
Slater et al.[61] (2001) Oral micronized estradiol 1 mg daily for 16 months vs	RETRO Healthy postmenopausal women	N=33 9 to 16 months	Primary: Serum estrone sulfate levels Secondary: Not reported	Primary: There were higher levels of serum estrone sulfate after long-term treatment with oral estradiol than transdermal estradiol. The serum estrone sulfate levels were 38.8 ng/mL at 15 months for oral estradiol, 1.8 ng/mL at nine months for transdermal estradiol 0.05 mg/day, and 3.2 ng/mL at nine months for transdermal estradiol 0.1 mg/day. The increase in serum estrone sulfate level was only significant in the oral estradiol group when compared to baseline ($P<0.01$).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
transdermal estradiol patch 0.05 mg/day or 0.1 mg/day, changed twice weekly for 9 months vs placebo for 9 months				Secondary: Not reported
Pornel[62] (1996) Transdermal estradiol patch (Menorest®†) 50 µg/24 hours vs CEE (Premarin®) 0.625 mg/day (Study 1) or transdermal estradiol patch (Estraderm®) 50 µg/24 hours (Study 2)	DB, PG, RCT (Study 1); OL, PG (Study 2) Postmenopausal women	N=214 (Study 1) N=205 (Study 2) Duration not specified	Primary: Hot flashes and other menopausal symptoms, serum estradiol, lipid profile, adverse events Secondary: Not reported	Primary: There were improvements in menopausal symptoms with all treatment groups. There were no significant differences in serum estradiol levels or systemic adverse events between treatment groups. There were small reductions in cholesterol in both studies. Menorest® was better tolerated and had a lower incidence of erythema, and pruritus. Secondary: Not reported
Ayton et al.[63] (1996) Estradiol vaginal ring (Estring®) vs	MC, OL, PG, RCT Postmenopausal women with symptoms and signs of urogenital atrophy	N=194 12 weeks	Primary: Urogenital symptoms Secondary: Patient preference	Primary: No significant difference was noted between treatment groups in improvement of vaginal dryness and dyspareunia, resolution of atrophic signs, vaginal mucosal maturation indices, and vaginal pH. No significant difference was noted between treatment groups in incidences of intercurrent bleeding episodes.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
CEE vaginal cream (Premarin®), 1 g (0.625 mg of CEE)				Secondary: The vaginal ring was significantly preferred and accepted by more patients than the vaginal cream (P<0.0001).
Studd et al.[64] (1996) Transdermal estradiol patch (Menorest®†) 50 µg/24 hours twice weekly vs CEE (Premarin®) 0.625 mg orally once daily Both groups in combination with dydrogesterone 20 mg orally for the last 12 days of each 28 day cycle	RCT Postmenopausal women	N=32 1 year	Primary: Menopausal symptoms, bone loss prevention as measured by bone mineral density Secondary: Not reported	Primary: Both treatments resulted in similar relief of menopausal symptoms (vasomotor, psychological, and urogenital symptoms) and reduction of hot flashes. Both treatments resulted in similar lumbar spine and hip densitometry results. Both treatments resulted in similar incidences of adverse events. Secondary: Not reported
Gordon et al.[65] (1995) Study 1: Estradiol patch 0.05 or 0.1 mg/day changed once weekly vs placebo	RCT Healthy postmenopausal women with hot flashes	N=24 18 days	Primary: Frequency and severity of hot flashes, subjects' and investigators' global assessment of treatment Secondary: Not reported	Primary: There were significant improvements from baseline in frequency and severity of hot flashes and higher global assessment scores with all treatments in both studies. In Study 2, there was more improvement that did not reach statistical significance in hot flashes with the estradiol patch 0.1 mg/day than with CEE and less improvement with estradiol patch 0.05 mg/day than with CEE. The patches were generally well tolerated. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Study 2: Estradiol patch 0.05 or 0.1 mg/day changed once weekly vs CEE 0.625 mg orally once daily				Not reported
Shifren et al.[66] (2008) CEE 0.625 mg/day plus micronized progesterone 100 mg/day for 12 weeks vs transdermal estradiol 0.05 mg/day plus micronized progesterone 100 mg/day for 12 weeks	OL, XO Naturally menopausal women	N=27 24 weeks	Primary: CRP, IL-6, E- and P-selectin, ICAM-1 and vascular cell adhesion molecule-1, serum amyloid A, transferrin, prealbumin, IGF-I, SHBG, TBG, CBG Secondary: Not reported	Primary: Nine parameters changed significantly during oral CEE: CRP (192%; P<0.001); E-selectin (-16.3%; P=0.003); P-selectin (-15.3%; P=0.012); ICAM-1 (-5%; P=0.015); transferrin (5.3%; P=0.024); IGF-I (-30.5%; P<0.001); SHBG (113%; P<0.001); TBG (38%; P<0.001); and CBG (20%; P<0.001). With transdermal estradiol, only three parameters changed significantly and to a lesser degree: ICAM-1 (-2.1%; P=0.04); IGF-I (-12.5%; P<0.001); and SHBG (2.6%; P=0.042). During oral CEE the intrasubject changes in CRP correlated strongly with the changes in serum amyloid A (r=0.805; P<0.001), and were only weakly associated with the changes in SHBG (r=0.248; non-significant), TBG (0.430; P=0.031), and CBG (r=0.072; non-significant). The log-log relationship between CRP and IL-6 observed at baseline showed a parallel shift during oral CEE, suggesting an amplified hepatic response or a greater sensitivity to IL-6 stimulation. Secondary: Not reported
Santoro et al.[67] (2017) Oral CEE 0.45 mg daily	DB, MC, RCT Women, aged 42 to 58, within three	N=727 48 months	Primary: The proportion of women who were symptomatic (reported	Primary: At screening, 86% of all participants reported at least mild hot flashes, while moderate-severe hot flashes were reported by 44%. By six months post-randomization, moderate-severe hot flashes had decreased to 28.3% of women randomized to placebo, 7.4% of women randomized to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs transdermal estradiol 50 mcg daily vs placebo both with oral micronized progesterone 200 mg daily for 12 days each month	years of their final menstrual period		moderate/severe symptoms) at each follow-up visit Secondary: Differences in treatment effect by race/ethnicity and body mass index	transdermal estradiol and 4.2% of women randomized to oral CEE (P<0.001 for each active treatment vs placebo). Night sweats were reported by 68% of women at screening, with 35% being moderate-severe. At six months, moderate-severe night sweats declined to 19% with placebo, 5.3% with transdermal and 4.7% with oral CEE (P<0.0001 for each active treatment vs placebo). This initial magnitude of symptom reduction was maintained throughout the study in all treatment groups. At baseline, the proportion of women reporting insomnia did not differ between treatment groups (placebo 34%, oral CEE 29%, and transdermal 35%, P=0.3). Insomnia decreased substantially and comparably by six months in all groups and this decrease was maintained throughout the trial. At 36 and 48 months, oral CEE was significantly more effective in reducing insomnia vs placebo (P=0.002 and 0.05), and at 48 months transdermal estradiol was more effective than placebo (P=0.004). Baseline reports of irritability were similar between treatment groups (placebo 15%, oral CEE 17%, and transdermal estradiol 19%, P=0.6) and decreased comparably by about half in all groups at six months, to 7.5%, 6.9% and 5.8%, respectively, and did not differ between treatment groups at any time point. Secondary: For each symptom, the relationship of race/ethnicity and BMI to treatment effect was calculated. Due to small numbers of women for some of the time points, a fully-interacted model could not be constructed for night sweats or irritability. The effects of oral CEE as well as transdermal estradiol vs placebo on hot flashes and insomnia showed no significant interaction by BMI or race/ethnicity.
Vrablik et al.[68] (2008) Oral 17β-estradiol for 12 weeks vs	OL, XO Hysterectomized women	N=41 24 weeks	Primary: Plasma lipid and lipoprotein levels, AIP Secondary: Not reported	Primary: Oral estrogen replacement therapy resulted in a significant increase in HDL-C and apolipoprotein A-I levels, whereas it significantly decreased TC and LDL-C and increased TG concentrations. Transdermal estrogen replacement therapy had no such effect. Oral estrogen replacement therapy led to a significant TG enrichment of HDL-C (0.19±0.06 vs 0.27±0.07 mmol/L, P<0.001) and LDL particles (0.23±0.08 vs 0.26±0.10 mmol/L, P<0.001) compared with baseline,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
transdermal 17β-estradiol for 12 weeks				whereas transdermal therapy did not have any effect on lipoprotein subclasses composition. The difference between the two treatments was statistically significant for HDL-C:TG and LDL-C:TG (0.27±0.07 vs 0.19±0.05 mmol/L, P<0.001 and 0.26±0.10 vs 0.22±0.07 mmol/L, P<0.001, respectively). The transdermal but not oral estrogen replacement therapy significantly reduced the AIP compared with baseline (-0.17±0.26 vs -0.23±0.25; P=0.023), making the difference between the therapies statistically significant (-0.23±0.25 vs -0.18±0.22; P=0.017). Oral administration of estrogen replacement therapy resulted in TG enrichment of LDL and HDL particles. Transdermal estrogen replacement therapy did not change the composition of the lipoproteins and produced a significant improvement of AIP. Compared with transdermal estrogen replacement therapy, orally administered estrogen replacement therapy changes negatively the composition of plasma lipoproteins. Secondary: Not reported
Gupta et al.[69] (2008) Transdermal estradiol patch vs vaginal estradiol ring	RCT Postmenopausal women	N=24 12 weeks	Primary: Serum estradiol, estrone, estrone sulfate, FSH, luteinizing hormone, and SHBG were measured by immunoassay at baseline and six and 12 weeks Secondary: Not reported	Primary: The estradiol patch significantly increased serum estrone and estradiol levels at six and 12 weeks (P<0.01); there was no significant increase in serum estrone and estradiol levels with the estradiol ring. Both the patch and the ring significantly reduced vaginal pH at six (P<0.001) and 12 (P<0.001) weeks and significantly reduced the percentage of vaginal parabasal cells at 12 weeks with no significant difference between the two groups. Both preparations increased the proportion of superficial cells; the increase was significant only with the estradiol patch (P=0.04). Secondary: Not reported
Lethaby et al.[70]	MA (30 RCTs)	N=6,235	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2016) Intravaginal estrogen preparations (ring, tablets, cream) .	Postmenopausal women	≥12 weeks	Efficacy (improvement in symptoms) and safety (endometrial thickness) Secondary: Improvement in symptoms (clinician-assessed), other adverse events (breast disorders e.g., breast pain, enlargement or engorgement, total adverse events, excluding breast disorders) and adherence to treatment	There was no evidence of a difference in the proportions of women who reported improvement in symptoms of vaginal atrophy between the following treatment comparisons: estrogen ring and estrogen cream, estrogen ring and estrogen tablets, estrogen tablets and estrogen cream, estrogen cream and isoflavone gel. However, a higher proportion of women reported improvement in symptoms in the following active treatments compared with placebo: estrogen ring vs placebo, estrogen tablets vs placebo, and estrogen cream vs placebo. In the case of estrogen tablets vs placebo and using a random-effect model for analysis of the data because of substantial heterogeneity, there was no longer evidence of a difference in effect on improvement in symptoms. With respect to safety, a higher proportion of women who received estrogen cream showed evidence of increase in endometrial thickness compared to those who were treated with estrogen ring, which may have been due to the higher doses of cream used. However, there was no evidence of a difference in the proportions of women with increase in thickness of the lining of the womb between estrogen tablets and estrogen cream. Secondary: From the overall body of the findings, there was no conclusive evidence of a difference in efficacy between the various estrogenic preparations compared with each other. For safety, there was no conclusive evidence of a difference in the main adverse events (endometrial thickness, breast disorders and total adverse events) between estrogenic preparations vs each other or placebo.
Trials of Combination Estrogen Products				
Hulley et al.[71] (1998) CEE 0.625 mg plus MPA 2.5 mg, in one tablet, once daily vs	DB, MC, PC, RCT Postmenopausal women with established coronary disease, younger than 80 years of age (mean age was 66.7	N=2,763 4.1 years (average follow-up duration)	Primary: Occurrence of nonfatal MI or CHD death Secondary: Coronary revascularization, unstable angina,	Primary: There were no significant differences between groups in occurrences of MI or CHD death (HR, 0.99; 95% CI, 0.80 to 1.22). There were more CHD events in the hormone-treated group compared with placebo in the first year of treatment and fewer events in years four and five. The HR was 1.52 in year one, 1.00 in year two, 0.87 in year three, and 0.67 in years four and five (P=0.009).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo	years), with an intact uterus		CHF, cardiac arrest, stroke or transient ischemic attack, peripheral arterial disease, all-cause mortality, fractures, cancers, thromboembolic events, gallbladder disease	Secondary: There were no significant differences between groups in the rates of fractures (P=0.59 to 0.82), cancers (P=0.33 to 0.60), and total mortality (P=0.56). There were more of the following outcomes in the hormone group compared with the placebo group: venous thromboembolic events (P=0.002), deep vein thromboses (P=0.004), pulmonary emboli (P=0.08), and gallbladder diseases (P=0.05).
Hulley et al.[72] (2002) HERS and HERSII CEE 0.625 mg once daily plus MPA 2.5 mg once daily vs placebo	DB, PC, RCT followed by OL, OS Postmenopausal women with coronary disease and average of 67 years of age at enrollment in study	N=2,321 4.1 years (HERS) followed by 2.7 years of open-label observational study (HERS II)	Primary: Thromboembolic events, biliary tract surgery, cancer, fracture, total mortality Secondary: Not reported	Primary: The percentages of patients that reported >80% adherence to hormone therapy were 81, 78, 74, 67, 50, and 45% for years one through six, respectively. Hormone therapy was associated with a significant increase in the incidence of deep vein thrombosis compared with placebo (4.5 events per 1,000 person-years vs 2.2; P=0.02). Hormone therapy was associated with a significant increase in the incidence of PE compared with placebo (2.0 events per 1,000 person-years vs 0.7; P=0.03). The incidence of biliary tract surgery was significantly increased with hormone therapy compared with placebo (19.1 events per 1,000 person-years vs 12.9; P=0.005). The rate of cancer was 19% higher in the hormone therapy group than in the placebo group, but did not reach statistical significance (P=0.08 to 0.48). There were no significant differences in the rates of fractures or death between the groups (P>0.05 for both). Secondary: Not reported
Grady et al.[18]	DB, MC, PC, RCT	N=2,763	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2002) HERS and HERSII CEE 0.625 mg plus MPA 2.5 mg once daily vs placebo for HERS trial, followed by hormone therapy prescribed at personal physicians' discretion for HERS II study	Postmenopausal women with CHD, average 67 years of age at enrollment	6.8 years (4.1 years for HERS, then 2.7 years of follow-up for HERS II)	Nonfatal MI and CHD death Secondary: Coronary revascularization, hospitalization for unstable angina or CHF, nonfatal ventricular arrhythmia, sudden death, stroke or transient ischemic attack, and peripheral arterial disease	There were no significant differences in the rates of CHD events between groups. The HR was 0.99 (95% CI, 0.81 to 1.22) in HERS, 1.00 (95% CI, 0.77 to 1.29) in HERS II, and 0.99 (95% CI, 0.84 to 1.17) overall. There were no significant differences between groups for nonfatal MI (P>0.05). Secondary: There were no significant differences between groups for any of the secondary cardiovascular outcomes (P>0.05 for all) with the exception of higher incidence of nonfatal ventricular arrhythmia in the hormone group compared to the placebo group (HR, 3.30; 95% CI, 1.08 to 10.1). There was no trend of lower risk for CHD events with longer duration of hormone therapy (P=0.18) during the follow-up period of HERS II.
Maki et al.[73] (2007) CEE 0.625 mg plus MPA 2.5 mg daily vs placebo daily Treatments were given for 4 months.	DB, MC, PC, RCT Generally healthy, postmenopausal women with an intact uterus	N=158 22 months	Primary: Change from baseline of memory, attention, and subjective cognition Secondary: Change from baseline at month four on additional measures of cognitive function, emotional status, sexuality, and sleep	Primary: Except for an increase in sexual thoughts and sexual interest with hormone therapy (P=0.10 and P=0.006, respectively), there were no significant differences on any cognitive or QOL measures. Secondary: Compared to placebo, symptomatic women in the hormone therapy group showed an improvement in vasomotor symptoms (P=0.001). Specific data was not provided; however, when compared to baseline and placebo, hormone therapy was associated with an improvement in both the incidence and severity of vasomotor symptoms.
Manson et al.[74] (2003) WHI	RCT Postmenopausal women, 50 to 79	N=16,608 5.2 years (planned	Primary: CHD (nonfatal MI or death due to CHD)	Primary: Hormone therapy was associated with an increase in the risk of CHD. The risk of CHD was highest after the first year of hormone use, with a HR of 1.81 (95% CI, 1.09 to 3.01).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
CEE 0.625 mg once daily plus MPA 2.5 mg, in one tablet, once daily vs placebo	years of age at baseline	duration was 8.5 years)	Secondary: Not reported	There was a trend toward a decreasing risk of CHD over time with hormone use, which was statistically significant. The HR for CHD was 1.34 (95% CI, 0.821 to 2.18) after 2 years of hormone therapy, 1.27 (95% CI, 0.64 to 2.50) after 3 years, 1.25 (95% CI, 0.74 to 2.12) after 4 years, 1.45 (95% CI, 0.81 to 2.59) after 5 years, and 0.70 (95% CI, 0.42 to 1.14) after 6 years or longer. Secondary: Not reported
WHI Writing Group[16] (2002) CEE 0.625 mg plus MPA 2.5 mg, in one tablet, once daily vs placebo	DB, MC, PC, RCT Healthy postmenopausal women, 50 to 79 years of age with an intact uterus	N=16,608 5.2 years (mean follow-up duration)	Primary: CHD (nonfatal MI and CHD death), invasive breast cancer Secondary: Stroke, PE, endometrial cancer, colorectal cancer, hip fracture, and death due to other causes	Primary: The estimated HR for CHD was 1.29 (95% CI, 1.02 to 1.63) and breast cancer was 1.26 (95% CI, 1.00 to 1.59). Thus, there were absolute excess risk of an additional seven CHD events and eight invasive breast cancers per 10,000 person-years of treatment with CEE plus MPA. Secondary: The estimated HR for stroke was 1.41 (95% CI, 1.07 to 1.85), PE was 2.13 (95% CI, 1.39 to 3.25), colorectal cancer was 0.63 (95% CI, 0.43 to 0.92), endometrial cancer was 0.83 (95% CI, 0.47 to 1.47), hip fracture was 0.66 (95% CI, 0.45 to 0.98), and death due to other causes was 0.92 (95% CI, 0.74 to 1.14). Thus, there were absolute excess risks of an additional eight strokes and eight PEs per 10,000 person-years of treatment with CEE plus MPA. There were absolute risk reductions of six fewer colorectal cancers and five fewer hip fractures per 10,000 person-years of treatment with hormone therapy.
Reeves et al.[75] (2006) Estrogen (dose not specified) vs	ES, OS Postmenopausal women registered with incident breast	N=14,102 registered with incident breast cancer 2.7 years (mean time for all women	Primary: Incidence of breast cancer and risk of breast cancer Secondary: Not reported	Primary: 14,102 breast cancers were diagnosed and 11,869 (86%) were invasive. The RRs of invasive breast cancer in current users compared with never users of hormone therapy varied according to tumor histology overall (P<0.0001), for users of estrogen-only therapy (P=0.0001), and for users of estrogen-progesterone therapy (P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
estrogen plus progesterone (dose not specified) vs tibolone vs non estrogen therapy		from date of last contact to end of follow-up)		RRs for both estrogen-only and estrogen- progesterone therapy were greatest for invasive lobular, mixed ductal-lobular and lobular cancer. These risks were generally higher in current users of combined hormone therapy compared with estrogen-only therapy. At estimated duration of use of <5 years, five to nine years, and >10 years, estrogen-only therapy was associated with a lower RR of invasive ductal, lobular, and tubular breast cancer when compared to estrogen plus progesterone therapy. Secondary: Not reported
Rossouw et al.[76] (2007) CEE 0.625 mg/day or placebo (women post hysterectomy) OR CEE 0.625 mg/day plus MPA 2.5 mg/day or placebo (women without hysterectomy)	DB, MC, PC, RCT Healthy postmenopausal women, 50 to -79 years of age based on hysterectomy status	N=27,347 5.2 years (mean follow-up duration	Primary: CHD (nonfatal MI, CHD death, or silent MI) and stroke, mortality and a global index for trial monitoring Secondary: Not reported	Primary: In women with less than 10 years since the start of menopause, the HR for CHD was 0.76 (95% CI, 0.50 to 1.16); with 10 to 19 years, 1.10 (95% CI, 0.84 to 1.45); and 20 or more years, 1.28 (95% CI, 1.03 to 1.58) (P=0.02). In women of 50 to 59 years of age, the HR for CHD was 0.93 (95% CI, 0.65 to 1.33). Hormone therapy increased the risk of stroke (HR, 1.32; 95% CI, 1.12 to 1.56), but risk did not vary significantly by age or time since menopause. The effects of hormone therapy on total mortality favored younger women (HR of 0.70 for 50 to 59 years; 1.05 for 60 to 69 years, and 1.14 for 70 to 79 years; P=0.06). Secondary: Not reported
Saltpeter et al.[77] (2006) CEE, oral esterified estrogens or transdermal estrogen, alone or in combination with a progestin	MA Postmenopausal women	N=33,315 (107 trials) 1.5 years (mean trial duration; range 0.15 to 5 years)	Primary: Net treatment effects for each analysis were pooled using random effects model, subgroup analysis evaluated the effects of transdermal and	Primary: Subgroup analyses showed that oral agents produced greater reductions in LDL-C:HDL-C (-17.4%; 95% CI, -20.0 to -14.9) than transdermal agents (-8.4%; 95% CI, -13.8 to -2.8; P=0.004). Conjugated estrogens produced greater reductions (-22.4%; 95% CI, -25.6 to -19.1) than oral esterified estrogens (-11.3%; 95% CI, -13.2 to -9.4; P<0.0001). Unopposed estrogens and combined hormone therapy produced similar results.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo, calcium supplementation, or no treatment			oral treatment and treatment in diabetic and nondiabetic women Secondary: Not reported	Only conjugated estrogens reduced BP (-2.2%; 95% CI, -4.1 to -0.3). Transdermal agents (-0.8%; 95% CI, -3.3 to -1.6) and oral esterified estrogens (-1.3%; 95% CI, -3.1 to -0.5) were not significant. In women without diabetes, hormone therapy reduced abdominal fat (-6.8%; 95% CI, -11.8 to -1.9), HOMA-IR (-12.9%; 95% CI, -17.1 to -8.6) and new-onset diabetes (RR, 0.7; 95% CI, 0.6 to 0.9). Subgroup analyses showed no significant difference in calculated insulin resistance (HOMA-IR) between transdermal agents and oral agents, conjugated and esterified estrogens, or unopposed and combined treatment. In women with diabetes, hormone therapy reduced fasting glucose (-11.5%; 95% CI, -18.0 to -5.1), HOMA-IR (-35.8%; 95% CI, -51.7 to -19.8), LDL-C:HDL-C (-15.7%; 95% CI, -18.0 to -13.5), lipoprotein(a) (-25.0%; 95% CI, -32.9 to -17.1), mean BP (-1.7%; 95% CI, -2.9 to -0.5), E-selectin (-17.3%; 95% CI, -22.4 to -12.1), fibrinogen (-5.5%; 95% CI, -7.8 to -3.2) and plasminogen activator inhibitor-1 (-25.1%; 95% CI, -33.6 to -15.5). Secondary: Not reported
Chlebowski et al.[78] (2003) WHI CEE 0.625 mg plus MPA 2.5 mg, in one tablet, once daily vs placebo	DB, MC, PC, RCT Postmenopausal women 50 to 79 years of age, with an intact uterus	N=16,608 5.2 years (mean follow-up duration)	Primary: Breast cancer number and characteristics, frequency of abnormal mammograms Secondary: Not reported	Primary: There were more cases of total (HR, 1.24; P<0.001) and invasive (HR, 1.24; P=0.003) breast cancer in the hormone-treated group than in the placebo group. Invasive breast cancers in the hormone-treated group compared to placebo group were larger (P=0.04), more likely to be node positive (P=0.03), and diagnosed at a significantly more advanced stage (P=0.04). There was a higher percentage of abnormal mammograms in the hormone-treated group than in the placebo group after the first year in all age groups (P<0.001) and in women 50 to 59 years of age (P<0.001) as well. Secondary: Not reported
Hays et al.[79]	DB, MC, PC, RCT	N=16,608	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2003) WHI CEE 0.625 mg plus MPA 2.5 mg, in one tablet, once daily vs placebo	Postmenopausal women 50 to 79 years of age, with an intact uterus	(at baseline and at one year) N=1,511 (for subgroup analysis at three years) 3 years	QOL measures that included functional status, depression score, sleep quality, sexual functioning, cognitive functioning, and menopausal symptoms Secondary: Not reported	There were significant improvement with hormone therapy compared to placebo from baseline to year one in sleep quality (P<0.001), physical functioning (P<0.001), and bodily pain (P<0.001). Among the 574 women 50 to 54 years of age with moderate-to-severe vasomotor symptoms at baseline, hormone therapy at year 1 was associated with significant improvement in sleep (P=0.02) only. All other changes in QOL scores from baseline to year one were nonsignificant (P>0.05 for all). There were no clinically significant effects on health-related QOL measures at three years of treatment with hormone therapy (P>0.05 for all measures). Secondary: Not reported
Shumaker et al.[80] (2003) CEE 0.625 mg plus MPA 2.5 mg vs placebo	RCT Women 65 years of age or older, with an intact uterus, free of probable dementia	N=4,532 5 years	Primary: Incidence of probable dementia Secondary: Incidence of mild cognitive impairment	Primary: The rate of probable dementia in the estrogen plus progestin group was significantly higher than in the placebo group (HR, 2.05; 95% CI, 1.21 to 3.48; 45 vs 22 per 10,000 person-years; P=0.01). Secondary: There was no significant difference in the rate of mild cognitive impairment between the treatment and placebo groups (HR, 1.07; 95% CI, 0.74 to 1.55; 63 vs 59; P=0.72).
Cravioto et al.[81] (2011) CEE/MPA 0.625/5.0 mg daily for the first 10 days of every month vs placebo	DB, PC, RCT Women with systemic lupus erythematosus with any 2 of the following criteria: amenorrhea ≥6 months, serum FSH ≥30 IU/L, menopausal	N=106 24 months	Primary: Severity of menopausal symptoms Secondary: Treatment discontinuation rates and reasons, safety	Primary: Vasomotor factor decreased significantly over time (P=0.002) with differential patterns in relation to treatment (P=0.027); with combination hormone therapy, the reduction was more pronounced compared to placebo, at between 1.5 and 2.0 vs between 0.35 and 0.80 points, respectively (scale of 0 to 6). The score reductions with both treatments were observed since the first month of follow-up. Psychological, subjective-somatic, and organic-somatic factors also showed significant reductions along time (P<0.001), but their patterns were similar with respect to treatment (0.123<P<0.727). With these three factors, baseline scores decreased with both treatments since the first month of follow-up, but a tendency for returning to baseline scores was observed after one

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	symptoms, and ≥48 years of age			year. The sensory-somatic factors did not change significantly over time (P=0.065), nor did the pattern differ between treatments (P=0.968). During the two year follow-up period, global mean scores for all the factors except for subjective-somatic tended to be smaller with combination HT compared to placebo; however, the effect size of this treatment did not reach significance in any of the five factors. Secondary: Three patients receiving combination hormone therapy and one patient receiving placebo discontinued the trial due to thrombosis. One patient from each treatment group died due to sepsis. However, neither this medical reason nor the other withdrawal causes were significantly different between the two treatments. Few patients reported adverse events during the trial. Headache, nausea, melasma, galactorrhea, and dysmenorrhea were reported with each treatment, intermittently and at low frequency (≤6%). Mastalgia was more common with combination hormone therapy compared to placebo at one and six months of treatment (10.20 vs 13.33%; P<0.03).
Van de Weijer et al.[82] (2002) 17β-estradiol 50, 75, or 100 µg/24 hours for 2 weeks followed by 17β-estradiol/ levonorgestrel (50/10, 75/15, or 100/20 µg/24 hours) for 2 weeks of each month	MC, RCT, XO Postmenopausal women	N=468 1 year	Primary: Bleeding patterns Secondary: Not reported	Primary: Higher frequencies of cyclic bleeds, intermittent bleeding, and mean duration of cyclic bleeding were reported with higher dosages of estradiol/levonorgestrel. Recurrence of cyclic bleeds was acceptable for 90% of the subjects. Secondary: Not reported
Sanada et al.[83] (2004)	RCT Postmenopausal Japanese women	N=36 3 months	Primary: TG, VLDL-C, LDL-C, HDL-C	Primary: There was a significant decrease in TG and VLDL levels compared with baseline (226.0±43.9 to 110.5±44.1 mg/dL; P<0.01) in the transdermal estradiol group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
CEE 0.625 mg once daily plus MPA 2.5 mg once daily vs transdermal estradiol plus MPA 2.5 mg once daily	who developed serum TG concentrations >150 mg/dL after taking CEE plus MA for 12 months		Secondary: Not reported	There were no significant changes in the LDL-C and HDL-C levels in the transdermal estradiol group compared with CEE group. Secondary: Not reported
Cunha et al.[84] (2010) Group 1: Placebo vs Group 2: estradiol/ norethindrone 1/0.5 mg/day for 2 months, followed by placebo vs Group 3: estradiol/ norethindrone 1/0.5 mg/day for 4 months, followed by placebo	DB, PC, PRO, RCT Postmenopausal women receiving estrogen/ progestogen hormone therapy in full doses (CEE/MPA, or progesterone equivalents) for ≥6 months, wanting to discontinue combination hormone therapy due to personal reasons, and combination hormone therapy was prescribed to treat climacteric vasomotor symptoms	N=60 6 months	Primary: Climacteric symptoms evaluated by the Blatt-Kupperman Menopause Index and hot flush score at two, four, and six months Secondary: Not reported	Primary: For both the Blatt-Kupperman Menopause Index and hot flush score, a statistically significant increase in the values were observed at the first evaluation after withdrawing the combination hormone therapy (i.e., after two, four, and six months for Groups 1, 2, and 3), respectively. The hot flush score was statistically different between groups that had already discontinued combination hormone therapy compared to patients who were still receiving treatment at the time of observation; however, there was no significant difference in the first evaluation subsequent to withdrawing combination hormone therapy (two months: Group 1 vs Group 2; P<0.001; Group 1 vs Group 3; P=0.006; and Group 2 vs Group 3; P=0.485; four months: Group 1 vs Group 2; P=1.000; Group 1 vs Group 3; P=0.003; and Group 2 vs Group 3; P=0.010; and six months: Group 1 vs Group 2, Group 1 vs Group 3, and Group 2 vs Group 3; P=1.000 for all). Secondary: Not reported
Simon et al.[85] (2003) Ethinyl estradiol 5 µg plus	DB, MC, PG, RCT Healthy postmenopausal	N=357 1 year	Primary: Incidence and duration of vaginal bleeding	Primary: There were significantly lower incidences of bleeding in the ethinyl estradiol/norethindrone treatment group compared with CEE/MPA group (P<0.05 at all time points).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
norethindrone acetate 1 mg, in one tablet, once daily vs placebo vs CEE 0.625 mg plus MPA 2.5 mg, in one tablet, once daily (OL arm)	women with an intact uterus		Secondary: Not reported	There was no difference in bleeding incidences in the ethinyl estradiol/norethindrone treatment group and placebo group at months four, five, and seven through 12 (P>0.05). The duration of bleeding and/or spotting was significantly shorter in the ethinyl estradiol/norethindrone group than in the CEE/MPA group (P≤0.05). There was a larger percentage of amenorrhea in the ethinyl estradiol/norethindrone group than in the CEE/MPA group (P<0.05). Secondary: Not reported
Simon et al.[86] (2001) Ethinyl estradiol 5 µg once daily vs ethinyl estradiol 5 µg plus norethindrone acetate 0.25 mg once daily vs ethinyl estradiol 5 µg plus norethindrone acetate 1 mg once daily vs	DB, PC, RCT Postmenopausal women	N=945 1 year	Primary: Incidences of bleeding and/or spotting Secondary: Not reported	Primary: There were significantly higher percentages of amenorrhea with ethinyl estradiol/norethindrone acetate treatment than CEE/MPA treatment. At the end of six months, the incidence of amenorrhea was significantly lower with 5 µg ethinyl estradiol plus 1 mg NA (P=0.009) and 10 µg ethinyl estradiol plus 1 mg norethindrone acetate (P=0.006) compared with CEE/MPA. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ethinyl estradiol 10 µg once daily vs ethinyl estradiol 10 µg plus norethindrone acetate 0.5 mg once daily vs ethinyl estradiol 10 µg plus norethindrone acetate 1 mg once daily vs CEE 0.625 mg plus MPA 2.5 mg once daily				
Simon et al.[87] (2003) 1 mg norethindrone acetate/5 µg ethinyl estradiol (FemHRT®) vs	RETRO Women who were new users of six hormone therapy regimens	N=7,120 9 months	Primary: Treatment continuation rates Secondary: Not reported	Primary: The treatment continuation rate was significantly higher among women taking FemHRT® compared to Prempro®. Significantly higher rates of treatment continuation were observed in women >55 years of age, those who did not switch hormone therapy during the nine months study period, those who received care in the central and northeast regions of the United States, and those who received treatment from obstetricians/gynecologists versus primary care physicians. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
0.625 mg CEE/2.5 mg or 5 mg MPA (Prempro®)				
Archer et al.[88] (1999) Transdermal estradiol 50 µg/day (Vivelle®) vs transdermal estradiol 50 µg plus norethindrone acetate 140, 250, or 400 µg/day (Combipatch®)	DB, MC, RCT Postmenopausal women, aged 40 to 70, with an intact uterus	N=625 1 year	Primary: Incidence of endometrial hyperplasia, bleeding and/or spotting, vasomotor events Secondary: Not reported	Primary: There were significantly fewer cases of endometrial hyperplasia in the estradiol/norethindrone acetate treated group than in the estradiol group (P<0.001). There was a longer mean duration of irregular bleeding or spotting in the estradiol group compared to the estradiol/norethindrone acetate. There was a higher incidence of no uterine bleeding in the estradiol/norethindrone acetate group than in the estradiol group. Similar reductions in mean number of hot flashes and intensity of sweating were observed with all treatment groups. Secondary: Not reported
Johnson et al.[89] (2002) CEE 0.625 mg plus MPA 2.5 mg, in one tablet, daily (Prempro®) vs 17β-estradiol 1 mg plus norethindrone acetate 0.5 mg, in one tablet, daily (Activella®)	DB, MC, PRO, RCT Healthy postmenopausal women	N=438 6 months	Primary: Bleeding profiles Secondary: Lipid profiles	Primary: Treatment with Activella® resulted in a larger percentage of women with no bleeding and no spotting (P=0.001) compared to treatment with Prempro®. Secondary: There was a significant improvement in TG (-8.5 vs 11.7%; P<0.001) and TC (-9.1 vs -6.9%) in the Activella® group compared to Prempro® group.
Godsland et al.[90] (1993)	PC, RCT	N=61 18 months	Primary: Intravenous glucose tolerance	Primary: There were no changes in glucose or insulin concentrations with transdermal therapy.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Oral therapy with CEE 0.625 mg daily plus levonorgestrel 0.075 mg daily for 12 days of each 28 day cycle vs transdermal therapy with continuous 17β-estradiol plus norethindrone acetate 0.25 mg daily for 14 days of each 28-day cycle vs placebo	Postmenopausal women		tests, plasma glucose, insulin, and C-peptide concentrations Secondary: Not reported	Oral hormone therapy lowered glucose tolerance and increased plasma insulin response. There was greater insulin resistance compared with baseline during the combined estrogen/progestin phase than in the estrogen only phase. Secondary: Not reported
Whitcroft et al.[91] (1994) Oral therapy with CEE 0.625 mg daily plus dl-norgestrel 0.15 mg daily for 12 days of each cycle vs transdermal therapy with 17β-estradiol 0.05 mg daily plus norethindrone acetate 0.25 mg	PC, RCT Healthy postmenopausal women	N=61 3 years	Primary: Fasting serum lipid and lipoprotein concentrations Secondary: Not reported	Primary: Both oral and transdermal hormone therapy significantly reduced serum TC (P<0.001) and LDL-C (P<0.01) from three months of treatment and effects were maintained at three years of treatment. Both oral and transdermal hormone therapy significantly reduced serum TG concentrations (P<0.05) from six months of treatment and effects were maintained over three years of treatment only with the transdermal group. HDL-C declined in both oral and transdermal treatment groups, as well as placebo group (P<0.05 for all). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
daily for 14 days of each cycle vs placebo				
Hirvonen et al.[92] (1987) Estradiol plus MPA, dose not specified vs estradiol plus levonorgestrel, dose not specified vs estradiol valerate 2 mg daily	DB, XO Postmenopausal women	N=36 Duration not specified	Primary: Menopausal symptoms, lipid profile, bleeding episodes Secondary: Not reported	Primary: There were no differences in relief of menopausal symptoms between treatment groups. Women on the estradiol/MPA treatment significantly improved the atherogenic index, which is the LDL-C:HDL-C. Women on the estradiol/levonorgestrel treatment showed deterioration in the atherogenic index. There was more withdrawal bleeding in the estrogen plus progestin groups than in the unopposed estrogen group (78 vs 22%). Secondary: Not reported
White et al.[93] (2006) Drospirenone 1, 2, or 3 mg with 17β estradiol 1 mg or once daily in the morning vs 17β estradiol 1 mg alone once daily each morning	DB, MC, PC, RCT Postmenopausal women, 45 to 75 years of age, with mean seated clinic SBP 140 to 179 mm Hg and DBP between 90 to 109 mm Hg in the untreated state	N=750 Study duration not specified; placebo phase was 3 to 4 weeks and treatment phase was 8 weeks	Primary: Mean change from baseline at week eight in clinic and in ambulatory SBP Secondary: Changes from baseline in the clinic and 24-hour DBP, assessment of the hourly changes in ambulatory SBP and DBP	Primary: While the mean reduction in clinic BP in the 17β estradiol alone group and 1mg drospirenone plus 17β estradiol group was not statistically significant, the mean reductions in clinic BP in the 3 and 2 mg drospirenone plus 17β estradiol groups were statistically significant. These reductions were, -13.8/ -8.5 and -12.1/-9.2 mm Hg, in the 3 and 2 mg drospirenone plus 17β estradiol groups, respectively, while the reductions for placebo were -8.7/-5.0 mm Hg (SBP reductions; P=0.0004 and 0.0195 for 3 and 2 mg doses; and for DBP reductions; P<0.0001 for both). Secondary: Measures of ambulatory BP showed significant reductions from baseline at a mean of 24-hour SBP in both the 2 and 3 mg drospirenone plus 17β estradiol treatment groups compared to placebo. These reductions were, -6.1 and -4.7 mm Hg in the 3 and 2 mg drospirenone plus 17β estradiol

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo				groups respectively, compared to a mean SBP change in the placebo group of -1.2 mm Hg. (P values for SBP reductions vs placebo were <0.0001 and 0.009 respectively). There were no differences in ambulatory BP for 1 mg drospirenone plus 17β estradiol and 17β estradiol alone vs placebo.
Preston et al.[94] (2005) Drospirenone with 17β estradiol daily for 28 days vs placebo daily for 28 days	DB, MC, PC, RCT Postmenopausal women, 44 to 70 years of age, with or without type 2 diabetes mellitus and using an angiotensin-converting enzyme or angiotensin II receptor antagonist	N=230 28 days	Primary: Number and percentage subjects who developed hyperkalemia (K ≥5.5 mEq/L) and changes from baseline in seated clinic BP Secondary: Not reported	Primary: No statistical differences were observed in the overall number and percentage of subjects with hyperkalemia for drospirenone with 17β estradiol versus placebo. No subject had symptoms or electrocardiographic changes related to hyperkalemia. A reduction in BP was observed at -8.6/-5.8 mm Hg in patients receiving drospirenone with 17β estradiol vs -3.7/-2.9 mm Hg in the placebo group; P<0.01 for both SBP and DBP. Secondary: Not reported
Lobo et al.[95] (2018) REPLENISH 17β-estradiol/ progesterone (Bijuva®) (1/100, 0.5/100, 0.5/50, or 0.25/50 mg) vs placebo	DB, MC, RCT Women 40 to 65 years of age with vasomotor symptoms and a uterus	N=1,835 12 months	Primary: Incidence of endometrial hyperplasia; mean changes in frequency and severity of moderate-to-severe vasomotor symptoms from baseline to weeks four and 12 with active treatments compared with placebo in the modified intent-to-treat vasomotor symptoms population (n=726)	Primary: No cases of endometrial hyperplasia were observed with any estradiol–progesterone dose (0% incidence; primary safety endpoint). The coprimary outcomes of vasomotor symptom frequency significantly decreased (P<0.05) from baseline to weeks four and 12 with all doses of estradiol–progesterone compared with placebo (except for 0.5 mg estradiol and 50 mg progesterone at week four) in the modified intent-to-treat vasomotor symptoms population. Secondary: The incidence of treatment-emergent adverse events was low in all treatment groups; differences in treatment-emergent adverse events with estradiol–progesterone compared with placebo were not clinically important. Most treatment-emergent adverse events were mild or moderate in severity. The most common treatment-related, treatment-emergent adverse events (3% or greater of women) with an incidence numerically higher for estradiol–progesterone (at any dose) than with placebo were breast tenderness, headache, nausea, pelvic pain, vaginal bleeding, and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Secondary: Adverse events; mean changes from baseline in frequency and severity of moderate-to-severe vasomotor symptoms at each week up to week 12	vaginal discharge. Adverse events leading to discontinuation occurred in 7.3 to 11% with estradiol–progesterone vs 6.6% with placebo. Significantly more women had clinically meaningful reductions in vasomotor symptom frequency with estradiol–progesterone compared with placebo (P<0.05 to P<0.001) at week four (46 to 59% vs 33%) and week 12 (68 to 73% vs 52%).
Kaunitz et al.[96] (2020) REPLENISH 17β-estradiol/ progesterone (Bijuva®) (1/100, 0.5/100, 0.5/50, or 0.25/50 mg) vs placebo	DB, MC, RCT Women 40 to 65 years of age with vasomotor symptoms, a uterus, and with moderate to severe hot flushes (≥7/day or ≥50/week)	N=726 12 months	Primary: Responder rate (responders defined as women who had at least 50% or 75% reductions in moderate to severe VMS frequency) Secondary: Moderate to severe VMS-free days; proportion of women with no severe VMS	Primary: Compared with placebo, significantly more women randomized to the treatment group responded to treatment at weeks four and 12. At week four, approximately half of the women (49% to 62%) on treatment had at least a 50% reduction in their weekly moderate to severe VMS (vs 33% for placebo; all, P<0.01), this proportion increased to approximately three quarters of women (73% to 81%) by week 12 (vs 58% for placebo; all, P<0.05). The proportion of women with at least a 75% reduction in their weekly moderate to severe VMS was 23% to 41% for those randomized to treatment compared with 12% for placebo at week four (all, P<0.05), increasing to 50% to 68% with the treatment group, and 32% with placebo at week 12 (all, P<0.01). Secondary: At week 12, women in the treatment groups had significantly more days per week without moderate to severe VMS compared with placebo (1.9 to 3.0 days for treatment groups vs 1.3 days for placebo; all, P<0.05). Significant differences (P<0.05) were detected as early as week three for the highest dose (1/100), at week four for the 0.5/100 and 0.25/50 doses and at week six for the 0.5/50 dose. The proportion of women without severe hot flushes at week 12 was 43% to 56% for all treatment doses versus 26% for placebo (P≤0.01).
White et al.[97] (2005)	DB, MC, PC, RCT	N=213	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Drospirenone 3 mg with 1 mg 17β estradiol daily in the morning vs placebo daily in the morning	Postmenopausal women, aged 45 to 80 years, with seated clinic SBP of 140 to 159 mm Hg and/or the DBP was 90 to 99 mm Hg	Duration not specified	Mean change from baseline at week 12 in clinic BP Secondary: Changes from baseline in the 24-hour systolic and diastolic BPs and heart rate, as well as other ambulatory monitoring parameters and mean changes from baseline of serum potassium	Mean reductions in clinic BP in the drospirenone with 17β estradiol group averaged -14.1/-7.9 mm Hg, and the respective reductions for the placebo group were -7.1/-4.3 mm Hg (P<0.001 for both SBP and DBP). Secondary: Drospirenone with 17β estradiol significantly lowered pulse pressure compared to the placebo group by -3.5 mm Hg (P=0.007). No significant changes were observed in heart rate.
Archer et al.[98] (2005) Estradiol 1.0 mg vs estradiol 1.0 mg plus 0.5, 1.0, 2.0, or 3.0 mg of drospirenone (estradiol plus drospirenone)	DB, MC, PG, RCT Postmenopausal women with an intact uterus (42 to 75 years of age)	N=1,142 1 year	Primary: Endometrial hyperplasia Secondary: Bleeding patterns, hot flush frequency and severity, urogenital symptoms, and health-related QOL	Primary: Compared to estradiol alone, the combinations of drospirenone and estradiol were effective in protecting against endometrial hyperplasia. The probability of hyperplasia was 0.060 (95% CI, 0.043 to 0.078) for the estradiol monotherapy group, 0.007 for the 2 mg estradiol plus drospirenone group, and nonsignificant for the remaining drospirenone/estradiol groups. Secondary: A greater proportion of women in all estradiol plus drospirenone treatment groups had bleeding in cycles one through three compared to women in the estradiol monotherapy group (P<0.001). Beginning at week two, there was a decrease in hot flushes from baseline at all time points (P≤0.008 in all treatment groups). At cycle 13, a decrease in mean body weight from baseline was observed in the 2 mg estradiol plus drospirenone and 3 mg estradiol plus drospirenone groups (P<0.001 for both), while the decrease was not statistically significant in the 0.5 mg estradiol plus drospirenone and 1 mg estradiol plus drospirenone groups.
Schurmann et al.[99] (2004)	MC, PC, RCT	N=225	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Drospirenone 1, 2 or 3 mg combined with estradiol (1 mg) vs placebo	Healthy post-menopausal Caucasian women, 45 to 66 years of age, who complained of at least five moderate-to-severe hot flushes per day on at least 7 of the 14 days preceding the study	16 weeks of treatment; followed with 2 weeks of follow-up	Change in the frequency and the intensity of hot flushes from baseline Secondary: Other menopausal symptoms (sweating periods, sleep problems, depressed mood, nervousness, and urogenital symptoms), vaginal bleeding, and adverse events	Hot flushes significantly decreased in frequency for all treatment groups (range, 86 to 90%) in comparison to placebo (45%; P≤0.001) and remained suppressed at study end, 16 weeks. Secondary: Drospirenone and estradiol treatment decreased the intensity and severity of sweating, sleep problems, depression, nervousness, and urogenital symptoms. The majority of the adverse events were mild or moderate, and similar rates were observed in all groups. Furthermore, no serious adverse events or clinically significant laboratory abnormalities were attributed to the treatment.
Lin et al.[100] (2011) Estradiol/ drospirenone daily vs placebo	DB, MC, PC, PG, RCT Chinese postmenopausal women 45 to 65 years of age with moderate to severe vasomotor symptoms; documentation of ≥24 moderate to severe hot flushes over 7 consecutive days during a 3 week screening period; an intact uterus with endometrial thickness <5 mm, or	N=249 16 weeks (2 weeks of follow-up)	Primary: Relative change in number of hot flushes per week, absolute changes in the severity of moderate to severe hot flushes and in the severity of all hot flushes from baseline to weeks three to 16 Secondary: Changes in other climacteric symptoms from baseline to week 16, safety	Primary: The number of hot flushes per week decreased progressively with both treatments over the 16 week period, but was consistently lower with combination therapy compared to placebo from week two onward. Over the treatment period weeks three to 16, the number of hot flushes per week was 11.1±15.1 and 22.4±17.3 with combination therapy and placebo, representing absolute decreases of 45.9±29.3 and 27.5±28.1, respectively. These absolute changes corresponded to relative decreases in the number of hot flushes per week of 80.4 and 51.9% with combination therapy and placebo, a significant treatment difference of 28.5% in favor of combination therapy (P<0.0001). Combination therapy was associated with numerically greater reductions in the severity of moderate to severe hot flushes over weeks three to 16 compared to placebo. The change in severity of all hot flushes between baseline and treatment (weeks three to 16) was -0.61 and -0.43 with combination therapy and patients receiving placebo (P≤0.05). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	a normal endometrial biopsy if endometrial thickness >5 mm; last menstrual bleed ≥1 year before, or bilateral oophorectomy ≥6 weeks before, or last natural menstrual bleed ≥6 months previously, with a serum FSH ≥40 mIU/mL; a negative urinary pregnancy test; and a negative bilateral mammography result			Among patients who experienced moderate to severe sweating at baseline, 4.1 (7/169) and 22.2% (12/45) of patients receiving combination therapy and placebo continued to experience moderate to severe sweating at week 16. A significantly higher proportion of patients were free of sweating symptoms after 16 weeks with combination therapy (48.1 vs 73.4%; P<0.0001). Among patients who experienced vaginal dryness at baseline, a significantly greater proportion of patients receiving combination therapy no longer had this symptom compared to placebo (87.7 [93/106] vs 60.0% [21/35]; P<0.001). Depressive moods, nervousness and pollakiuria followed a similar trend of greater reductions in frequency after 16 weeks of combination therapy compared to placebo, but these differences did not reach significance. Incidences of depressive mood were reduced from 42.1% at baseline to 4.0% after combination therapy, and from 49.2 to 12.5% with placebo. Corresponding values for nervousness were from 50 to 51% with both treatments to 6.9 and 17.9% with combination therapy and placebo. At baseline, pollakiuria was present in 29 to 32% of patients and of these, 90.2 and 72.2% no longer experienced this symptom with combination therapy and placebo. Mild to moderate insomnia was present at baseline in 71.6 and 65.6% of patients randomized to combination therapy and placebo. At week 16, similar proportions of patients (17.9 and 19.6%, respectively) continued to experience insomnia with both treatments. Occurrences of nocturia were similar between the two treatments at baseline (33.3 and 37.7%), and of these patient, 75.9 and 81.0% of patients were free from this symptom at week 16. The proportion of patients free from arthralgia increased from 44.3% at baseline to 75.1% after combination therapy, and from 29.5 to 58.9% with placebo. Proportion of patients free from myalgia increased from 69.9 to 86.1% with combination therapy, and from 57.4 to 78.6% with placebo.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Results for the Clinical Global Impressions scale assessment in patients available at week 18 showed a more favorable effect for combination therapy compared to placebo; 87.9 vs 47.3% of patients were 'much improved' or 'very much improved' (P<0.001). A higher proportion of patients receiving combination therapy experienced bleeding and spotting compared to placebo (number of bleeding/spotting days in each 28-day period: 1.7 to 4.8 vs 0.2 to 0.9 days). The cumulative amenorrhea rate in patients who completed the trial increased from 34.4% after cycle one to 67.2% after cycle four with combination therapy, and from 85.2 to 93.4% with placebo. A total of 71 patients (29.1 vs 26.2%) reported at least one adverse event, including 46 patients reporting a possibly treatment-related event (20.8 vs 13.1%). The most common adverse event was breast tenderness (8.7 vs 1.6%). The majority of events were mild to moderate in severity, with severe events including breast tenderness, headache, breast swelling, ankle fracture, increased blood TGs, joint swelling, and abdominal neoplasm. Three serious adverse events were reported and were considered to be nontreatment-related.
Rowan et al.[101] (2006) Study 1: Norethindrone acetate/ethinyl estradiol at either 0.2 mg/1 µg, 0.5 mg/2.5 µg, 1 mg/5 µg, or 1 mg/10 µg, or placebo Study 2: norethindrone acetate/ethinyl estradiol 0.5 mg/2.5 µg, 1 mg/5 µg, or 1	Post-hoc analysis of 3 studies Study 1=DB, MC, PC, PG; postmenopausal women Study 2=DB, MC, PG; postmenopausal women Study 3=DB, MC, PC, PG; postmenopausal women	N= 220,531 Study 1=16 weeks Study 2=12 weeks Study 3=24 months	Primary: Postmenopausal symptoms, the effects on bone and endometrium Secondary: Not reported	Primary: In study 1, norethindrone acetate/ethinyl estradiol 0.5 mg/2.5 µg was associated with significant reductions from baseline in mean weekly total hot flush frequency from week 4 (63.6%) through week 16 (73.7%; P<0.05). In study 2, the frequency of moderate or severe hot flushes was decreased by 61.1% at week 4 (P<0.05) and by 82.2% at week 12 (P<0.001) with norethindrone acetate/ethinyl estradiol 0.5 mg/2.5 µg. Furthermore, the mean intensity score was significantly lower than that with placebo at weeks eight and 12 (for both; P=0.001). In study 3, the cumulative amenorrhea rates were approximately 90% in the norethindrone acetate/ethinyl estradiol 0.5 mg/2.5 µg and placebo groups at 12 months. At 24 months, lumbar spine bone mineral density was maintained with norethindrone acetate/ethinyl estradiol 0.5 mg/2.5 µg, but was significantly decreased from baseline at 7.4% in the placebo group

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg/10 µg, or placebo Study 3: Progestin/estrogen therapy (norethindrone acetate/ethinyl estradiol 0.2 mg/1 µg, 0.5 mg/2.5 µg, 1 mg/5 µg, or 1 mg/10 µg), unopposed estrogen monotherapy (ethinyl estradiol 1, 2.5, 5, or 10 µg), or placebo				(P<0.001). At 24 months, endometrial hyperplasia was not observed in the group receiving norethindrone acetate/ethinyl estradiol 0.5 mg/2.5 µg. Secondary: Not reported
Battaglia et al.[102] (2009) Estradiol/ drospirenone 1 mg/2mg vs estradiol/ norethisterone acetate 1 mg/0.5mg	RCT Postmenopausal women	N=30 6 months	Primary: Effects on BP and other surrogate markers of cerebrovascular and cardiovascular risk. Secondary: Not reported	Primary: The basal pulsatility index and the back pressure of the ophthalmic artery were similar in groups 1 and 2. After six months, no changes were observed. The nitrites/nitrates values were not different between groups 1 and 2 both in basal conditions and after therapy. The brachial artery flow-mediated vasodilatation and the pulsatility index of the brachial artery did not show any difference in groups 1 and 2 both in basal conditions and after the therapy. The 24-hour BP monitoring showed no significant differences in the 24-hour time, daytime, and nighttime values either in basal conditions or after therapy. All participants were found to be dippers normally (nocturnal reduction ≥10% in comparison with diurnal values). The wake-up BP values were similar in the studied participants.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Furness et al.[103] (2009) Estrogen therapy, combined continuous estrogen-progestin therapy, sequential estrogen-progestin therapy	MA Postmenopausal women 40 to 75 years of age	N = 38,702 (45 RCT) >12 months	Primary: Frequency of endometrial hyperplasia (of any type) or adenocarcinoma (assessed by endometrial biopsy) Secondary: Adherence to therapy, rates of additional interventions, and withdrawals due to adverse events	Primary: Unopposed estrogen was associated with increased risk of endometrial hyperplasia at all doses, and durations of therapy between one and three years. For women with a uterus, the risk of endometrial hyperplasia with hormone therapy comprising low dose estrogen continuously combined with a minimum of 1 mg norethisterone acetate or 1.5 mg MPA is not significantly different from placebo (1 mg estradiol/norethindrone acetate: OR, 0.04; 95% CI, 0 to 2.8; 1.5 mg MPA: no hyperplasia events). Secondary: Adherence was greater in both continuous and sequentially combined regiments than in unopposed estrogen regimens. There were significant numbers of participants in most of the trials included who withdrew from the trial prior to completion (10 to 50%) due to adverse events, lack of efficacy, or other reasons. Only one study assessed the rate of unscheduled biopsies and found a significant increase associated with moderate dose unopposed estrogen therapy (1 RCT: OR, 11.8; 95% CI 7.0 to 19.9).
Canonico et al.[104] (2008) Oral estrogen with or without progestogen vs transdermal estrogen with or without progestogen	MA of 8 OS and 9 RCT Women using hormone replacement therapy (age not reported)	N=not reported Duration varied	Primary: Risk of VTE Secondary: Not reported	Primary: MA of OS showed that oral estrogen but not transdermal estrogen increased the risk of VTE. Compared to nonusers of estrogen, the OR of first-time VTE in current users of oral estrogen was 2.5 (95% CI, 1.9 to 3.4) and in current users of transdermal estrogen was 1.2 (0.9 to 1.7). Past users of oral estrogen had a similar risk of VTE to never users (P values were not reported). The risk of VTE in women using oral estrogen was higher in the first year of treatment compared to treatment for more than one year (P<0.05). No noticeable difference in the risk of VTE was observed between unopposed oral estrogen and opposed oral estrogen. Results from nine RCTs confirmed the increased risk of VTE among women using oral estrogen (2.1; 95% CI, 1.4 to 3.1; P value not reported).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The combination of oral estrogen and thrombogenic mutations or obesity further enhanced the risk of VTE, whereas transdermal estrogen did not seem to confer additional risk in women at high risk of VTE. Secondary: Not reported
Morch et al.[105] (2009) Oral, transdermal, and vaginal estrogen products with or without a progestogen component	PRO cohort study Danish women 50 to 79 years of age from 1995 through 2005 who had no hormone-related cancers before study entry	N=909,949 Average follow-up 8 years	Primary: Incidence of ovarian cancer Secondary: Not reported	Primary: Compared to women who never took hormone therapy, current users of hormones had incidence rate ratios for all ovarian cancers of 1.38 (95% CI, 1.26 to 1.51) and 1.44 (95% CI, 1.30 to 1.58) for epithelial ovarian cancer (P values not reported). The risk declined with years since last use: 0 to 2 years, 1.22; >2 to 4 years, 0.98; >4 to 6 years, 0.72, and >6 year, 0.63. For current users the risk of ovarian cancer did not differ significantly with different hormone therapies or duration of use. The incidence rates in current and never users of hormones were 0.52 and 0.40 per 1,000 years, respectively, for an absolute risk increase of 0.12 (95% CI, 0.01 to 0.17 per 1,000 years; P value not reported). This approximates one extra ovarian cancer for roughly 8,300 women taking hormone therapy each year. Regardless of the duration of use, the formulation, estrogen dose, regimen, progestin type, and route of administration, hormone therapy was associated with an increased risk of ovarian cancer. Secondary: Not reported
Jaakkola et al.[106] (2012) Estrogen plus progesterone	Cohort, PRO Women who had used estrogen/ progesterone therapy in 1994 to	N=243,857 Duration not specified	Primary: Incidence of cervical precancerous or cancerous lesions	Primary: Among patients receiving combination hormone therapy, there were 210 patients with squamous lesions (178 precancerous, 32 cancerous) and there were 79 patients with glandular lesions (14 precancerous, 65 adenocarcinomas). The use of combination hormone therapy was not associated with incidence of precancerous lesions, but the risk for

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Patient population was compared to background population.	2008 for ≥6 months, ≥50 years of age were identified		Secondary Not reported	squamous cell carcinoma decreased (standardized incidence ratio, 0.41; 95% CI, 0.28 to 0.58) and that for adenocarcinoma increased (1.31; 95% CI, 1.01 to 1.67). After use of combination hormone therapy for five years, the risk for squamous cell carcinoma decreased (standardized incidence ratio, 0.34; 95% CI, 0.16 to 0.65), and the risk for adenocarcinomas increased (1.83; 95% CI, 1.24 to 2.59). Secondary: Not reported
Lobo et al.[107] (2009) SMART-1 Single tablets of BZA (10, 20, or 40 mg), each with CEE (0.625 or 0.45 mg) daily vs raloxifene 60 mg daily vs placebo taken daily	AC, DB, MC, PC, RCT Healthy, postmenopausal women age 40 to 75 with an intact uterus	N=3,397 2 years	Primary: Hot flushes, breast pain, vaginal atrophy, metabolic parameters, adverse events Secondary: Not reported	Primary: All doses of BZA/CEE provided significantly better relief of hot flushes than placebo at most time points (P<0.01). BZA/CEE groups also demonstrated significant decreases in hot flush number and severity compared to raloxifene. Treatment with BZA (10 mg)/CEE (0.625 or 0.45 mg) and BZA (20 mg)/CEE (0.625 or 0.45 mg) was significantly more effective than placebo in increasing the mean proportion of superficial cells from baseline to most time points (P<0.001). Breast pain occurred with similar frequency for subjects in the BZA/CEE, raloxifene, and placebo groups, and there were no significant differences in the incidence of breast pain among the groups for any 28-day interval. Reductions in LDL cholesterol for all BZA/CEE doses (range, -5.7 to -10.9%) were significantly greater compared to placebo (range, -0.1 to 2.2%) at all time points (P<0.01). Increases in HDL cholesterol for all BZA/CE doses (range, 7.0 to 13.5%) were significantly greater compared to placebo (range, 1.3 to 5.4%) at all time points (P<0.05), and significantly greater compared to raloxifene (range, 3.1 to 6.6%) at most time points (P<0.05). Overall, the incidence of adverse events and serious adverse events was similar among treatment groups. There were no significant differences in the incidence of treatment-emergent adverse events among groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Overall, the incidence of VTEs was similar for subjects treated with BZA/CEE or placebo (0.76 vs 1.56 per 1,000 women-years, respectively; RR, 0.48; 95% CI, 0.05 to 4.66). The cardiovascular adverse events of interest included myocardial infarction, coronary artery disease, and coronary artery insufficiency. The incidence of cardiovascular adverse events was low (<1%) across all treatment groups, with no significant differences among groups. Secondary: Not reported
Pickar et al.[108] (2009) SMART-1 Single tablets of BZA (10, 20, or 40 mg), each with CEE (0.625 or 0.45 mg) daily vs raloxifene 60 mg daily vs placebo taken daily	AC, DB, MC, PC, RCT Healthy, postmenopausal women age 40 to 75 with an intact uterus	N=3,397 2 years	Primary: Incidence of endometrial hyperplasia at 12 months in the efficacy evaluable population (EEP) Secondary: Adverse events	Primary: At month 12, the incidence of endometrial hyperplasia for all BZA/CEE doses was <1% (predefined acceptable limit was ≤2%), except for BZA (10 mg)/CEE (0.625 mg) (3.81%; CI, 2.27 to 5.99). No hyperplasia was observed with BZA (40 mg)/CEE (0.625 mg), BZA (20 or 40 mg)/CEE (0.45 mg), raloxifene, and placebo. The lowest effective dose of BZA that protected the endometrium from the stimulatory effects of CEE (0.45 and 0.625 mg) was 20 mg, as indicated by acceptable rates of endometrial hyperplasia after one year (primary endpoint) and two years of exposure. Secondary: The incidence of treatment-emergent adverse effects was not significantly different among treatment groups (P=0.696).
Archer et al.[109] (2009) SMART-1 Single tablets of BZA (10, 20, or 40 mg), each with CEE (0.625 or 0.45 mg) daily	AC, DB, MC, PC, RCT Healthy, postmenopausal women age 40 to 75 with an intact uterus	N=3,397 2 years	Primary: Cumulative amenorrhea profiles and the incidence of bleeding or spotting Secondary:	Primary: Cumulative amenorrhea profiles for subjects treated with BZA 20 or 40 mg with CEE 0.625 or 0.45 mg were similar to those observed for placebo-treated subjects during the first and second year of therapy and were similar to those with raloxifene 60 mg during year one of treatment, with the exception of a lower rate of amenorrhea during cycles one through 13 for BZA 20 mg/CEE 0.45 mg compared to raloxifene 60 mg (83 vs 88%, respectively; P<0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs raloxifene 60 mg daily vs placebo taken daily			Not reported	Treatment with BZA 20 or 40 mg with CEE 0.625 or 0.45 mg was associated with a low incidence of bleeding or spotting events that was not significantly different compared to placebo. Secondary: Not reported
Lindsay et al.[110] (2009) SMART-1 Single tablets of BZA (10, 20, or 40 mg), each with CEE (0.625 or 0.45 mg) daily vs raloxifene 60 mg daily vs placebo taken daily	AC, DB, MC, PC, RCT Healthy, postmenopausal women age 40 to 75 with an intact uterus Osteoporosis Prevention I Substudy: Women >5 years postmenopause (N=1,454) Osteoporosis Prevention II Substudy: Women 1 to 5 years postmenopause (N=861)	N=3,397 2 years	Primary: Change in BMD of the lumbar spine at month 12 Secondary: BMD of the hip, bone turnover biomarkers (BTM)	Primary: In substudies I and II, all BZA/CEE doses significantly increased (P<0.001) the adjusted mean percent change in BMD from baseline to 12 and 24 months vs decreases observed with placebo. Compared to raloxifene, the percent increase in lumbar spine BMD from baseline to month 24 was significantly higher for all BZA/CEE treatment groups (P<0.05) for women one to five years postmenopause. Among women >5 years postmenopause, BMD significantly improved relative to raloxifene (P<0.05) for all BZA/CEE doses, except those with BZA (40 mg). Secondary: In substudy I, total hip BMD was significantly higher (P<0.001) with all BZA/CEE doses from baseline to months 12 and 24 compared to the decreases observed with placebo. Compared to raloxifene, mean percent increases in total hip BMD were significantly higher (P<0.05) from baseline to month 24 with BZA (10 mg)/CEE (0.625 or 0.45 mg) and BZA (20 mg)/CEE (0.625 mg). In substudy II, all BZA/CEE doses were significantly higher (P<0.01) for total hip BMD than with placebo at months 12 and 24. Total hip BMD was significantly better (P<0.05) than with raloxifene for BZA (10 mg)/CEE (0.625 or 0.45 mg), and BZA (20 mg)/CEE (0.45 mg) at month 24. In substudy II, at all time points, median percent changes from baseline in serum osteocalcin and C–telopeptide were significantly greater with all BZA/CEE doses than with placebo (P<0.001).
Pinkerton et al.[111] (2009) SMART-2	DB, MC, PC, RCT	N= 332 12 weeks	Primary: Changes from baseline in the	Primary: All groups demonstrated a significant reduction (P<0.001) from baseline for the mean daily number of moderate and severe hot flushes at all time

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
BZA 20 mg/CEE 0.45 mg once daily vs BZA 20 mg/CEE 0.625 mg once daily vs placebo once daily	Healthy postmenopausal women, 40 to 65 years of age with an intact uterus, with moderate to severe hot flushes (≥7/day or 50/week)		average daily number of moderate and severe hot flushes and the severity of hot flushes at weeks 4 and 12 Secondary: Participants who had at least a 50% or 75% reduction in the number of hot flushes from baseline, time to reach a 50% decrease from baseline in the number of hot flushes for at least 3 consecutive days, the MOS sleep scale, Menopause-Specific Quality of Life (MENQOL), and the presence of breast pain	points. At weeks four and 12, these decreases were significantly greater with both BZA/CEE doses than with placebo (P<0.001). At week 12, BZA 20 mg/CEE 0.45 mg and BZA 20 mg/CEE 0.625 mg reduced hot flushes from baseline by 74% (10.3 [baseline] vs 2.8 [week 12]) and 80% (10.4 vs 2.4), respectively, compared to 51% (10.5 vs 5.4) for placebo. Similarly, the mean daily severity of hot flushes significantly improved (P<0.001) from baseline with BZA 20 mg/CEE 0.45 or 0.625 mg at all time points. Secondary: Overall, significantly more (P<0.001) BZA/CEE-treated women responded at both the 75% and 50% level compared to placebo at weeks four and 12. Significantly more women taking BZA 20 mg/CEE 0.625 mg compared to BZA 20 mg/CEE 0.45 mg were 75% responders. Similarly at weeks four and 12, significantly more participants treated with BZA/CEE than with placebo had at least a 75% (P<0.01) or 50% (P<0.001) decrease when mild, moderate, and severe hot flushes were assessed. The median time to reach a 50% reduction in hot flushes for at least three consecutive days was significantly shorter for BZA 20 mg/CEE 0.45 mg (15 days) and BZA 20 mg/CEE 0.625 mg (14 days) compared to placebo (30 days; P≤0.001). Compared to placebo-treated participants, those receiving BZA/CEE treatment had significant improvements from baseline (P<0.001) at week 12 for time to fall asleep, sleep adequacy, sleep disturbance, and sleep problem indices I and II, as assessed by the MOS sleep scale. A significant improvement (P<0.010) in the number of hours slept each night was also observed in participants taking BZA 20 mg/CEE 0.625 mg compared to placebo.
Utian et al.[112] (2009) SMART-2 BZA 20 mg/CEE 0.45 mg once daily vs	DB, MC, PC, RCT Healthy postmenopausal women, 40 to 65 years of age with an intact uterus, with moderate to severe	N= 332 12 weeks	Primary: Medical Outcomes Study (MOS) sleep scale and Menopause-Specific Quality of Life (MENQOL) questionnaires and the Menopause	Primary: At Week 12, both doses of BZA/CEE showed significant improvements (P<0.001) in scores for time to fall asleep, sleep disturbance, sleep adequacy, and sleep problems indexes I and II compared to placebo. Both BZA/CEE treatment groups showed significant improvements in vasomotor and total scores on the MENQOL questionnaire relative to placebo (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
BZA 20 mg/CEE 0.625 mg once daily vs placebo once daily	hot flushes (≥7/day or 50/week)		Symptoms Treatment Satisfaction Questionnaire (MS-TSQ) Secondary: Not reported	Results of the MS-TSQ showed that BZA/CEE-treated subjects reported significantly greater satisfaction compared to placebo-treated subjects in the following 4 categories: ability to control hot flushes during the day (P<0.001) and night (P<0.001), effect on quality of sleep (P<0.001), and effect on mood or emotions (P<0.05).
Yu et al.[113] (2013) SMART-2 BZA 20 mg/CEE 0.45 mg once daily vs BZA 20 mg/CEE 0.625 mg once daily vs placebo once daily	DB, MC, PC, RCT Healthy postmenopausal women, 40 to 65 years of age with an intact uterus, with moderate to severe hot flushes (≥7/day or 50/week)	N= 332 12 weeks	Primary: Number of days per week without hot flushes from baseline to week 12, percentage of women who experienced no hot flushes at week 12 Secondary: Not reported	Primary: From baseline to week 12, the mean number of days per week without moderate-to-severe hot flushes steadily increased for both doses of BZA/CEE compared to placebo. These effects were significant for both doses starting at week three (P<0.05 for BZA 20 mg/CEE 0.45 mg and P<0.01 for BZA 20 mg/CEE 0.625 mg) and sustained through week 12. A significantly higher number of days per week without moderate-to-severe hot flushes was seen for BZA 20 mg/CEE 0.625 mg compared to BZA 20 mg/CEE 0.45 mg (P<0.05) starting at week four. At week 12, the mean number of days per week without moderate-to-severe hot flushes was higher for both BZA/CEE treatment groups (2.8 and 3.7 days for BZA 20 mg/CEE 0.45 and 0.625 mg, respectively) compared to the placebo group (1.0 days). Similarly, the mean number of days without any hot flushes at week 12 was higher for the BZA/CEE treatment groups (1.8 and 2.8 days for BZA 20 mg/CEE 0.45 and 0.625 mg, respectively) than for the placebo group (0.6 days). At week 12, the percentage of women who had no moderate-to-severe hot flushes was significantly higher for both BZA/CEE doses compared to placebo (25.0% for BZA 20 mg/CEE 0.45 mg (P<0.01) and 40.6% for BZA 20 mg/CEE 0.625 mg (P<0.001) versus 5.8% for placebo. Secondary: Not reported
Pinkerton et al.[114] (2017) SMART-2	DB, MC, PC, RCT Healthy postmenopausal	N= 332 12 weeks	Primary: Time to transient and stable	Primary: At baseline, women had an average of about 10 hot flushes per day.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
BZA 20 mg/CEE 0.45 mg once daily vs BZA 20 mg/CEE 0.625 mg once daily vs placebo once daily	women, 40 to 65 years of age with an intact uterus, with moderate to severe hot flushes (≥7/day or 50/week)		reductions in hot flush frequency Secondary: Not reported	All three treatment groups experienced transient 10% reductions in hot flushes within one day of treatment, 20% reductions within one to two days, and 30% reductions within three days. Median time to a transient 50% reduction in hot flushes was eight days with CEE 0.45 mg/BZA 20 mg, 9.5 days with CEE 0.625 mg/BZA 20 mg, and 10 days with placebo (test of equality over strata log-rank test, P=0.026). Median time to a 90% reduction was 32 days with CEE 0.45 mg/BZA 20 mg, 22.5 days with CEE 0.625 mg/BZA 20 mg, and more than 12 weeks (i.e., not reached during the study) for placebo (P<0.001) Shorter times to stable response relative to placebo were observed within the first three to seven days of treatment. For example, median time to a stable 50% reduction was nine days with CEE 0.45 mg/BZA 20 mg, 10 days with CEE 0.625 mg/BZA 20 mg, and 38 days with placebo (test of equality over strata log-rank test, P<0.001). Median time to a 90% reduction was 83 days with CE 0.45 mg/BZA 20 mg, 29 days with CEE 0.625 mg/BZA 20 mg, and more than 12 weeks (i.e., not reached during the study) for placebo (P<0.001). Stable improvements of 60% to 100% took longer to achieve with CEE 0.45 mg/BZA 20 mg than with the higher dose of CEE 0.625 mg/BZA 20 mg. Women treated with CEE 0.45 mg/BZA 20 mg did not achieve a median time to a 100% reduction in hot flushes during the 12-week trial. Secondary: Not reported
Kagan et al.[115] (2010) SMART-3 BZA 20 mg/CEE 0.45 mg once daily vs BZA 20 mg/CEE 0.625 mg once daily	AC, DB, MC, PC, RCT Healthy postmenopausal women, 40 to 65 years of age with an intact uterus, vaginal cytological smear showing vaginal pH >5.0, and moderate to	N=652 12 weeks	Primary: Proportion of vaginal superficial cells, proportion of parabasal cells, vaginal pH, severity of the most bothersome vulvar/vaginal symptom at 12 weeks	Primary: Mean increases in percentage of superficial cells from baseline to week 12 were significantly greater with BZA 20 mg/CEE 0.625 or 0.45 mg compared to placebo (P<0.01) and BZA 20 mg (P<0.001). Mean decreases from baseline to week 12 in percentage of parabasal cells were also significantly greater with both BZA/CEE doses than with placebo (P<0.001) or BZA 20 mg (P<0.001). Mean vaginal pH significantly decreased from baseline to week 12 with both BZA/CEE doses (P<0.001). No significant change from baseline was observed with placebo or BZA 20 mg. The mean vaginal pH decrease was significantly lower than that of the placebo group for the BZA 20 mg/CEE 0.625 group (P<0.001) but not the BZA 20 mg/CEE 0.45 mg group (P<0.116). Compared to BZA 20 mg,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs BZA 20 mg once daily vs placebo once daily	severe symptoms of vulvovaginal atrophy at screening		Secondary: Not reported	the mean vaginal pH change at week 12 was significantly lower than that with both BZA/CEE doses (P<0.001). At week 12, participants treated with BZA 20 mg/CEE 0.625 mg, but not those treated with BZA 20 mg/CEE 0.45 mg, had significantly greater improvements in their most bothersome symptom compared to participants treated with placebo (P=0.048). The most bothersome symptom improved significantly more with both BZA/CEE doses compared to BZA 20 mg at week 12.
Bachmann et al.[116] (2010) SMART-3 BZA 20 mg/CEE 0.45 mg once daily vs BZA 20 mg/CEE 0.625 mg once daily vs BZA 20 mg once daily vs placebo once daily	AC, DB, MC, PC, RCT Healthy postmenopausal women, 40 to 65 years of age with an intact uterus, vaginal cytological smear showing vaginal pH >5.0, and moderate to severe symptoms of vulvovaginal atrophy at screening	N=652 12 weeks	Primary: Arizona Sexual Experiences (ASEX) Scale, Menopause-Specific Quality of Life (MENQOL) questionnaire, and Menopause Symptoms Treatment Satisfaction Questionnaire (MS-TSQ) Secondary: Not reported	Primary: Treatment with BZA 20 mg/CEE 0.45 or 0.625 mg was associated with improvement in sexual function at week 12, based on individual item scores and the total ASEX score. Compared to BZA 20 mg, there was significant improvement in total ASEX scores with BZA/CEE at week 12 (p<0.001), as well as in scores for ease of arousal, orgasm, and lubrication (p<0.05). Both doses of BZA/CEE significantly improved vasomotor function, sexual function and total scores on the MENQOL questionnaire at week 12 compared to placebo or BZA 20 mg (p<0.05). Subjects treated with BZA 20 mg/CEE 0.625 mg also reported significant improvement in physical function scores compared to placebo (p<0.05). Subjects in the BZA/CEE treatment groups reported significantly greater overall satisfaction on the MS-TSQ compared to subjects in the placebo group (p<0.05) or the BZA 20-mg group (p<0.001). Secondary: Not reported
Mirkin et. al.[117] (2013) SMART-4 BZA 20 mg/CEE 0.45 mg once daily vs	DB, MC, PC, AC, PG, RCT Healthy postmenopausal women, 40 to 65 years of age with an intact uterus	N= 1,061 12 months	Primary: Endometrial hyperplasia, lumbar spine BMD Secondary:	Primary: At one year, no cases of endometrial hyperplasia were identified in the BZA 20 mg/CEE 0.45 mg group, while three cases (1.1%) were confirmed for the BZA 20 mg/CEE 0.625 mg group. All active treatment groups showed significant increases from baseline in lumbar spine BMD at one year (P<0.001) compared to placebo, which showed significant decreases from baseline (P<0.001). The increases for

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
BZA 20 mg/CEE 0.625 mg once daily vs CEE 0.45 mg/MPA 1.5 mg once daily vs placebo once daily			Hip BMD, amenorrhea, breast pain	BZA 20 mg/CEE 0.45 and 0.625 mg were significantly greater than those for placebo (P<0.001 for all) but were significantly less than those observed for CEE 0.45 mg/MPA 1.5 mg (P<0.001). Secondary: For BMD at the total hip, BZA 20 mg/CEE 0.45 and 0.625 mg showed significantly greater increases from baseline compared to placebo (P<0.001). The increase for BZA 20 mg/CEE 0.625 mg was not statistically different from that for CEE 0.45 mg/MPA 1.5 mg. Based on subject daily diary reporting, both BZA/CEE groups showed high rates of cumulative amenorrhea over one year of treatment (ranges of 85.3 to 99.2% and 82.9 to 96.5% for BZA 20 mg/CEE 0.45 and 0.625 mg, respectively). These rates were generally similar to those for placebo (82.0 to 95.4%) but were significantly higher than those for CEE 0.45 mg/MPA 1.5 mg (48.9 to 83.2%; P<0.001). The percentage of subjects in the BZA/CEE treatment groups who reported ≥1 day of breast pain during 4-week cycles over the first three months of therapy (ranges of 5.7 to 9.2% and 5.0 to 6.7% for BZA 20 mg/CEE 0.45 and 0.625 mg, respectively) was similar to that for placebo (4.6 to 9.8%). Compared to CEE 0.45 mg/MPA 1.5 mg (13.3 to 14.6%), significantly lower incidences of breast pain were observed for BZA 20 mg/CEE 0.45 mg (weeks 5 to 8 and 9 to 12; P<0.05) and for BZA 20 mg/CEE 0.625 mg (weeks 1 to 4, 5 to 8, and 9 to 12; P<0.01).
Pinkerton et al.[118] (2013) SMART-5 BZA 20 mg/CEE 0.45 mg once daily vs BZA 20 mg/CEE 0.625 mg once daily	DB, MC, PC, AC, PG, RCT Healthy postmenopausal women, 40 to 65 years of age with an intact uterus, no endometrial hyperplasia or breast cancer at screening or use of	N= 1,843 (N=940 for breast density substudy) 12 months	Primary: Change from baseline in percent dense breast tissue Secondary: Not reported	Primary: At 12 months, there were no significant differences between the BZA-CE or BZA and placebo groups in change from baseline in percent dense breast tissue as determined by mammography. The CEE–MPA group demonstrated a significant (P<0.001) increase in percent dense breast tissue compared to placebo in the modified intent-to-treat population. BZA 20 mg–conjugated estrogens 0.45 and 0.625 mg demonstrated noninferiority compared to placebo in the change from baseline in percent dense breast tissue at 12 months. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs BZA 20 mg once daily vs CEE 0.45 mg/MPA 1.5 mg once daily vs placebo once daily	HT or SERM-containing medications within eight weeks of screening.			
Pinkerton et al.[119] (2014) SMART-5 BZA 20 mg/CEE 0.45 mg once daily vs BZA 20 mg/CEE 0.625 mg once daily vs BZA 20 mg once daily vs CEE 0.45 mg/MPA 1.5 mg once daily vs	DB, MC, PC, AC, PG, RCT Healthy postmenopausal women, 40 to 65 years of age with an intact uterus, no endometrial hyperplasia or breast cancer at screening or use of HT or SERM-containing medications within eight weeks of screening.	N= 1,843 12 months	Primary: BMD at 12 months, endometrial hyperplasia at 12 months, breast density at 12 months Secondary: Cumulative amenorrhea, breast pain	Primary: CEE 0.45 mg/BZA 20 mg, BZA 20 mg, and CEE 0.45 mg/MPA 1.5 mg significantly increased lumbar spine, total hip, and femoral neck BMD compared to placebo (P<0.01 for all) and showed significantly greater decreases from baseline in serum bone turnover markers compared to placebo (P<0.01 for all) at 12 months. There were no differences among groups in the incidence of fractures. Rates of endometrial hyperplasia were <1% and similar for CEE 0.45 mg/BZA 20 mg, BZA 20 mg, CEE 0.45 mg/MPA 1.5 mg, and placebo. CEE 0.45 mg/BZA 20 mg (P<0.05) and CEE 0.45 mg/MPA 1.5 mg (P<0.001) showed significantly greater increases from baseline in endometrial thickness compared to placebo. Secondary: The percentage of subjects reporting at least one day of breast tenderness was similar for CEE 0.45 mg/BZA 20 mg, BZA alone, and placebo but significantly lower than that for CEE/MPA (P<0.001 versus placebo and P<0.01 versus CEE/BZA or BZA alone for all time periods). Rates of cumulative amenorrhea were similar for CEE 0.45 mg/BZA 20 mg, BZA 20 mg, and placebo over one year of treatment and significantly higher than those for CEE/MPA at each time point (P<0.001). Incidences of adverse events and treatment-emergent adverse events were similar

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo once daily				with CEE/BZA and placebo; more subjects in the CEE/MPA group discontinued the study due to adverse events compared to other groups.
Pinkerton et al.[120] (2014) BZA 20mg/CEE 0.45 vs BZA 20mg/CEE 0.625 mg vs placebo	PH Subgroups of women from the SMART-1 and SMART-2 trials who were either <5 or ≥5 years since menopause (YSM)	N=1,592 12 weeks	Primary: Frequency and severity of hot flushes, health-related quality of life (HRQoL), sleep, satisfaction with treatment, cumulative amenorrhea, and breast pain Secondary: Not reported	Primary: In both the SMART-1 and SMART-2 trials, BZA 20mg/CEE 0.45 and 0.625 mg treatment showed a significantly greater decrease in the average daily number of moderate-to-severe hot flushes in both the <5 and ≥5 YSM subgroups at three months compared to placebo. The BZA 20 mg/CEE 0.45 and 0.625 mg groups in both studies showed significantly greater improvement from baseline in total MENQOL scores at three months compared to placebo (P≤0.05). There was no difference between subjects who were <5 or ≥5 YSM. In the SMART-1 trial, both the <5 and ≥5 YSM subgroups showed significant improvement from baseline in some sleep parameters with BZA/CEE treatment compared to placebo at three months. Similarly, in the SMART-2 trial, both BZA/CEE doses showed significantly greater improvement from baseline in various sleep parameters for the <5 and ≥5 YSM subgroups compared to placebo at three months. Satisfaction with treatment was assessed in the SMART-2 trial. BZA 20 mg/ CEE 0.45 and 0.625 mg improved subjects' satisfaction with treatment compared to placebo in both the <5 and ≥5 YSM subgroups. A significantly greater percentage of BZA/CEE-treated subjects in both the <5 and ≥5 YSM subgroups were satisfied with treatment overall (range, 69 to 83%) at month three compared to placebo (range, 32 to 51%; P<0.05). Overall, treatment with BZA 20mg/CEE 0.45 and 0.625 mg in the SMART-1 and SMART-2 trials was associated with low rates of breast pain (range, 2 to 13%), similar to that for placebo (range, 0 to 9%), in both subgroups. Secondary: Not reported
Komm et al.[121] (2015)	MA of the SMART trials	N=6109	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
SMART trials BZA 20 mg/CEE 0.45 mg once daily vs BZA 20 mg/CEE 0.625 mg once daily vs BZA/CEE any dose vs placebo	Healthy, non-hysterectomized, postmenopausal women	Up to 2 years	VTEs, CHD, and cerebrovascular events Secondary: Not reported	The incidence of VTEs with CE 0.45 mg/BZA 20 mg was low (0.2%) and similar to placebo (0.1%), as was the incidence in the group of women given any dose of CE/BZA (0.1%). There were no VTEs in any participants given CE 0.625 mg/BZA 20 mg. Stroke occurred in one (0.06%) participant in the CE 0.45 mg/BZA 20 mg group, one (<0.06%) in the CE 0.625 mg/BZA 20 mg group, and four (0.08%) among all participants who received any CE/BZA dose. There were two adjudicated TIAs in the CE 0.45 mg/BZA 20 mg group and eight (0.2%) among participants treated with any CE/BZA dose. None occurred in the CE 0.625 mg/BZA 20 mg or placebo groups. Adjudicators confirmed CHD events in four (0.3%) participants given CE 0.45 mg/BZA 20 mg, four (0.3%) given CE 0.625 mg/BZA 20 mg, a total of 14 (0.3%) given any CE/BZA dose, and three (0.2%) with placebo. Rates of MI were 0.2%, 0.1%, 0.1%, and 0.2%, respectively. Secondary: Not reported

*Estradot® is marketed in the United States as Vivelle-Dot®.
†Menorest® is marketed in the United States as Vivelle®.
‡Product is not available in the United States.
Study design abbreviations: AC=active-controlled, DB=double-blind, DD=double-dummy, ES=extension study, MA=meta-analysis, MC=multicenter, OL=open-label, OS=observational study, PC=placebo-controlled, PG=parallel-group, PH=post-hoc analysis, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, XO=cross-over
Miscellaneous abbreviations: 3MSE= Modified Mini-Mental State Examination, AIP=atherogenic index of plasma, AUC=area under the curve, BMD=bone mineral density, BP=blood pressure, BZA= bazedoxifene, CABG= coronary artery bypass graft, CBG=cortisol binding globulin, CEE=conjugated equine estrogen, CHD=coronary heart disease, CHF= congestive heart failure, CI=confidence interval, CRP=C-reactive protein, DBP=diastolic blood pressure, FI=fluctuation index, FSH= follicle-stimulating hormone, HDL-C= high-density lipoprotein cholesterol, HR=hazard ratio, HOMA-IR=homeostasis model assessment of insulin resistance, ICAM=intracellular adhesion molecule, IGF-1=insulin-like growth factor 1, IL-6=interleukin-6, LDL-C= low-density lipoprotein cholesterol, MI= myocardial infarction, MPA=medroxyprogesterone, OR=odds ratio, PCI= percutaneous coronary interventions, PE=pulmonary embolism, QCT=quantitative computed tomography, QOL=quality of life, RR=relative risk, SBP=systolic blood pressure, SHBG=sex hormone binding globulin, SMART= selective estrogens, menopause, and response to therapy trials, TBG=thyroxine binding globulin, TC=total cholesterol, TG=triglyceride, VLDL-C=very-low-density lipoprotein cholesterol, VTE=venous thromboembolism, WHI=Women's Health Initiative, WHIMS=Women's Health Initiative Memory Study

Additional Evidence

Dose Simplification
Two studies demonstrated that continuous administration of hormone therapy was better tolerated than sequential administration, which led to an improvement in compliance. Doren et al. found that women who were treated with continuous estrogen and progestin therapy (estradiol 2 mg, estriol 1 mg, and norethisterone 1 mg) had better compliance than women who were treated sequentially with estradiol valerate 2 mg daily and medroxyprogesterone acetate 5 mg daily for 12 days of the month (93 vs 66%, respectively). The most frequent reason for discontinuation of therapy was uterine bleeding.[122] Eiken et al. found that the continuous administration of estradiol and norethisterone improved compliance compared to the sequential administration of the same product. The eight year compliance rate for the continuous combination regimen was 46% compared to 32% for the sequential regimen. The difference in compliance rates was due to monthly bleeding associated with the sequential regimen.[123]

Stable Therapy
Place et al. evaluated women whose menopausal symptoms were satisfactorily controlled on conjugated estrogens. Participants were randomly selected to continue with oral therapy or to switch to transdermal estradiol. The results showed that women who switched to transdermal therapy had similar relief of menopausal symptoms as the women who remained on oral conjugated estrogens.[49]

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 12. Relative Cost of the Estrogens

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Estradiol	tablet, topical gel, topical spray, transdermal patch, vaginal cream, vaginal ring, vaginal tablet	Climara®*, Divigel®*, Elestrin®, Estrace®*, Estring®, Evamist®, Menostar®, Minivelle®*, Vagifem®*, Vivelle-Dot®*	$$$$	$
Estradiol acetate	vaginal ring	Femring®	$$$$$	N/A
Estradiol cypionate	injection	Depo-Estradiol®	$$$$	N/A

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Estradiol valerate	injection	Delestrogen®*	$$	$$$$
Estradiol and drospirenone	tablet	Angeliq®	$$$$	N/A
Estradiol and levonorgestrel	transdermal patch	Climara Pro®	$$$$	N/A
Estradiol and norethindrone	tablet, transdermal patch	Activella®*, Amabelz®*, Combipatch®, Mimvey®*	$$$$$	$
Estradiol and norgestimate	tablet	Prefest®	$$$$	N/A
Estradiol and progesterone	capsule	Bijuva®	$$$$$	N/A
Estrogens, conjugated	injection, tablet, vaginal cream	Premarin®	$$$$$	N/A
Estrogens, conjugated and bazedoxifene	tablet	Duavee®	$$$$$	N/A
Estrogens, conjugated and medroxyprogesterone	tablet	Premphase®, Prempro®	$$$$$	N/A
Estrogens, esterified	tablet	Menest®	$$$	N/A
Norethindrone and ethinyl estradiol	tablet	Jinteli®*	$$$$	$$

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

X. Conclusions

The estrogens are approved for the treatment of vasomotor symptoms associated with menopause, vulvar and vaginal atrophy, abnormal uterine bleeding, hypoestrogenism, prevention of postmenopausal osteoporosis, as well as for the palliative treatment of prostate and breast cancer.[1-3] They are available in a variety of dosage forms, including injectable, oral, topical, transdermal, and vaginal preparations. Estradiol, estradiol valerate, estradiol-norethindrone, and norethindrone-ethinyl estradiol are available in a generic formulation.

The recommendations for the use of hormone therapy have changed since the Women's Health Initiative studies were published.[4-14] The use of hormone therapy was associated with an increased risk of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis.[16-17] There are no recommendations for the use of menopausal hormonal therapy for cardiovascular prevention at this time. Long-standing evidence suggests either no benefit or increased risk for women when hormonal therapy is used. However, researchers have and continue to investigate the potential for a "timing hypothesis" where hormonal therapy may be of benefit (related to cardiovascular risk) among women closer to the time of menopausal onset. Providers are recommended to review each woman's risk factor profile and provide a tailored and shared decision-making discussion when menopausal hormonal therapy is considered, even among younger perimenopausal women..[7,11-14] In the absence of contraindications, in women aged younger than 60 years or within 10 years of menopause onset, systemic hormone therapy is an appropriate therapy to protect against bone loss.[4,6-7] Hormone therapy remains the most effective treatment for moderate-to-severe menopausal symptoms.[414]

It is recommended that the lowest possible dose be used for the shortest amount of time.[4-7,12-13] Vaginal formulations are recommended for women who only have symptoms of vulvar and vaginal atrophy.[7,10,13] Systemic progestogen is required for endometrial protection of unopposed estrogen therapy.[4,7,12-13]

A variety of clinical trials have been conducted with the estrogens, which have evaluated efficacy, safety, tolerability, as well as pharmacokinetic and pharmacodynamic end points. Numerous studies have demonstrated a similar improvement in menopausal symptoms with the various estrogen preparations.[7,10,37,39,43,45-53,56-58,62-65,67,70,92] There were no studies found in the medical literature that compared the continuous administration of a combination product versus the concomitant administration of the individual components. There is no evidence that natural estrogens are more or less hazardous than synthetic estrogens at equivalent doses.[1-3]

The efficacy and safety of bazedoxifene with conjugated estrogens have been evaluated in the phase 3 Selective estrogens, Menopause And Response to Therapy (SMART) trials conducted in generally healthy postmenopausal women.[107-119] Bazedoxifene-conjugated estrogens have shown an improvement in menopausal symptoms and

bone loss and a favorable safety profile when compared to placebo.[107-121] There were no studies found that compared bazedoxifene-conjugated estrogens to another selective estrogen receptor modifier and estrogen combination regimen.

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

Therefore, all brand products 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 estrogen 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 Alpha-Glucosidase Inhibitors
AHFS Class 682002
November 8, 2023

I. Overview

Diabetes mellitus is a chronic condition which results in hyperglycemia. It is differentiated into four main classes: 1) type 1 diabetes; 2) type 2 diabetes; 3) gestational diabetes; and 4) other types (drug- or chemical-induced, genetic defects in β-cell function or insulin action, and diseases of the exocrine pancreas). Type 2 diabetes is the most prevalent form of the disease in the United States. Inadequate glycemic control may lead to both acute and long-term complications, including microvascular and macrovascular events. There are a variety of oral and injectable antidiabetic agents currently available to treat diabetes. The antidiabetic agents are categorized into 12 different American Hospital Formulary Service (AHFS) classes, which differ with regards to their mechanism of action, efficacy, safety profiles, tolerability, and ease of use.

The alpha-glucosidase inhibitors are approved for use as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. The antihyperglycemic action of acarbose results from a competitive, reversible inhibition of pancreatic alpha-amylase and membrane-bound intestinal alpha-glucoside hydrolase enzymes. The antihyperglycemic action of miglitol results from a reversible inhibition of membrane-bound intestinal alpha-glucoside hydrolase enzymes. This enzyme inhibition leads to a delay in glucose absorption and subsequent lowering of postprandial hyperglycemia.[1-2]

The alpha-glucosidase inhibitors that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Acarbose and miglitol are available in a generic formulation. This class was last reviewed in November 2021.

Table 1. Alpha-Glucosidase Inhibitors Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Acarbose	tablet	Precose®*	acarbose
Miglitol	tablet	N/A	miglitol

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

II. Evidence-Based Medicine and Current Treatment Guidelines

Current clinical guidelines are summarized in Table 2. Please note that guidelines addressing the treatment of type 2 diabetes are presented globally, addressing the role of various medication classes.

Table 2. Treatment Guidelines Using the Alpha-Glucosidase Inhibitors

Clinical Guideline	Recommendation(s)
American Diabetes Association: **Standards of Care in Diabetes (2023)**[3]	Current criteria for the diagnosis of diabetes • The following are the criteria for a diagnosis of diabetes: glycosylated hemoglobin (HbA_{1c}) ≥6.5%, or a fasting plasma glucose (FPG) ≥126 mg/dL, or a two-hour plasma glucose ≥200 mg/dL during an oral glucose tolerance test or patients with classic symptoms of hyperglycemia, or classic symptoms of hyperglycemia or hyperglycemic crisis (random plasma glucose ≥200 mg/dL). Prevention or delay of type 2 diabetes • Refer adults with overweight/obesity at high risk of type 2 diabetes, as typified by the Diabetes Prevention Program (DPP), to an intensive lifestyle behavior change program to achieve and maintain a weight reduction of at least 7% of initial body weight through healthy reduced-calorie diet and ≥150 minutes/week of moderate-intensity physical activity.

Clinical Guideline	Recommendation(s)
	• A variety of eating patterns can be considered to prevent diabetes in individuals with prediabetes. • Metformin therapy for prevention of type 2 diabetes should be considered i in adults at high risk of type 2 diabetes, as typified by the DPP, especially those aged 25 to 59 years with BMI ≥35 kg/m^2, higher FPG) (e.g., ≥110 mg/dL), and higher A1C (e.g., ≥6.0%), and in individuals with prior gestational diabetes mellitus (GDM). • Long-term use of metformin may be associated with biochemical vitamin B12 deficiency; consider periodic measurement of vitamin B12 levels in metformin-treated individuals, especially in those with anemia or peripheral neuropathy. Glycemic goals in adults • An A1C goal for many nonpregnant adults of <7% (53 mmol/mol) without significant hypoglycemia is appropriate. • If using ambulatory glucose profile (AGP)/glucose management indicator (GMI) to assess glycemia, a parallel goal for many nonpregnant adults is time in range (TIR) of >70% with time below range (TBR) <4% and time <54 mg/dL <1%. For those with frailty or at high risk of hypoglycemia, a target of >50% TIR with <1% TBR is recommended. • On the basis of health care provider judgment and patient preference, achievement of lower A1C levels than the goal of 7% may be acceptable and even beneficial if it can be achieved safely without significant hypoglycemia or other adverse effects of treatment. • Less stringent A1C goals (such as <8% [64 mmol/mol]) may be appropriate for patients with limited life expectancy or where the harms of treatment are greater than the benefits. HCPs should consider deintensification of therapy if appropriate to reduce the risk of hypoglycemia in patients with inappropriate stringent A1C targets. Pharmacologic therapy for type 1 diabetes • Most individuals with type 1 diabetes should be treated with multiple dose insulin injections (three to four injections per day of basal and pre-prandial insulin) or continuous subcutaneous (SC) insulin infusion therapy. • Most patients should use rapid-acting insulin analogs to reduce hypoglycemia risk. • Patients with type 1 diabetes should receive education on how to match prandial insulin doses to carbohydrate intake, premeal blood glucose, and anticipated physical activity. Pharmacologic therapy for type 2 diabetes • Healthy lifestyle behaviors, diabetes self-management education and support, avoidance of clinical inertia, and social determinants of health should be considered in the glucose-lowering management of type 2 diabetes. Pharmacologic therapy should be guided by person-centered treatment factors, including comorbidities and treatment goals. • In adults with type 2 diabetes and established/high risk of atherosclerotic cardiovascular disease, heart failure, and/or chronic kidney disease, the treatment regimen should include agents that reduce cardiorenal risk. • Pharmacologic approaches that provide adequate efficacy to achieve and maintain treatment goals should be considered, such as metformin or other agents, including combination therapy. • Weight management is an impactful component of glucose-lowering management in type 2 diabetes. The glucose-lowering treatment regimen should consider approaches that support weight management goals. • Metformin should be continued upon initiation of insulin therapy (unless contraindicated or not tolerated) for ongoing glycemic and metabolic benefits.

Clinical Guideline	Recommendation(s)
	• Early combination therapy can be considered in some individuals at treatment initiation to extend the time to treatment failure. • The early introduction of insulin should be considered if there is evidence of ongoing catabolism (weight loss), if symptoms of hyperglycemia are present, or when A1C levels (>10% [86 mmol/mol]) or blood glucose levels (≥300 mg/dL [16.7 mmol/L]) are very high. • A person-centered approach should guide the choice of pharmacologic agents. Consider the effects on cardiovascular and renal comorbidities, efficacy, hypoglycemia risk, impact on weight, cost and access, risk for side effects, and individual preferences. • Among individuals with type 2 diabetes who have established atherosclerotic cardiovascular disease or indicators of high cardiovascular risk, established kidney disease, or heart failure, a sodium–glucose cotransporter 2 inhibitor and/or glucagon-like peptide 1 receptor agonist with demonstrated cardiovascular disease benefit is recommended as part of the glucose-lowering regimen and comprehensive cardiovascular risk reduction, independent of A1C and in consideration of person-specific factors. • In adults with type 2 diabetes, a glucagon-like peptide 1 receptor agonist is preferred to insulin when possible. • If insulin is used, combination therapy with a glucagon-like peptide 1 receptor agonist is recommended for greater efficacy, durability of treatment effect, and weight and hypoglycemia benefit. • Recommendation for treatment intensification for individuals not meeting treatment goals should not be delayed. • Medication regimen and medication-taking behavior should be reevaluated at regular intervals (every three to six months) and adjusted as needed to incorporate specific factors that impact choice of treatment. • Clinicians should be aware of the potential for over-basalization with insulin therapy. Clinical signals that may prompt evaluation of over-basalization include basal dose more than ~0.5 units/kg/day, high bedtime–morning or post-preprandial glucose differential, hypoglycemia (aware or unaware), and high glycemic variability. Indication of over-basalization should prompt reevaluation to further individualize therapy.
American Diabetes Association/ European Association for the Study of Diabetes: **Management of Hyperglycemia in Type 2 Diabetes. A consensus report by the American Diabetes Association and the European Association for the Study of Diabetes (2022)**[4]	Consensus recommendations • All people with type 2 diabetes should be offered access to ongoing diabetes self-management education and support programs. • Providers and health care systems should prioritize the delivery of person-centered care. • Optimizing medication adherence should be specifically considered when selecting glucose-lowering medications. • Medical nutrition therapy focused on identifying healthy dietary habits that are feasible and sustainable is recommended in support of reaching metabolic and weight goals. • Physical activity improves glycemic control and should be an essential component of type 2 diabetes management. • Adults with type 2 diabetes should engage in physical activity regularly (>150 min/week of moderate- to vigorous-intensity aerobic activity) and be encouraged to reduce sedentary time and break up sitting time with frequent activity breaks. • Aerobic activity should be supplemented with two to three resistance, flexibility, and/or balance training sessions/week. Balance training sessions are particularly encouraged for older individuals or those with limited mobility/poor physical function. • Metabolic surgery should be considered as a treatment option in adults with type 2 diabetes who are appropriate surgical candidates with a BMI ≥40.0 kg/m^2 (BMI

Clinical Guideline	Recommendation(s)
	≥37.5 kg/m^2 in people of Asian ancestry) or a BMI of 35.0 to 39.9 kg/m^2 (32.5 to 37.4 kg/m^2 in people of Asian ancestry) who do not achieve durable weight loss and improvement in comorbidities (including hyperglycemia) with nonsurgical methods. • In people with established CVD, a GLP-1 RA with proven benefit should be used to reduce MACE, or an SGLT2i with proven benefit should be used to reduce MACE and HF and improve kidney outcomes. • In people with CKD and an eGFR ≥20 ml/min per 1.73 m^2 and a urinary albumin/creatinine ratio >3.0 mg/mmol (>30 mg/g), an SGLT2i with proven benefit should be initiated to reduce MACE and HF and improve kidney outcomes. Indications and eGFR thresholds may vary by region. If such treatment is not tolerated or is contraindicated, a GLP-1 RA with proven cardiovascular outcome benefit could be considered to reduce MACE and should be continued until kidney replacement therapy is indicated. • In people with HF, SGLT2i should be used because they improve HF and kidney outcomes. • In individuals without established CVD but with multiple cardiovascular risk factors (such as age ≥55 years, obesity, hypertension, smoking, dyslipidemia, or albuminuria), a GLP-1 RA with proven benefit could be used to reduce MACE, or an SGLT2i with proven benefit could be used to reduce MACE and HF and improve kidney outcomes. • In people with HF, CKD, established CVD, or multiple risk factors for CVD, the decision to use a GLP-1 RA or SGLT2i with proven benefit should be independent of background use of metformin. • SGLT2i and GLP-1 RA reduce MACE, which is likely to be independent of baseline HbA1c. In people with HF, CKD, established CVD, or multiple risk factors for CVD, the decision to use a GLP-1 RA or an SGLT2i with proven benefit should be independent of baseline HbA1c. • In general, selection of medications to improve cardiovascular and kidney outcomes should not differ for older people. • In younger people with diabetes (<40 years), consider early combination therapy. • In women with reproductive potential, counseling regarding contraception and taking care to avoid exposure to medications that may adversely affect a fetus are important.
American Association of Clinical Endocrinologists/ American College of Endocrinology: **Clinical Practice Guidelines for Developing a Diabetes Mellitus Comprehensive Care Plan (2022)**[5]	<u>Antihyperglycemic Pharmacotherapy for Persons with Type 2 Diabetes</u> • Individualized pharmacotherapy for persons with T2D should be prescribed based on evidence for benefit that includes glucose lowering, avoidance of hypoglycemia and weight gain, and reduction of cardio-renal risk. • Persons with T2D and their health care professionals should use patient-centered shared decision-making to agree on therapy targets and treatments as well as a regimen for glucose monitoring (i.e., BGM, structured BGM, or CGM). • Glycemic targets include A1C, BGM, and, for those using CGM, achievement of CGM targets such as time in range (TIR), percentage in low and very low range, time above range, and glycemic variability. Nonglycemic targets include avoidance of hypoglycemia, control of BP, lipids, other CVD risk factors, and achieving and maintaining a healthy body weight. • Independent of glycemic control, targets, or treatment, if there is established or high risk for ASCVD, HF, and/or CKD, clinicians should prescribe a GLP-1 RA or an SGLT2i with proven efficacy for the specific condition(s) of the person with T2D being treated. • DM therapy should be individualized based on level of glycemia and the presence of comorbidities, complications, and access. Metformin is often the preferred initial therapy. Other agents may be appropriate as first line or in addition to

Clinical Guideline	Recommendation(s)
	metformin to reduce BG and/or to address specific comorbidities (such as ASCVD, HF, CKD, obesity, NAFLD), independent of glucose-lowering effects. • For some recently diagnosed individuals with T2D and more severe hyperglycemia (A1C ≥7.5%), unlikely to attain the A1C target with a single agent, early combination pharmacotherapy should be considered, usually to include metformin plus another agent that does not cause hypoglycemia, especially a GLP-1 RA, SGLT2i, or dipeptidyl peptidase 4 (DPP-4) inhibitor. • For newly diagnosed persons with T2D and an entry A1C >9.0% and/or ≥1.5% above target, one should initiate, along with lifestyle modifications, dual- or possibly triple-combination pharmacotherapy usually including metformin. Basal insulin along with noninsulin therapy is recommended if there are significant signs or symptoms of hyperglycemia, especially including catabolism (e.g., weight loss) or a very high A1C >10% (86 mmol/mol) or BG levels (≥300 mg/dL [16.7 mmol/L]). • Clinicians should discuss with persons with T2D the likelihood that most persons with T2D ultimately require a combination of multiple complementary antihyperglycemic agents, in addition to lifestyle interventions, to attain and maintain optimal glycemic control. • The DM care team should assess medication adherence and safety and glycemic control in persons with T2D quarterly or more frequently as needed. Subsequent visits will depend upon the metabolic targets achieved and the stability of metabolic control. • Persons with T2D who start on metformin should continue it unless intolerance or contraindications occur. When intensification of antihyperglycemic treatment is needed, other agents should be added to metformin. • Most persons with T2D who require intensification of antihyperglycemic therapy with a GLP-1 RA or insulin should initially be prescribed a GLP-1 RA. If further intensification is required, one should prescribe a basal insulin or a switch to a fixed-ratio combination of a basal insulin and a GLP-1 RA (insulin glargine U100 + lixisenatide [GlarLixi] or insulin degludec + liraglutide [IdegLira]). • Insulin should be prescribed for persons with T2D when noninsulin antihyperglycemic therapy fails to achieve target glycemic control or when a person has symptomatic hyperglycemia. • Long-acting basal insulin analogs are the recommended initial choice of insulin therapy for persons with T2D. The insulin analogs glargine (U100 or U300), degludec (U100 or U200), or detemir are preferred over intermediate-acting Neutral Protamine Hagedorn (NPH) insulin because analog insulins have demonstrated less hypoglycemia in some studies. Glargine U300 and degludec can be associated with less hypoglycemia than glargine U100 or detemir. • Many persons with T2D receiving basal insulin and not at goal A1C can have significantly improved glycemia by the addition of a GLP-1 RA or being switched to a fixed-ratio combination basal insulin–GLP-1 RA (GlarLixi or IdegLira). One of these changes should be considered before adding a meal-time insulin for postprandial glycemic control. • When control of postprandial hyperglycemia is needed and a basal insulin and a GLP-1 RA are already being used, preference should be given to rapid-acting insulins (the analogs lispro, aspart, and glulisine or the rapid-acting inhaled human insulin powder) over regular human insulin. The former have a more consistent and a more rapid onset and offset of action with less risk of hypoglycemia. • Ultra-rapid-acting insulins (faster-acting insulin aspart, lispro aabc, and [human insulin] inhalation powder) may allow a decrease in the time between insulin administration and food intake and reduce the postprandial peak of PG as compared with rapid-acting insulins. The significance of this on long-term complications is unknown.

Clinical Guideline	Recommendation(s)
	• Basal-bolus insulin regimens or continuous subcutaneous insulin infusion (CSII) (i.e., insulin pump) allow for adjustment of insulin doses according to carbohydrate intake and activity levels and are recommended for intensive insulin therapy in persons with T2D. • Premixed insulin formulations (fixed combinations of shorter- and longer-acting components) of human or analog insulin may be considered for persons with T2D who have consistent dietary and exercise patterns and in whom adherence to more intensive insulin regimens is problematic. However, these preparations have reduced dosage flexibility and may increase the risk of hypoglycemia compared with basal insulin or basal-bolus regimens. • In persons with T2D who are treated with basal-bolus insulin therapy, adding a GLP-1 RA, or switching to a fixed-ratio combination of a GLP-1 RA and a basal insulin, or adding an SGLT2i or pramlintide (less commonly used) may be able to reduce postprandial hyperglycemia, A1C, and weight. GLP-1 RAs may also allow reduction or discontinuation of bolus insulin in some individuals. <u>How should insulin therapy be used for management of persons with type 1 diabetes?</u> • Insulin must be used to treat all persons with T1D. • Physiologic insulin replacement regimens, which provide both basal and prandial (meal-related or bolus) insulin, are recommended for most persons with T1D. • Achievement of glucose targets using either MDI of insulin or CSII, is needed to prevent development of life-threatening crises, such as acute hyperglycemic crises (DKA and hyperglycemic hyperosmolar state) and catabolic state. • A multi-component self-management DM education program is recommended for persons with T1D. Ideally, this is provided by a professional with expertise (i.e., certified diabetes care and education specialist) in the topics of healthy lifestyle, insulin technique including prandial insulin dosing guided by carbohydrate counting and diet adjustments for special situations, such as physical activity and prolonged fasting. Instruction is also needed in how to deal with sick days and prevention of DKA and hypoglycemia, and other relevant issues. Due to changes in DM self-management practices and each individual's medical history, personal and cultural background, and educational needs, specific education topics may need to be repeated at regular intervals. • The ideal insulin regimen should be personalized to an individual's needs and glycemic targets, attempting to better emulate physiological insulin replacement to maintain near normoglycemia, to prevent the development and progression of DM complications, while minimizing hypoglycemia and providing flexibility for specific daily life situations/scenarios such as: exercise, sleep, acute illness, psychological stress, etc. • Insulin regimens usually should involve the use of insulin analogs for most persons with T1D and include the following approaches: o MDI, which usually involve 1 to 2 subcutaneous injections daily of basal insulin to suppress ketogenesis and gluconeogenesis and to control glycemia between meals and overnight, and subcutaneous injections of prandial insulin or use of inhaled insulin before each meal to control meal-related glycemic excursions. CGM is the preferred method of glucose monitoring for all individuals with T1D. o Insulin pump therapy (CSII) provides constant/continuous infusion of fast-acting insulin driven by mechanical force and delivered via a cannula inserted under the skin. CSII can improve (or enhance) glycemic control and should be an option for insulin delivery for appropriate persons with DM. Ideally, these individuals should also use CGM as stated in R13.6.a. o Automated insulin delivery systems (AIDs), which include an insulin pump, an integrated CGM, and computer software algorithm, aim to better emulate physiological insulin replacement and achieve glycemic targets. This technology is recommended for many persons with T1D since its use

Clinical Guideline	Recommendation(s)
	has been shown to increase TIR while often reducing hypoglycemia or at least without causing increased hypoglycemia. ○ Open-loop (use of a pump and sensor which do not communicate) and sensor-augmented pump (SAP) systems: (CGM communicates with pump facilitating needed adjustments to basal rate; temporary interruption of insulin delivery when glucose levels are low or forecast to be low within 30 min). Insulin pump with a CGM or an SAP is recommended to manage persons with DM treated with intensive insulin management who prefer not to use AIDs or have no access to them. How should diabetes mellitus in pregnancy be managed? • For women with GDM, the following treatment goals are recommended: preprandial glucose concentration ≤95 mg/dL and either a 1-h post-meal glucose ≤140 mg/dL or a 2-h post-meal glucose ≤120 mg/dL to decrease adverse fetal outcomes. • All women with preexisting DM (T1D, T2D, or previous GDM) need access to preconception care and counseling to ensure adequate nutrition, healthy weight, and glucose control before conception, during pregnancy, and in the postpartum period. • Rapid-acting insulin analogs (insulin-lispro, insulin-aspart) should be used to treat postprandial hyperglycemia in pregnant women. • Options for basal insulin include long-acting insulin (e.g., NPH, detemir, or glargine) or rapid-acting insulin via a CSII. Regular insulin, although not recommended as first-line therapy, is acceptable to use in managing pregnant women with DM when rapid-acting insulin analogs are not available. • Insulin is the preferred therapeutic choice for pregnant women with GDM or T2D, but metformin has been given a category B for pregnancy with accumulating clinical evidence of metformin's safety during the first trimester and beyond. Metformin has been shown to improve pregnancy and fetal outcomes except for increased rates of infants with SGA and later onset of obesity. The prescriber should discuss the potential risks and benefits of oral agent therapy during pregnancy as well as the need for longer-term outcome studies.
American Association of Clinical Endocrinologists/ American College of Endocrinology: **Consensus Statement on the Comprehensive Type 2 Diabetes Management Algorithm (2023)**[6]	Principles underlying the algorithm • Lifestyle modification underlies all therapy. • Maintain or achieve optimal weight. • Choice of antihyperglycemic therapy reflects glycemic targets, atherosclerotic cardiovascular disease (ASCVD), congestive heart failure (CHF), chronic kidney disease (CKD), overweight/obesity, and nonalcoholic fatty liver disease (NAFLD). • Choice of therapy includes ease of use and access. • Optimal hemoglobin A1c (A1C) is ≤6.5% or as close to normal as is safe and achievable for most patients. • Individualize all glycemic targets (A1C, glucose management indicator [GMI], time in range [TIR], fasting blood glucose [FBG], and PPG). • Get to goal as soon as possible (adjust ≤3 months). • Avoid hypoglycemia. Hypoglycemia, defined as blood glucose (BG) <70 mg/dL, is associated with an increased risk for adverse outcomes including mortality. • CGM is highly recommended to assist persons with diabetes in reaching goals safely. • Comorbidities must be managed for comprehensive care. Algorithm summative information

Clinical Guideline	Recommendation(s)
	• The algorithm is intended as a more concise document than the guideline, providing easily accessible, visual guidance for decision-making in the clinic setting. • In this 2023 algorithm, there continues to be an emphasis on lifestyle modification and treatment of overweight/obesity as key pillars of the management of prediabetes and DM. • The importance of appropriate management of the atherosclerotic risk factors of dyslipidemia and hypertension is highlighted. • One notable new theme is an obvious emphasis on a complication-centric approach, beyond glucose levels, to frame decisions regarding first-line pharmacologic choices for the treatment of persons with diabetes. • The algorithm is divided into discrete graphic sections that outline the principles for management of T2D and guide management of adiposity-based chronic disease (ABCD), prediabetes, and atherosclerotic risk factors of dyslipidemia and hypertension. In addition, the algorithms for antihyperglycemic agents include both complication-centric and glucose-centric approaches, and there is direction for insulin initiation and titration. Tables summarizing the benefits and risks of antihyperglycemic medications (updated) and weight-loss pharmacotherapy (new) are provided.

American Academy of Pediatrics: **Management of Newly Diagnosed Type 2 Diabetes Mellitus (T2DM) in Children and Adolescents (2013)**[7]	• Clinicians must ensure that insulin therapy is initiated for children and adolescents with T2DM who are ketotic or in diabetic ketoacidosis and in whom the distinction between types 1 and 2 diabetes mellitus is unclear and, in usual cases, should initiate insulin therapy for patients.
	  ○ Who have random venous or plasma blood glucose (BG) concentrations ≥250 mg/dL.
	  ○ Whose HbA_{1c} is >9%.
	• In all other instances, clinicians should initiate a lifestyle modification program, including nutrition and physical activity, and start metformin as first-line therapy for children and adolescents at the time of diagnosis of T2DM.
	• Monitoring of HbA_{1c} concentrations is recommended every three months and intensifying treatment is recommended if treatment goals for finger-stick BG and HbA_{1c} concentrations are not being met.
	• Advise patients to monitor finger-stick BG concentrations in patients who:
	  ○ Are taking insulin or other medications with a risk of hypoglycemia; or
	  ○ Are initiating or changing their diabetes treatment regimen; or
	  ○ Have not met treatment goals; or
	  ○ Have intercurrent illnesses.
	• Incorporate the Academy of Nutrition and Dietetics' *Pediatric Weight Management Evidence-Based Nutrition Practice Guidelines* in dietary or nutrition counseling of patients with T2DM at the time of diagnosis and as part of ongoing management.
	• Encourage children and adolescents with T2DM to engage in moderate-to-vigorous exercise for at least 60 minutes daily and to limit nonacademic "screen time" to less than two hours a day.

American Diabetes Association: **Type 1 Diabetes in Children and Adolescents: A Position Statement by the American Diabetes Association (2018)**[8]	<u>Blood Glucose Management: Monitoring and Treatment</u> • Most children with type 1 diabetes should be treated with intensive insulin regimens via either multiple daily injections of prandial insulin and basal insulin or continuous subcutaneous insulin infusion. • An HbA_{1c} target of <7.5% should be considered in most children and adolescents but should be individualized based on the needs and situation of the patient and family. • Children and adolescents with type 1 diabetes should have blood glucose levels monitored up to six to ten times/day including premeal, pre-bedtime, and as needed

Clinical Guideline	Recommendation(s)
	for safety (e.g., exercise, driving, illness, or the presence of symptoms of hypoglycemia). • Continuous blood glucose monitoring should be considered in all children and adolescents whether using insulin injections or an insulin pump. • In pediatric patients with type 1 diabetes automated insulin delivery systems can improve glycemic control and reduce hypoglycemia. <u>Lifestyle Management</u> • Individualized medical nutrition therapy is recommended for children and adolescents with type 1 diabetes. • Monitoring carbohydrate intake, whether by carbohydrate counting or experience-based estimation, is key to achieving optimal glycemic control. • Exercise if recommended for all children and adolescents with type 1 diabetes. The suggested goal is 60 minutes of moderate to vigorous aerobic activity daily with muscle-strengthening and bone-strengthening activities three times a week. • Children and adolescents with type 1 diabetes should be educated about prevention and management of potential hypoglycemia during and after exercise. • Strategies to prevent hypoglycemia during exercise, after exercise, and overnight following exercise include reducing prandial insulin dosing for the meal/snack preceding exercise, increasing carbohydrate intake, eating bedtime snacks, using continuous blood glucose monitoring, and/or reducing basal insulin doses. <u>Behavioral Aspects of Self-Management</u> • Children and adolescents with diabetes should be assessed for psychosocial issues and family stresses that could impact diabetes management at diagnosis and routine follow-up. • Consider including children in consent processes as early as cognitive development indicates understanding of health consequences of behavior. • Offer adolescents time by themselves with their care provider(s) starting at age 12 years, or when developmentally appropriate. <u>Complications and Comorbidities</u> • Diabetic Ketoacidosis o All individuals with type 1 diabetes should have access to an uninterrupted supply of insulin. Lack of access and insulin omissions are major causes of diabetic ketoacidosis. o Patients with type 1 diabetes should have continuous access to medical support for sick-day management. • Hypoglycemia o The recommended treatment of hypoglycemia (blood glucose <70 mg/dL) in conscious patients is 15 g of glucose, although any form of carbohydrate can be used. If hypoglycemia continues after 15 minutes, treatment should be repeated. Once blood glucose has returned to normal patients should consider consuming a meal/snack and/or reduce insulin. o All individuals with type 1 diabetes should be prescribed glucagon and families/caregivers should be educated on administration. o Treatment regimens should be reevaluated in those with hypoglycemia unawareness or one or more episodes of severe hypoglycemia. • Diabetic Kidney Disease o Annual screening for albuminuria with a random spot urine sample for albumin-to-creatinine ratio should be considered at puberty or at age >10 years, whichever is earlier, once the child has had diabetes for 5 years. o An angiotensin-converting-enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB), titrated to normalization of albumin excretion, may be considered when elevated urinary albumin-to-creatinine ratio is documented.

Clinical Guideline	Recommendation(s)
	• Retinopathy o An initial dilated and comprehensive eye examination is recommended at age 10 years or after puberty has started, whichever is earlier, once the patient has had diabetes for three to five years. o Annual routine follow-up is recommended but may be given every two years based on the advice of an eye care professional. • Neuropathy o Consider an annual comprehensive foot exam for adolescents at the start of puberty or at age 10 years, whichever is earlier, once the patient has had type 1 diabetes for 5 years. • Hypertension o Children and adolescents with type 1 diabetes should have blood pressure monitored at each visit. Elevated blood pressure should be confirmed on three separate days. o Initial treatment of high-normal blood pressure should include dietary modification and increased exercise. Pharmacologic treatment should be considered if blood pressure is not controlled after three to six months. o In patients with conformed hypertension pharmacologic treatment should be added to lifestyle modification at diagnosis. o ACE inhibitors and ARBs should be considered for initial treatment. • Dyslipidemia o A fasting lipid profile should be taken in children ≥10 years of age or older after the diagnosis of diabetes. Obtain a fasting lipid profile in children 10 years of age or older as soon as convenient after the diagnosis of diabetes o If lipids are abnormal, initial therapy should consist of optimizing glucose control and medical nutrition therapy using a Step 2 American Heart Association diet that restricts saturated fat to 7% of total calories and dietary cholesterol to 200 mg/day. o If lipids remain abnormal after six months of lifestyle intervention, consider adding a statin in children at least 10 years of age.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the alpha-glucosidase 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 Alpha-Glucosidase Inhibitors[1,2,10]

Indication(s)	Acarbose	Miglitol
Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus	✔	✔

IV. Pharmacokinetics

The pharmacokinetic parameters of the alpha-glucosidase inhibitors are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Alpha-Glucosidase Inhibitors[9]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Acarbose	0.5 to 2.0	Negligible (% not reported)	Intestinal wall (extensive, % not reported)	Renal (2), Feces (51)	2
Miglitol	100	<4	Hepatic (% not reported)	Renal (>95)	2

V. Drug Interactions

Major drug interactions with the alpha-glucosidase inhibitors are listed in Table 5.

Table 5. Major Drug Interactions with the Alpha-Glucosidase Inhibitors[9]

Generic Name(s)	Interaction	Mechanism
Acarbose	Digoxin	Impaired digoxin absorption is suspected; therefore, serum digoxin concentrations may be reduced, decreasing its therapeutic effects.

VI. Adverse Drug Events

The most common adverse drug events reported with the alpha-glucosidase inhibitors are listed in Table 6.

Table 6. Adverse Drug Events (%) Reported with the Alpha-Glucosidase Inhibitors[1,2,10]

Adverse Events	Acarbose	Miglitol
Dermatologic		
Hypersensitive skin reactions	✔	-
Rash	✔	4.3
Gastrointestinal		
Abdominal pain	19	11.7
Diarrhea	31	28.7
Flatulence	74	41.5
Ileus/subileus	✔	-
Hepatic		
Hepatitis	✔	-
Jaundice	✔	-
Transaminases increased	<4	-
Other		
Edema	✔	-
Low serum iron	-	9.2

✔ Percent not specified.
- Event not reported.

VII. Dosing and Administration

The usual dosing regimens for the alpha-glucosidase inhibitors are listed in Table 7.

Table 7. Usual Dosing Regimens for the Alpha-Glucosidase Inhibitors[1,2,10]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Acarbose	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus:	Safety and effectiveness in pediatric patients have not been established.	Tablet: 25 mg 50 mg 100 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Tablet: initial, 25 mg TID with meals; maintenance, 25 to 50 mg TID; maximum, 50 mg TID (≤60 kg) or 100 mg TID (>60 kg)		
Miglitol	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus: Tablet: initial, 25 mg TID with meals; maintenance, 50 mg TID; maximum, 100 mg TID	Safety and effectiveness in pediatric patients have not been established.	Tablet: 25 mg 50 mg 100 mg

TID=three times daily

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the alpha-glucosidase inhibitors are summarized in Table 8.

Table 8. Comparative Clinical Trials with the Alpha-Glucosidase Inhibitors

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Cardiovascular Outcomes Trials				
Holman et al.[11] (2017) ACE Acarbose 50 mg TID vs placebo	DB, MC, PC, RCT Chinese patients ≥50 years of age with coronary heart disease and impaired glucose tolerance	N=6,522 Median of 5.0 years	Primary: Five-point composite of cardiovascular death, non-fatal MI, non-fatal stroke, hospital admission for unstable angina, and hospital admission for heart failure Secondary: Three-point composite outcome (cardiovascular death, non-fatal MI, and non-fatal stroke), death from any cause, cardiovascular death, fatal or non-fatal MI, fatal or non-fatal stroke, hospital admission for unstable angina, hospital admission for heart failure, development of	Primary: The primary five-point composite outcome occurred in 14% (3.33 per 100 person-years) of acarbose group participants and in 15% (3.41 per 100 person-years) of placebo group participants (HR, 0.98; 95% CI, 0.86 to 1.11, P=0.73). Secondary: No significant differences were seen between treatment groups for the secondary three-point composite outcome, death from any cause, cardiovascular death, fatal or non-fatal MI, fatal or non-fatal stroke, hospital admission for unstable angina, hospital admission for heart failure, or impaired renal function. Diabetes developed less frequently in the acarbose group (13%; 3.17 per 100 person-years) compared with the placebo group (16%; 3.84 per 100 person-years; rate ratio, 0.82; 95% CI, 0.71 to 0.94; P=0.005).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			diabetes, and development of impaired renal function	
Chiasson et al.[12] (2003) Acarbose 100 mg TID vs placebo	DB, MC, PC, RCT Patients 40 to 70 years of age, with a BMI 25 to 40 kg/m^2 with impaired glucose tolerance test and a FPG 100 to 140 mg/dL	N=1,429 3.3 years (mean duration)	Primary: Number of patients who developed major cardiovascular events Secondary: New cases of hypertension	Primary: Fifteen patients receiving acarbose and 32 patients receiving placebo experienced any cardiovascular event. Acarbose was associated with a 49% RR reduction in the development of any cardiovascular event (HR, 0.51; 95% CI, 0.25 to 0.95; P=0.03) and a 2.5% absolute risk reduction. There was a significant reduction in the risk of MI associated with acarbose treatment; one patient experienced a MI with acarbose and 12 patients with placebo (HR, 0.09; 95% CI, 0.01 to 0.72; P=0.02). Five patients receiving acarbose experienced angina compared to 12 patients receiving placebo (P=0.13). Eleven patients receiving acarbose experienced revascularization procedures and 20 patients receiving placebo (P=0.18). One patient receiving acarbose experienced cardiovascular death compared to two patients receiving placebo (P=0.63). No patient receiving acarbose and two patients receiving placebo experienced congestive heart failure. Two patients receiving acarbose and four patients receiving placebo experienced a cerebrovascular event or stroke (P=0.51). One patient in each group experienced peripheral vascular disease (P=0.93). Secondary: Seventy eight (11%) of the 682 patients receiving acarbose developed hypertension compared to 115 (17%) of the 686 patients receiving placebo. There was a 34% RR decrease in the incidence of new hypertension cases associated with acarbose (HR, 0.66; 95% CI, 0.49 to 089; P=0.006) and a 5.3% absolute risk reduction. Reduction in the risk of cardiovascular events (HR, 0.47; 95% CI, 0.24 to 0.90; P=0.02) and hypertension (HR, 0.62; 95% CI, 0.45 to 0.86; P=0.004) associated with acarbose was significant after adjusting for the major risk factors.
Diabetes Prevention Trials				

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Chiasson et al.[13] (2002) Acarbose 100 mg TID vs placebo	DB, MC, PC, RCT Patients 40 to 70 years of age, with a BMI 25 to 40 kg/m^2, and impaired glucose tolerance test according to the WHO criteria, and a FPG 100 to 140 mg/dL	N=1,429 3.3 years (mean duration)	Primary: The development of diabetes on the basis of a yearly oral glucose tolerance test Secondary: Not reported	Primary: One hundred seventeen (17%) patients developed diabetes in the acarbose group compared to 178 (26%) patients in the placebo group (HR, 0.68; 95% CI, 0.54 to 0.85; P=0.0010), resulting in an absolute reduction of 8.7% and a relative reduction of 32.4% when a FPG of 7.0 mmol/L or greater was reported on two consecutive visits as the criterion for the development of diabetes. When any two positive oral glucose tolerance tests with a two-hour plasma glucose of 11.1 mmol/L or greater, 105 (15%) patients converted to diabetes in the acarbose group compared to 165 (24%) patients in the placebo group (HR, 0.64; 95% CI, 0.4981 to 0.8129; P=0.003) for an absolute reduction of 8.7% and a relative reduction of 36.4%. Based on one abnormal plasma glucose concentration, cumulative incidence of diabetes was 221 (32%) patients in the acarbose group and 285 (42%) patients in the placebo group (relative hazard, 0.75; 95% CI, 0.63 to 0.90; P=0.0015). Probability of reverting to normal glucose tolerance over time was significantly higher in patients on acarbose than in those on placebo (P<0.001). Secondary: Not reported
Van de Laar et al.[14] (2006) Acarbose vs placebo, metformin, diet and exercise, or both	MA (5 trials) Patients with impaired glucose tolerance or impaired fasting blood glucose	N=2,360 1 to 6 years	Primary: Occurrence of type 2 diabetes Secondary: Cardiovascular morbidity and mortality, glycemic control, lipids, BP, body weight	Primary: In the comparison of acarbose to placebo, the incidence of or conversion to type 2 diabetes was reduced (RR, 0.78; 95% CI, 0.68 to 0.90). Neither acarbose nor metformin had significant effects on the incidence of type 2 diabetes when compared to one another. However, when compared to diet and exercise, acarbose had beneficial effects on the incidence of type 2 diabetes (RR, 0.40; 95% CI, 0.17 to 0.96). Secondary: There were no significant effects on total mortality or mortality due to cardiovascular causes in trials comparing acarbose to placebo. In one trial

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				(STOP-NIDDM), a decreasing effect on the incidence of cardiovascular disease as a combined end point (MI, angina, revascularization procedures, cardiovascular death, congestive heart failure, cerebrovascular events, and peripheral vascular disease) was reported (RR, 0.47; 95% CI, 0.26 to 0.86). Acarbose decreased PPG by 0.61 mmol/L (95% CI, 0.27 to 0.95) compared to placebo. In the EDIT study, acarbose significantly decreased FPG and PPG in comparison to placebo (P=0.0043 and P=0.0075, respectively). In comparison to metformin, acarbose showed a decreasing effect on PPG (1.40 mmol/L; 95% CI, 0.55 to 2.25). Similarly, acarbose vs diet and exercise also showed significant reductions in FPG and PPG (-1.37 [95% CI, -0.50 to -2.24] and -2.79 mmol/L [95% CI, -1.79 to -3.79]). There were no significant effects on DBP and SBP in trials comparing acarbose to placebo. However, metformin showed significant decreases in both TC and DBP in comparison to acarbose (0.90 mmol/L [95% CI, 0.19 to 1.61] and 6 mm Hg [95% CI, 2.81 to 9.19], respectively). Acarbose decreased body weight by 1.2 kg (95% CI, 0.5 to 1.8) and BMI by 0.3 kg/m^2 (95% CI, 0.1 to 0.5) compared to placebo.
Type 2 Diabetes – Monotherapy				
Buse et al.[15] (1998) PROTECT Acarbose 25 to 50 mg TID The dose remained at 50 mg TID, or the dose was increased to 100 mg TID, or a sulfonylurea was added, or the dose of the sulfonylurea was increased.	MC, OL, PRO Patients ≥21 years of age with type 2 diabetes who were inadequately controlled with either diet alone or diet and a sulfonylurea	N=6,142 28 weeks	Primary: Change in baseline HbA_{1c} Secondary: Change in baseline PPG	Primary: Mean HbA_{1c} after 28 weeks was 8.41%. The mean change from baseline in HbA_{1c} at trial end was -0.66% (P<0.001). Secondary: Mean PPG level was 208.1 mg/dL after 28 weeks of therapy. The mean PPG level decreased by 41 mg/dL at trial end (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Hwu et al.[16] Asian Acarbose Study Group (2003) Acarbose 50 mg TID for 6 weeks, titrated up to 100 mg TID for 12 weeks vs placebo	DB, MC, PC, PG, RCT Asian patients 35 to 70 years of age with type 2 diabetes receiving insulin with inadequate control, an HbA_{1c} 8.0 to 11.0%, requiring ≥2 injections of intermediate insulin per day, and a BMI ≤35 kg/m^2	N=117 18 weeks	Primary: Change in baseline HbA_{1c} Secondary: Changes in baseline FPG, PPG, and lipids	Primary: HbA_{1c} improved with acarbose (-0.5±1.3%) and worsened with placebo (0.2±1.2%). The comparison between the two treatments showed a difference of -0.69% (95% CI, -1.18 to -0.20; P=0.008) in favor of acarbose. Secondary: FPG decreased with acarbose by trial end, but there was not a significant difference between placebo (0.04 mmol/L; 95% CI, -1.28 to 1.66; P=0.094). Differences between the two treatments were significant for the PPG data (-1.89 mmol/L; 95% CI, -3.50 to -0.28; P=0.029), but was not significant for the two-hour post-prandial data (-1.83 mmol/L; 95% CI, -3.67 to 0.00; P=0.051). There were no differences between the two treatments, from baseline to trial end, for TG, TC, and LDL-C (P=0.378, P=0.935, P=0.294, respectively). There was a small decrease in HDL-C with acarbose (P=0.049).
Josse et al.[17] (2003) Acarbose 50 to 100 mg TID vs placebo	DB, PC, RCT Patients >65 years of age with type 2 diabetes treated with diet alone	N=192 1 year	Primary: Change in HbA_{1c}, FPG, fasting insulin, relative insulin sensitivity, and glucose; insulin incremental AUC Secondary: Not reported	Primary: Differences in the change from baseline in HbA_{1c} between acarbose and placebo was -0.6% (P<0.05). Acarbose 100 mg TID resulted in a greater HbA_{1c} treatment effect compared to acarbose 50 TID (-0.9 vs -0.2%; P value not reported). Change in FPG level was greater with acarbose compared to placebo (-0.7 mmol/L; P<0.05). Change in fasting insulin was -9±4 and -9 pmol/L with acarbose and placebo; the difference was not significant (P value not reported). Acarbose showed a significant reduction in glucose and insulin incremental AUC compared to placebo (glucose, -2.1 mmol/h l [P<0.05] and insulin, -45 pmol/h l; [P<0.05]).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Acarbose showed a significant reduction in relative insulin resistance compared to placebo (–0.8; P<0.05). Secondary: Not reported
Lam et al.[18] (1998) Acarbose 50 mg TID for 4 weeks, titrated up to 100 mg TID for 20 weeks vs placebo	DB, MC, RCT Patients with type 2 diabetes, BMI <30 kg/m^2, HbA_{1c} 8.4 to 10.8%, and on maximal doses of glibenclamide* or gliclazide† and metformin for ≥6 months	N=90 24 weeks	Primary: Change in baseline HbA_{1c}, FPG, PPG, insulin levels, and fasting lipid levels Secondary: Not reported	Primary: Acarbose was associated with greater reductions in HbA_{1c} (-0.5±0.2 vs 0.1±0.2%; P=0.038), one-hour PPG (-2.3 ±0.4 vs 0.7±0.4 mmol/L; P<0.001) and body weight (-0.54±0.32 vs 0.42±0.29 kg; P<0.05). No significant differences between the two treatments with regards to FPG, lipids, or fasting and postprandial insulin levels (P values not reported). Gastrointestinal symptoms were the most common side effects with flatulence occurring the most compared to placebo (P<0.05). Secondary: Not reported
Lin et al.[19] (2003) Acarbose 100 mg TID vs placebo	DB, MC, PC, RCT Asian patients 35 to 70 years of age with type 2 diabetes for ≥3 months, HbA_{1c} 7.0 to 10.0%, stable body weight (≤35 kg), and uncontrolled by diet and sulfonylureas	N=69 24 weeks	Primary: Change in baseline HbA_{1c} Secondary: Change in baseline blood glucose (FPG and PPG), serum insulin (fasting and one-hour postprandial), urinary glucose, safety	Primary: Acarbose was associated with significantly greater reductions in HbA_{1c} (-0.91 vs 0.13%; P=0.0018) and PPG levels (-2.84 vs 0.28 mmol/L; P=0.002). Secondary: There were no significant differences between the treatment groups regarding changes in FPG (P=0.1941), fasting insulin (P=0.5003), insulin PPG (P=0.2799), urinary glucose (P value not reported), and body weight (P value not reported). Change in blood glucose (FPG and PPG) was significant for acarbose compared to placebo (P=0.0020). Adverse events occurred with similar frequency with both treatments except for drug-related gastrointestinal side effects with acarbose (48.5 vs 12.5%; P value not reported).
Mori et al.[20]	SA	N=10	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2011) Acarbose 300 mg/day, administered on 2 of 4 days vs no treatment	Adults with type 2 diabetes	4 days	Glucose fluctuations Secondary: Not reported	During treatment, significant decreases in median of 24-hour mean blood glucose (22.48 vs 32.78 mg/dL; P=0.004), 24-hour mean blood glucose fluctuations (453.27 vs 677.05 mgh/dL; P=0.002), and mean amplitude of glycemic excursions (65.00 vs 97.09; P=0.010) were achieved with acarbose compared to no treatment. Secondary: Not reported
Jian-bin et al.[21] (2011) Acarbose 50 mg TID vs no treatment All patients received existing insulin regimens. After an initial 3 day continuous glucose monitoring test, patients with mean amplitude of glycemic excursions >3.4 mmol/L received acarbose for 2 weeks (high group); patients with values <3.4 mmol/L did not receive	PRO Type 2 diabetics receiving premixed insulin BID for >3 consecutive months and HbA_{1c} <6.5%	N=106 (includes 20 control subjects who had normal glucose regulation) 3 days	Primary: Glycemic variability, hypoglycemia Secondary: Not reported	Primary: Among the 86 patients, the mean amplitude of glycemic excursions and mean of daily differences of type 2 diabetes groups were all higher compared to control patients (P<0.01). Twenty-four percent of patients in the high group (n=11) had a total of 13 hypoglycemic events, and 10 of the 13 events occurred at night. Five percent of patients in the low group (n=2) had a total of two hypoglycemic events, and both occurred at night (24 vs 5%; P<0.01). Mean amplitude of glycemic excursion value was correlated with hypoglycemia value and two-hour PPG value (P<0.05). After further treatment with acarbose and second continuous glucose monitoring, mean amplitude of glycemic excursions and mean of daily differences values in the high group were all significantly decreased (40%; P<0.01, and 15%; P<0.05, respectively), but remained higher compared to control patients (P<0.05). Two percent of patients (n=1) had a total of one hypoglycemic event. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
additional treatment (low group).				
Feinbock et al.[22] (2003) Acarbose 50 to 200 mg TID vs glimepiride 1 to 6 mg QD	MC, OL, PG, RCT Patients from 36 to 80 years of age with type 2 diabetes uncontrolled on diet alone, with an HbA_{1c} ≥7.8%, and BMI 24 to 35 kg/m^2	N=219 20 weeks	Primary: Number of responders in each group (defined as a FPG ≤7.8 mmol/L at the final visit) Secondary: Changes in HbA_{1c}, weight, PPG, and C-peptide levels from baseline	Primary: Glimepiride treatment was associated with a significant responder rate compared to acarbose, 61 vs 34% respectively (P<0.001). Glimepiride resulted in significant decreases in HbA_{1c} (2.5±2.2%) as compared to acarbose (1.8±2.2%; P=0.014). Secondary: FPG levels were significantly decreased with glimepiride as compared to acarbose (2.6±2.6 vs 1.4±2.8 mmol/L; P=0.004). There was a greater reduction in HbA_{1c} in the glimepiride group (2.5±2.2%) compared to the acarbose group (1.8±2.2%; P=0.014). Decreased glucose response to breakfast was significant for glimepiride compared to acarbose (P=0.0001). Weight loss was observed in the acarbose group (P=0.001) and glimepiride group (P=0.8) from baseline. C-peptide levels were higher in the glimepiride group compared to the acarbose group at study end point (5.44±2.26 vs 4.57±1.93 ng/mL; P=0.0004; intra-individual difference, 0.53 ±1.7 vs -0.31 ±1.72 ng/mL; P=0.002).
Zhou et al.[23] (2013) Acarbose 50 mg TID nateglinide 120 mg TID	AC, ML, OL, PG, RCT Patients 18 to 75 years who were antihyperglycemic agent–naive with type 2 diabetes (HbA_{1c} 6.5 to 9.0%)	N=103 2 weeks	Primary: Incremental area under the curve of postprandial blood glucose (AUCpp) during continuous glucose monitoring (CGM) Secondary:	Primary: Both treatment groups showed a significant decrease in the AUCpp of treatment (vs baseline, P<0.001), but the decrease achieved by the two therapies was not significantly different (nateglinide vs acarbose, P=0.691). Secondary: No significant differences between treatment groups occurred for secondary efficacy outcomes, except for therapy-mediated effects on insulin levels. The insulin concentrations in the nateglinide group increased at 30 minutes (P<0.0001) and at 120 minutes (P=0.0012),

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Additional CGM measures, serum glycated albumin, safety	with statistical differences between pretreatment and posttreatment. In contrast, compared with baseline, the insulin concentrations at the end point in the acarbose group decreased at 30 minutes and at 120 minutes with statistical differences between pretreatment and post-treatment (both P<0.0001). Both treatments were well-tolerated.
van de Laar et al.[24] (2004) Acarbose titrated to 100 mg TID vs tolbutamide titrated 2,000 mg daily in 3 divided doses	DB, RCT Newly diagnosed patients with type 2 diabetes between 40 to 70 years of age and a FPG level between 6.7 and 20.0 mmol/L after an 8-week dietary treatment period	N=96 30 weeks	Primary: Change in HbA_{1c} from baseline Secondary: Change in fasting and postload blood glucose and insulin levels, plasma lipids, tolerability	Primary: Both treatment groups showed a decrease in HbA_{1c}. The HbA_{1c} change from baseline for the acarbose group was -1.1 vs -1.8% for the tolbutamide group. The difference between the groups was 0.6% in favor of tolbutamide (90% CI, 0.3 to 0.9 and 95% CI, 0.2 to 1.0). Secondary: Difference in mean decrease of FPG was 1.0 mmol/L in favor of tolbutamide (95% CI, 0.3 to 1.7). No significant differences were seen in postload blood glucose, fasting and postload insulin levels, or lipids.
Wagner et al.[25] (2006) Acarbose 100 mg TID vs aerobic/anaerobic exercise group training for 50 minutes 3 times weekly vs acarbose 100 mg TID plus exercise	RCT Patients 45 to 60 years of age with type 2 diabetes for ≥3 months, HbA_{1c} <7.5%, and BMI 25 to 30 kg/m^2	N=62 12 weeks	Primary: Change in baseline HbA_{1c}, insulin sensitivity (M value), regional fat distribution, Vo_{2max} (a measure of physical fitness) Secondary: Not reported	Primary: At trial end, acarbose resulted in no effects on HbA_{1c}, FPG, M value, BMI, body composition, or Vo_{2max}. However, fasting plasma proinsulin level was significantly reduced (P=0.009). With exercise there were significant reductions in BMI, waist circumference, total and truncal fat, and total and intra-abdominal fat area. Although Vo_{2max} was unchanged, there was an increase in maximal workload (P=0.005) and in the M value (P=0.017). HbA_{1c} was unchanged. Acarbose plus exercise resulted in significant decreases in BMI, waist circumference, total and truncal fat, and total and intra-abdominal fat. Maximal workload, Vo_{2max}, and M values were all increased (P=0.028, P=0.046, and P=0.002, respectively). Additionally, fasting plasma proinsulin levels were significantly reduced (P=0.013), as well as HbA_{1c} (P value not reported). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Not reported
de Luis Roman et al (abstract).[26] (2004) Miglitol 50 mg BID for 1 week, followed by 50 mg TID	OL Patients with type 2 diabetes inadequately controlled (HbA_{1c} >7.5%) on sulfonylureas and insulin	N=33 3 months	Primary: Change in weight, height, BMI, SBP, DBP, HbA_{1c}, number of episodes of peripheral hypoglycemia, basal glucose, albuminuria, TC, LDL-C, HDL-C, TG, and transaminases Secondary: Not reported	Primary: Blood glucose and HbA_{1c} decreased 4.8 and 5.8%, respectively. There was a decrease in the number of hypoglycemia episodes (39.4% previous quarter vs 3% during the miglitol quarter). The required dose of sulfonylureas decreased (86.2±24.3 vs 64.6 ±21.9 mg/day; P<0.05). TC, HDL-C, and LDL-C were not modified. There was a reduction in TG from 145.2 ±111.0 to 133.1±79.0 mg/dL (P<0.05). Fifteen percent of patients experienced digestive discomfort, which disappeared two or three weeks after beginning the treatment. Secondary: Not reported
Aoki et al.[27] (2007) Miglitol, administered prior to breakfast vs miglitol, administered 15 minutes after the start of breakfast vs miglitol, administered 30	XO Adult patients with type 2 diabetes, BMI 26.7 kg/m^2 (mean), HbA_{1c} 9.3% (mean), and an average duration of diabetes of 7.4 years	N=13 180 minutes	Primary: Effect of plasma glucose at 0, 30, 60, 120, and 180 minutes after breakfast; effect on serum insulin Secondary: Not reported	Primary: At 30 and 60 minutes, plasma glucose levels were significantly decreased in those who took miglitol just before breakfast compared to control (P<0.05). At 60 and 120 minutes, plasma glucose levels were significantly decreased in those taking miglitol 15 minutes after breakfast (P<0.05) while those taking miglitol 30 minutes after breakfast had significant reductions at 120 and 180 minutes (P<0.05) compared to control. There were no significant differences between groups. The AUC of serum insulin was lower with all three groups compared to control. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
minutes after the start of breakfast vs placebo				
Johnston el al.[28] (1998) Miglitol 25 to 50 mg TID vs glyburide 1.25 to 20 mg QD vs placebo	DB, MC, PC, PG, RCT Patients ≥60 years of age with type 2 diabetes treated with diet alone for ≥12 weeks, HbA_{1c} 6.5 to 10.0%, and FPG >140 mg/dL	N=411 1 year	Primary: Change in baseline HbA_{1c} Secondary: Change in baseline plasma glucose, serum insulin, and TG	Primary: Mean placebo-subtracted HbA_{1c} reduction from baseline was -0.50% with miglitol 25 mg TID (P<0.05 vs glyburide), -0.41% with miglitol 50 mg TID (P<0.05 vs glyburide), -0.93% for glyburide QD, and -0.01% for placebo (P<0.05 vs all active treatments). Secondary: Changes in mean plasma glucose (AUC) were +716 mg·min/dL with placebo (P<0.05 vs all active treatments), -3,361 mg·min/dL with miglitol 25 mg TID, -5,462 mg·min/dL with miglitol 50 mg TID, and -3,615 mg·min/dL with glyburide (P=0.0001 for miglitol 50 mg TID vs placebo). Postprandial insulin levels were significantly greater with glyburide compared to placebo and miglitol (P<0.01). Mean changes from baseline to end point for fasting TG were 1.01 with placebo and miglitol 25 mg TID, 0.98 with miglitol 50 mg TID, and one with glyburide (P=0.573 for miglitol 50 mg vs placebo). Mean changes from baseline to end point for TG (AUC) were 1.01 with placebo, 1.03 with miglitol 25 mg TID, 1.00 with miglitol 50 mg TID, and 1.06 with glyburide (P=0.8559 miglitol 50 mg TID vs placebo). Hypoglycemia, weight gain, and routine and serious cardiovascular events were more frequent in the glyburide group (P<0.05 vs placebo and miglitol).
Tsujino et al.[29] Acarbose 50 mg, administered before each meal on day 2	RCT, XO Patients 20 to 79 years of age with type 2 diabetes,	N=10 4 days	Primary: Glucose variability Secondary: Not reported	Primary: No significant differences in regard to the range of increase in glucose levels from baseline to peak, time to peak PPG levels from the preprandial period, and AUC for glycemic variability from the preprandial period to three hours after each meal between the two treatments were observed.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs miglitol 100 mg, administered before each meal on day 2 Alternative treatments were administered on day 3 in a XO design.	taking α-glucosidase inhibitors without any other antidiabetic medications			The range of increase in glucose levels at 30 minutes (0.4 vs 30.7 mg/dL; P<0.0001) and 60 minutes (32.8 vs 67.5 mg/dL; P<0.0001) after lunch and 30, 60, and 90 minutes after dinner (3.3 vs 22.2 mg/dL; P=0.0249, 36.6 vs 67.5 mg/dL; P<0.0001, and 60.5 vs 81.6 mg/day; P=0.0073, respectively) were significantly smaller with miglitol compared to acarbose. Secondary: Not reported
van de Laar et al.[30] (2005) α-glucosidase inhibitor monotherapy	MA (41 trials) Patients with type 2 diabetes who received no other antidiabetic medication	N=8,130 ≥12 weeks	Primary: Mortality, morbidity, quality of life, glycemic control, insulin, or C-peptide levels, lipids, body weight, safety Secondary: Not reported	Primary: There was only limited data on mortality, morbidity, and quality of life. Three trials reported mortality outcomes and found no differences between treatments. Acarbose demonstrated an effect on glycemic control compared to placebo: HbA_{1c}, -0.8% (95% CI, -0.9 to -0.7); FPG, -2.3 mmol/L (95% CI, -2.7 to -1.9); and post-load glucose, -2.3 mmol/L (95% CI, -2.7 to -1.9). The effect on HbA_{1c} from acarbose 50 to 300 mg TID was not dose-dependent. There seemed to be a dose dependency with miglitol in regards to HbA_{1c}: miglitol 25, 50, 100, and 200 mg TID decreased HbA_{1c} by 0.46, 0.58, 0.79, and 1.26%, respectively. A decreasing effect on post-load insulin was found. There were no clinically relevant effects on lipids or body weight found. Adverse events were generally of gastrointestinal origin and dose dependent. Secondary: Not reported
Bolen et al.[31] (2007) Biguanides	MA (Analysis of 216 controlled trials and cohort studies, and 2 SRs)	N=136 (articles on intermediate outcomes)	Primary: Intermediate outcomes: HbA_{1c}, body weight, BP,	Primary: Results from clinical trials showed that most oral agents including TZDs, metformin, and repaglinide improved glycemic control to the same degree as sulfonylureas (absolute decrease in HbA_{1c} level of about 1%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs meglitinides vs TZDs vs α-glucosidase inhibitors vs second-generation sulfonylureas	Patients with type 2 diabetes	N=167 (articles on adverse events) N=68 (articles on microvascular outcomes and mortality) Duration varied	lipid panels, all-cause mortality, cardiovascular morbidity and mortality, microvascular outcomes Secondary: Adverse events: hypoglycemia, gastrointestinal problems, congestive heart failure, edema or hypervolemia, lactic acidosis, elevated liver enzymes, allergic reactions requiring hospitalization, other serious adverse events	Nateglinide and α-glucosidase inhibitors have slightly weaker effects, on the basis of indirect comparisons of placebo-controlled trials. TZDs were the only class with beneficial effect on HDL-C (mean relative increase, 3 to 5 mg/dL) but a harmful effect on LDL-C (mean relative increase, 10 mg/dL) compared to other oral agents. Metformin decreased LDL-C levels by about 10 mg/dL, whereas other oral agents had no effects on LDL-C. TZDs, second-generation sulfonylureas, and metformin had similarly minimal effects on SBP. Most agents except metformin increased body weight by 1 to 5 kg. In the ADOPT (A Diabetes Outcome Progression Trial), the incidence of cardiovascular events was lower with glyburide compared to rosiglitazone or metformin (1.8, 3.4, and 3.2%, respectively; $P<0.05$). In the RECORD study (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of glycemia in Diabetes), rosiglitazone plus metformin or a sulfonylurea compared to metformin plus a sulfonylurea had a HR of 1.08 (95% CI, 0.89 to 1.31) for the primary end point of hospitalization or death from cardiovascular disease. The HR was driven by more congestive heart failure in the rosiglitazone plus metformin group compared to the control group of metformin plus sulfonylurea (absolute risk, 1.7 vs 0.8%, respectively). Too few comparisons were made to draw firm comparative conclusions on microvascular outcomes. Secondary: According to several RCTs and some OS trials, sulfonylureas and repaglinide were associated with greater risk for hypoglycemia. In many RCTs, TZDs were associated with a higher risk for edema than sulfonylureas or metformin (absolute risk difference, 2 to 21%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				In cohort studies, TZDs were associated with higher risk for congestive heart failure although absolute risks were small (1 to 3%) and higher risk for mild anemia yet produced similarly low rates of elevated aminotransferase levels (<1%) compared to sulfonylureas and metformin. In many trials and a few OS trials, metformin was associated with greater risk for gastrointestinal problems compared to other oral diabetes agents. According to a SR of 176 comparative trials, lactic acidosis events were similar between metformin and other oral diabetes agents.
Saenz et al.[32] (2005) Metformin monotherapy vs placebo, sulfonylureas, TZDs, meglitinides, α-glucosidase inhibitors, diet, any other oral antidiabetic intervention, insulin	MA (29 RCTs) Adult patients with type 2 diabetes	N=5,259 ≥3 months	Primary: Incidence of any diabetes-related outcomes (sudden death, death from hyperglycemia or hypoglycemia, fatal or nonfatal MI, angina, heart failure, stroke, renal failure, amputation [of at least one digit], vitreous hemorrhage, retinopathy requiring photocoagulation, blindness in one eye, or cataract extraction); diabetes-related death (death from MI, stroke, peripheral vascular disease, renal disease, hypo-	Primary: Obese patients receiving metformin showed a greater benefit than chlorpropamide, glibenclamide*, or insulin for any diabetes-related outcomes (*P*=0.009) and for all-cause mortality (*P*=0.03). Obese patients receiving metformin showed a greater benefit than overweight patients on conventional treatment (diet) for any diabetes-related outcomes (*P*=0.004), diabetes-related death (*P*=0.03), all cause mortality (*P*=0.01), and MI (*P*=0.02). Secondary: Patients receiving metformin monotherapy showed a significant benefit for glycemic control, weight, dyslipidemia, and DBP. Metformin presents a strong benefit for HbA_{1c} when compared to diet and placebo. Additionally, metformin showed a moderate benefit for glycemic control, LDL-C, and BMI or weight when compared to sulfonylureas.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			glycemia or hyperglycemia, and sudden death); all-cause mortality Secondary: Changes in HbA_{1c}, FPG, quality of life, weight, BMI, lipids, insulin, C-peptide, BP, micro-albuminuria, glomerular filtration rate, renal plasma flow	
Richter et al.[33] (2006) Pioglitazone monotherapy (16 trials) vs acarbose (1 trial), metformin (4 trials), placebo (4 trials), repaglinide (1 trial), rosiglitazone (1 trial), or a sulfonylurea (8 trials) or pioglitazone combination therapy vs a similar combination with another compound	MA of DB (15) or OL (4) RCTs (last search conducted in August 2006, included PROactive Study), PG Adults with type 2 diabetes, trial duration of at least 24 weeks	22 trials N=6,200 randomized to pioglitazone treatment (total N not reported) 24 weeks to 34.5 months	Primary: Patient-oriented outcomes including mortality, morbidity and adverse effects Secondary: Health-related quality of life and HbA_{1c}	Primary: Only one trial (PROactive Study) evaluated mortality and morbidity as an end point. The primary composite end point (time from randomization to all-cause mortality, nonfatal MI, stroke, acute coronary syndrome, endovascular or surgical intervention on the coronary or leg arteries, or amputation above the ankle) did not show statistically significant differences between the pioglitazone and placebo group (HR, 0.90; 95% CI, 0.80 to 1.02; P=0.095). Time to the first event of the composite end point of death from any cause, MI and stroke indicated a statistically significant difference between pioglitazone and placebo (HR, 0.84; 95% CI, 0.72 to 0.98; P=0.027). The individual components of the primary composite end point did not disclose statistically significant differences between the intervention and control groups. Significantly more patients developed heart failure requiring hospitalization following administration of pioglitazone (6 vs 4% on placebo; P=0.007). The percentage of overall and serious adverse events was comparable between the intervention and control groups. Six trials reported a more pronounced (sometimes dose-related) decrease of hemoglobin after pioglitazone intake in comparison to other active compounds or placebo;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(9 trials including 2 trials vs rosiglitazone) Some studies had more than one treatment arm.				hemoglobin reductions ranged between -0.50 and- 0.75 g/dL. Fifteen trials evaluated body weight and observed an increase up to 3.9 kg after pioglitazone treatment; seven trials described a rise in BMI up to 1.5 kg/m^2. Eleven of the 22 included trials showed data on hypoglycemic episodes: compared to the active monotherapy control, pioglitazone treatment resulted in somewhat lower rates of hypoglycemia (P value not reported). The RR for development of edema with pioglitazone compared to the control was 2.86 (95% CI, 2.14 to 3.18; P<0.00001) when results from 18 trials were pooled. Secondary: No study investigated health-related quality of life. Active glucose-lowering compounds like metformin, glibenclamide‡, gliclazide* or glimepiride resulted in similar reductions of HbA_{1c} compared to pioglitazone treatment (P values not reported).
Monami et al.[34] (2008) Metformin vs sulfonylureas, α-glucosidase inhibitors, TZDs, glinides, GLP-1 agonists	MA Patients with type 2 diabetes mellitus	N=7,890 (27 RCT) Variable duration	Primary: Reduction in HbA_{1c} at 16 to 36 months Secondary: Not reported	Primary: Combining the results of different placebo-controlled trials, sulfonylurea, α-glucosidase inhibitors, and TZDs led to a reduction in HbA_{1c} by -0.85% (95% CI, 0.78 to 0.94], -0.61% (95% CI, 0.55 to 0.67), and -0.42% (95% CI, 0.40 to 0.44), respectively when combined with metformin. In direct comparisons, sulfonylureas led to a greater reduction in HbA_{1c} (0.17%; 95% CI, 0.16 to 0.18; P<0.05) than TZDs. Differences between sulfonylureas and α-glucosidase inhibitors, and between α-glucosidase inhibitors and TZDs, were not statistically significant. Secondary: Not reported
Type 2 Diabetes – Combination Therapy				
Zhang et al.[35] (2013) 36.8% of patients received acarbose (25 to 600 mg/day) as monotherapy;	MC, OS, PRO Patients aged ≥18 years and had untreated or pre-treated type 2 diabetes or an	N=15,034 (efficacy); 15,661 (safety) 3 months	Primary: Efficacy (2-hour PPG, HbA_{1c} and FBG at initial visit when acarbose was prescribed vs up to 3 months later),	Primary: Mean 2-hour PPG was reduced from 241.8 mg/dL at the initial visit to 170.2 mg/dL at the final visit. Mean HbA_{1c} decreased from 8.2% at the initial visit to 7.2% at the final visit. FBG decreased from 157.4 mg/dL at the initial visit to 124.8 mg/dL at the final follow-up visit.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
63.2% of patients received combination therapy, with acarbose being administered with one (37.5%), two (20.3%) or more (5.4%) anti-diabetic medications	indication for acarbose treatment and no acarbose treatment within the 3 months before study inclusion		safety (adverse events) Secondary: Not reported	The most common adverse events and drug-related adverse events were gastrointestinal disorders, mainly flatulence, abdominal distension, and diarrhoea. No other type of adverse event occurred in more than 0.5% of patients. Efficacy was rated as 'good' or 'very good' by 85.8% of physicians, 'sufficient' by 12.1%, and 'insufficient' by 2.1% of physicians (data were missing for 57 patients). The overall tolerability of acarbose was rated by physicians as 'very good' or 'good' by 85.7% of physicians, 'sufficient' by 13.5%, and 'insufficient' by 0.9% of physicians (data were missing for 144 patients). Overall, 95.7% of physicians and 95.3% of patients were 'very satisfied' or 'satisfied' with treatment.
Halimi et al.[36] (2000) Acarbose 50 to 100 mg TID and metformin 850 mg BID to TID vs metformin 850 mg BID to TID and placebo	DB, PC, PG, RCT Patients 30 to 70 years of age with type 2 diabetes, BMI 25 to 35 kg/m^2, having poor glycemic control despite receiving metformin ≥2 months before the study start	N=152 6 months	Primary: HbA_{1c} at trial end Secondary: Blood glucose, insulin profiles, TG	Primary: Mean difference in HbA_{1c} from baseline to trial end was -0.7±1.2% with acarbose compared to 0.2±1.3% with placebo (P=0.0001). Patients were classified as responders if their HbA_{1c} values at trial end were <7.0% or had decreased by <15% relative to baseline. The total numbers of responders were 25 of 49 (42%) patients receiving acarbose and 12 of 70 (17%) patients receiving placebo (P=0.002). Secondary: Mean difference in the fasting blood glucose level from baseline to trial end was -1.0±2.8 mmol/L with acarbose compared to 1.3±2.8 mmol/L with placebo (P=0.0001). Mean difference in two-hour PPG level from baseline to trial end was -1.4±3.8 mmol/L with acarbose compared to 1.1±3.5 mmol/L with placebo (P=0.0001). Mean changes between acarbose compared to placebo for TG, fasting and postprandial serum insulin were not significant (P value not significant).
Phillips et al.[37] (2003) Acarbose 50 mg to 100 mg BID and	DB, MC, PC, PG, RCT Patients ≥40 years of age with type 2	N=83 24 weeks	Primary: Change in baseline HbA_{1c} Secondary:	Primary: Mean HbA_{1c} increased with placebo from 7.82±0.83% at baseline to 8.10±1.06% at week 12 and 8.50±1.44% at trial end. The mean increase after 24 weeks was 0.68±1.17%, with a significant overall time effect (P=0.0001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
metformin (existing therapy) vs metformin (existing therapy) and placebo	diabetes for ≥6 months, BMI 25 to 35 kg/m^2, HbA_{1c} 7.0 to 10.0% at screening week and 6.8 to 10.2% at baseline, and inadequately controlled by metformin		Change in baseline FPG	With acarbose, mean HbA_{1c} decreased from 8.02±0.85% at baseline to 7.78±1.00% at week 12 (P=0.0261). At the trial end, mean HbA_{1c} increased to 7.97±1.10%. There was no significant overall time effect for acarbose (P value not reported). Adjusted least square means for the change in HbA_{1c} from baseline to trial end showed a decrease of 0.16±0.18% with acarbose compared to an increase of 0.86±0.16% with placebo. There was a significant difference between the treatment groups of 1.02% (95% CI, 0.543 to 1.497; P=0.0001). Secondary: Mean FPG levels increased with placebo from baseline (9.41±1.99 mmol/L) to week four (10.06±2.43 mmol/L) to trial end (10.77±3.39 mmol/L). The levels only changed slightly with acarbose. Mean FPG increases were 1.36±2.88 mmol/L with placebo and 0.08±1.98 mmol/L with acarbose. The adjusted least square means showed increase at trial end with both treatments of 0.34±0.42 mmol/L with acarbose vs 1.48±0.39 mmol/L with placebo, with a significance of 1.132 mmol/L between the two treatments (95% CI, 0.056 to 2.208; P=0.0395).
Bayraktar et al.[38] (1996) Acarbose 50 to 100 mg TID and a sulfonylurea vs metformin 500 mg TID and a sulfonylurea	RCT, XO Patients from 30 to 63 years of age with type 2 diabetes for 2 to 20 years, HbA_{1c} >8.5%, FPG>7.7 mmol/L, or a PPG>10 mmol/L on maximum doses of gliclazide† (240 mg daily)	N=18 20 weeks	Primary: Changes in FPG, PPG, HbA_{1c}, TG, cholesterol, fibrinogen, insulin levels, and C-peptide levels from baseline Secondary: Not reported	Primary: Mean FPG, PPG, and HbA_{1c} decreased at the end of each combination treatment period as compared with baseline levels (P<0.05). PPG level in the acarbose group was lower than the level achieved by the group using metformin (P<0.05). There was a significant decrease between pre- and posttreatment 2-hour PPG levels in each group (-5.3±0.4 for acarbose vs -2.9±0.3 for metformin; P<0.05). There were small reductions in fibrinogen, insulin, and C-peptide levels in each group, but the differences were not statistically significant. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Not reported
Du et al.[39] (2017) SMART Acarbose 50 mg TID (could be titrated to 100 mg TID after 7 days of treatment) vs saxagliptin 5 mg QD All patients continued on their existing dose and regimen of metformin throughout the study	MC, OL, PG, RCT Chinese patients ≥18 years of age with type 2 diabetes inadequately controlled with metformin monotherapy with an HbA_{1c} between 7.5 and 11.0% at screening, and an HbA_{1c} between 7.0 and 11.0% and an FPG ≤13.3 mmol/L at the pre-randomization visit	N=488 24 weeks	Primary: Absolute change from baseline in HbA_{1c} at week 24 Secondary: Proportion of patients achieving a therapeutic glycemic response (defined as HbA_{1c} <7.0%), the proportion of patients with any gastrointestinal adverse events, the proportion of patients achieving therapeutic glycemic response without gastrointestinal adverse events, and the change from baseline in FPG, 2-hour PPG, β-cell function, and body weight	Primary: Saxagliptin was non-inferior to acarbose for glycemic control (HbA_{1c} change from baseline, -0.82% and -0.78%, respectively; difference, -0.04; 95% CI, -0.22 to 0.13%). Secondary: At week 24, 38.3% of patients receiving saxagliptin and 41.5% of patients receiving acarbose had achieved a therapeutic glycemic response. In the full analysis set, 5.5% of patients receiving saxagliptin and 24.7% of patients receiving acarbose reported gastrointestinal adverse events (risk ratio, 0.22; P<0.0001). This lower risk of gastrointestinal adverse events was also observed in the per protocol population (saxagliptin, 5.0% vs acarbose, 26.0%; risk ratio, 0.19; P<0.0001). Overall, 37.0% of patients and 28.8% of patients receiving saxagliptin and acarbose, respectively, achieved a therapeutic glycemic response without gastrointestinal adverse events. There was no significant difference between treatment groups for change from baseline to week 24 in FPG, 2-hour PPG and HOMA-β; however, greater weight loss was observed with acarbose compared with saxagliptin (P=0.0078).
Bao et al.[40] (2010) Glipizide XL vs	AC, OL, RCT Newly diagnosed type 2 diabetics, 30 to 70 years of age, with HbA_{1c} 7.0 to 9.8%, and no prior	N=40 8 weeks	Primary: Glycemic control, improvements in insulin secretion and sensitivity, glycemic variability, hypoglycemia	Primary: After eight weeks, FPG, two-hour post-oral glucose tolerance test plasma glucose, mean blood glucose, HbA_{1c}, glycated albumin, and HOMA-IR were significantly decreased with both treatments. HOMA-B increased significantly compared to baseline (P<0.01 for both). Compared to glipizide XL, combination therapy had significantly lower mean blood glucose and HOMA-IR values after eight weeks (P<0.05 for both). Mean changes in mean blood glucose, HbA_{1c}, and glycated albumin were all

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
glipizide XL plus acarbose	use of antidiabetic medications		Secondary: Not reported	greater with combination therapy compared to monotherapy, with only differences in mean blood glucose reaching significant. The overall glucose-lowering and -stabilizing effects were more pronounced with combination therapy. Over the duration of the trial, the decreases in mean amplitude of glycemic excursions and $AUC_{postprandial\ incremental}$ were significant with both treatments (P<0.01). There was also a significant decrease in mean of daily differences with combination therapy compared to baseline (P<0.01). Patients receiving combination therapy had significantly lower mean of daily differences, mean amplitude of glycemic outcomes, and $AUC_{postprandial\ incremental}$ values compared to patients receiving monotherapy after eight weeks (P<0.05 for all). There were no significant between-group differences in either the frequency or the duration of hypoglycemia. The mean duration of hypoglycemia was 88.8±84.7 minute per event with monotherapy and 176.3±123.5 minute per event with combination therapy (P=0.114). Patients receiving monotherapy had 0.7±0.4 events per day compared to 0.8±0.4 events per day in patients receiving combination therapy (P=0.612). There was no difference in total instances of severe hypoglycemia reported. Secondary: Not reported
Lopez-Alvarenga et al.[41] (1999) Acarbose 100 mg TID, chlorpropamide 500 mg daily, and metformin 1,200 mg daily vs	DB, RCT, XO Patients with type 2 diabetes from 35 to 70 years of age with BMI 23 to 35 kg/m^2, with a FPG >8.8 mmol/L despite maximal doses of chlorpropamide and	N=46 42 weeks	Primary: Change in FPG from baseline, body weight, HbA_{1c}, fasting insulin, fasting C-peptide, intravenous glucose tolerance test (incremental area), glucose meal	Primary: Changes in FPG from baseline were not significant for placebo (P=0.62), but were significant for acarbose (P=0.05) and insulin (P=0.003). Changes in HbA_{1c} from baseline were not significant for placebo (P=0.62) and acarbose (P=0.3), but were significant for insulin (P=0.008). Changes in body weight were not significant in any group (P=0.2 vs baseline). Changes in fasting insulin from baseline were not significant for placebo (P=0.38), but were significant for acarbose (P=0.03) and insulin (P=0.02).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
NPH insulin at bedtime, chlorpropamide 500 mg daily, and metformin 1,200 mg daily vs chlorpropamide (500 mg daily), metformin (1,200 mg daily), and placebo	metformin for at least 2 months		tests (incremental area) Secondary: Not reported	Changes in fasting C-peptide from baseline were not significant in any group, placebo (P=0.7), acarbose (P=0.5), and insulin (P=0.24). Changes in intravenous glucose tolerance test (incremental area) from baseline were not significant in any group, placebo (P=0.36), acarbose (P=0.91), and insulin (P=0.94). Changes in glucose meal tests (incremental area) from baseline were not significant for placebo (P=0.84) and insulin (P=0.08), but were for acarbose (P=0.02). Changes in insulin (incremental area) from baseline were not significant for any group, placebo (P=0.92), acarbose (P=0.3), and insulin (P=0.43). Thirty-seven percent of patients developed severe bloating during acarbose use. This was significant (P<0.05) compared to acarbose and placebo or insulin. Secondary: Not reported
Nemoto et al.[42] (2011) Miglitol 50 mg TID vs placebo All patients received existing insulin regimens.	DB, PC, RCT Patients ≥20 years of age with type 2 diabetes receiving insulin therapy, plasma glucose level at either 1 or 2 hours after a meal was ≥180 mg/dL, and HbA_{1c} ≥6.5%	N=107 12 weeks (plus an additional 4 to 10 week observation period)	Primary: Change in baseline PPG and HbA_{1c} Secondary: Safety	Primary: The mean decrease in PPG with miglitol was significantly larger compared to placebo (-60.3±70.1 vs 5.1±68.2 mg/dL; P<0.001). The decrease in plasma glucose AUC was significantly larger with miglitol compared to placebo (-102.8±122.2 vs 8.7±121.1 mgh/dL; P<0.001). Miglitol exhibited a significantly lower HbA_{1c} compared to placebo from week eight to trial end. The decrease from baseline in HbA_{1c} at week 12 was significantly greater with miglitol compared to placebo (-0.37±0.68 vs 0.04±0.56%; P<0.001). Secondary: The total incidence of adverse events was 78.5 and 76.0% with miglitol and placebo. Adverse events with high incidence included flatulence (20.6 vs 12.0%), abdominal distension (15.0 vs 4.0%), diarrhea (14.0 vs 4.0%), and hypoglycemia (39.3 vs 35.0%). The incidences of abdominal

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				distention and diarrhea were significantly higher with miglitol (P<0.05 for both). All hypoglycemic events were mild and improved without treatment, by ingestion of glucose, supplements, or meals.
Hsieh et al.[43] (2011) Miglitol 50 mg TID, titrated up to 100 mg TID vs placebo Patients received existing sulfonylurea regimens.	DB, MC, PC, RCT Chinese patients >20 years of age with type 2 diabetes, FPG 100 to 240 mg/dL, HbA_{1c} 6.5 to 10.0%, history of uncontrolled type 2 diabetes despite prior nutrition therapy; and stable dosing with a sulfonylurea for ≥8 weeks	N=105 24 weeks	Primary: Change in baseline HbA_{1c} Secondary: Change in baseline FPG, PPG, and post-prandial serum insulin; safety	Primary: Mean change in HbA_{1c} with miglitol was -0.85±0.12% compared to -0.19±0.11% with placebo (P<0.001). Secondary: No significant differences in the changes in FPG and post-prandial serum insulin were observed (P=0.052 and P=0.364). There was a significant difference in the change in PPG between the two treatments (P<0.001). Among the population, 49 (94.2%) patients receiving miglitol and 42 (79.3%) patients receiving placebo experienced at least one adverse event during the trial. A total of 59 and 39 adverse events occurred with miglitol and placebo, respectively. The most frequently reported adverse events were abdominal discomfort, diarrhea, hypoglycemia, and other; and there were no differences in the incidences of these events between the two treatments.
Standl et al.[44] (2001) Miglitol 25 mg to 100 mg TID, glibenclamide* 3.5 to 5 mg BID to QID, and metformin 500 to 850 mg daily vs glibenclamide* 3.5 to 5 mg BID to QID, metformin 500	DB, MC, PC, PG, RCT Patients 30 to 70 years of age with type 2 diabetes for ≥3 years; HbA_{1c} ≥7.5 to ≤10.5%; BMI ≤35 kg/m^2; stable body weight over the previous 3 months; and inadequately controlled on combination therapy of diet,	N=154 24 weeks	Primary: Change in baseline HbA_{1c} Secondary: FPG, PPG, fasting and postprandial serum insulin, TG, urinary glucose	Primary: Miglitol produced a significant reduction in HbA_{1c} (-0.55%; P=0.04) and PPG (-2.6 mmol/L; P=0.0009) compared to placebo. Secondary: FPG decreased with miglitol and was almost unchanged with placebo; the difference was not significant (P=0.10). Fasting insulin levels were unchanged with both treatments throughout the trial, with no significant difference between them (P=0.79). Postprandial insulin decreased from baseline to trial end, but the difference between the groups was not significant (P=0.26). Postprandial TG decreased slightly with miglitol and remained unchanged with placebo, and the difference was not significant (P=0.47).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
to 850 mg daily, and placebo	glibenclamide* and metformin			
Van Gaal et al.[45] (2001) Miglitol 25 to 100 mg TID and metformin 500 mg TID or 850 mg BID or TID vs metformin 500 mg TID or 850 mg BID or TID and placebo	DB, MC, PC, PG, RCT Patients 30 to 75 years of age with type 2 diabetes for ≥1 year, HbA_{1c} ≥7.5 to ≤10.5%, BMI 23 to 40 kg/m^2, stable body weight over the previous 3 months, and whose diabetes was inadequately controlled by diet and metformin	N=152 32 weeks	Primary: Change in baseline HbA_{1c} Secondary: Change in FPG, PPG, serum insulin, fasting and one-hour postprandial TG levels	Primary: There was a significant decrease in HbA_{1c} with miglitol compared to placebo (-0.21 vs 0.22%; P=0.011). Secondary: PPG decreased with both treatments, but the reduction was more significant with miglitol (from 16.5±3.8 mmol/L at baseline to 13.8±5.0 mmol/L at trial end) compared to placebo (from 16.3±3.4 mmol/L at baseline to 15.7±3.8 mmol/L at trial end). The baseline adjusted means were 13.8 mmol/L with miglitol vs 15.8 mmol/L with placebo (P=0.0007). Fasting insulin levels decreased more with miglitol compared to placebo, the difference was not significant (P value not reported). FPG, fasting and postprandial TG levels showed a descriptive advantage for miglitol, but did not reach a statistical difference. Mean FPG levels fell more with miglitol (baseline, 11.5±2.7 mmol/L; end of treatment, 10.8±3.6 mmol/L) compared to placebo (baseline, 11.6±3.1 mmol/L; end of treatment, 11.5±3.4 mmol/L; difference of adjusted means; P=0.15). Fasting TG levels fell with miglitol (treatment effect, -16.3 mg/dL) compared to placebo (treatment effect, 3.77 mg/dL; P=0.26). Similar results were seen for postprandial TG.
Chiasson et al.[46] (2001) Miglitol 100 mg TID vs metformin 500 mg TID vs	DB, MC, PC, RCT Patients >40 years of age with type 2 diabetes inadequately controlled by diet alone, HbA_{1c} 7.2 to 9.5%	N=324 36 weeks	Primary: Change in baseline HbA_{1c} Secondary: Change in baseline FPG and PPG, insulin levels, and TG	Primary: Mean change in HbA_{1c} from baseline was 0.38±0.12% with placebo, 0.02±0.10% with miglitol, -0.85±0.12% with metformin, and -1.39±0.11% with combination therapy. A reduction in mean placebo-subtracted HbA_{1c} of -1.78% was seen with combination therapy, and this was significantly different from metformin (-1.25%; P=0.002). Mean reductions in HbA_{1c} compared to placebo were -0.37% with miglitol, -1.25% with metformin, and -1.78% with combination therapy. The end of treatment mean HbA_{1c} was 8.5% with placebo, 8.2% with miglitol, 7.3% with metformin, and 6.9% with combination therapy. Significantly more patients (P=0.0014) receiving combination therapy

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
miglitol 100 mg TID plus metformin 500 mg TID vs placebo				(70.6%) were classified as responders (i.e., showed ≥15% reduction from baseline in HbA_{1c} or achieved an HbA_{1c} <7.0%) compared to metformin (45.5%). Secondary: Combination therapy resulted in better metabolic control compared to metformin for FPG (P=0.0025) and two-hour PPG AUC (P=0.0001). Changes in TG levels from baseline to trial end did not differ significantly between combination therapy compared to metformin, and showed no consistent trend (P value not reported).
Kheirbek et al.[47] (2013) Hypoglycemic medications (metformin, glyburide, glipizide, rosiglitazone, acarbose, chlorpropamide, glimepiride, pioglitazone, tolazamide, repaglinide, troglitazone, insulin, and DPP-4 inhibitors) *Defined as any use of the medication independent of dose or days of use	OS, RETRO Veterans with diabetes cared for at a Veterans Administration Capital area medical center	N=17,773 Variable duration	Primary: All-cause mortality Secondary: Not reported	Primary: After adjustments were made for severity of illness and patient demographics, the remaining variance in mortality was explained by exposure to five medications, listed in order of impact on risk-adjusted mortality: glipizide (OR=1.566), glyburide (OR=1.804), rosiglitazone (OR=1.805), insulin (OR=2.382), and chlorpropamide (OR=3.026). None of the other medications (metformin, acarbose, glimepiride, pioglitazone, tolazamide, repaglinide, troglitazone, and DPP-4 inhibitors) were associated with excess mortality beyond what could be expected from the patients' severity of illness or demographic characteristics. Insulin, glyburide, glipizide, and rosiglitazone continued to be associated with statistically significant increased mortality after controlling for possible drug interactions. Secondary: Not reported
Mearns et al.[48] (2015)	Network MA (62 RCTs)	N=32,185 3 to 12 months	Primary: Changes in HbA_{1c}, body weight, and SBP; risk of	Primary: All agents significantly reduced HbA_{1c} vs placebo; although, not to the same extent (range, 0.43% for miglitol to 1.29% for glibenclamide). Glargine, sulfonylureas, and nateglinide were associated with increased

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Hypoglycemic medications (Alpha-glucosidase inhibitors, DPP-4 inhibitors, colesevelam, meglitinides, GLP-1 analogs, long-acting, once-daily basal insulin, SGLT2 inhibitors, sulfonylureas, TZDs, and combinations of the above agents)	Patients with inadequately controlled type 2 diabetes on metformin alone		developing hypoglycemia and urinary and genital tract infection Secondary: Not reported	hypoglycemia risk vs placebo. SGLT2 inhibitors, GLP-1 analogs, miglitol, and empagliflozin/linagliptin significantly reduced body weight (range, 1.15 to 2.26 kg) whereas sulfonylureas, TZDs, glargine, and alogliptin/pioglitazone caused weight gain (range, 1.19 to 2.44 kg). SGLT2 inhibitors, empagliflozin/linagliptin, liraglutide, and sitagliptin decreased SBP (range, 1.88 to 5.43 mmHg). No therapy increased UTI risk vs placebo; however, SGLT2 inhibitors were associated with an increased risk of genital tract infection (RR range, 2.16 to 8.03). Secondary: Not reported

*Synonym for glyburide.
†Agent not available in the United States.
Drug regimen abbreviations: BID=twice daily, QD=once daily, QID=four times a day, TID=three times daily, XL=extended-release
Study abbreviations: AC=active comparator, DB=double-blind, MA=meta-analysis, MC=multicenter, OL=open-label, OS=observational study, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, SA=single arm, SR=systematic review, XO=crossover
Miscellaneous abbreviations: AUC=area under the curve, BMI=body mass index, BP=blood pressure, CI=confidence interval, DBP=diastolic blood pressure, DPP-4=dipeptidyl peptidase-4; FPG=fasting plasma glucose, GLP-1=glucagon-like peptide=1, HbA_{1c}= glycosylated hemoglobin, HOMA-B=homeostasis model assessment-beta cell function, HOMA-IR=homeostasis model assessment-estimated insulin resistance, HDL-C=high density lipoprotein cholesterol, HR=hazard ratio, LDL-C=low density lipoprotein cholesterol, MI=myocardial infarction, M value=insulin sensitivity, NPH=neutral protamine Hagedorn, PPG=postprandial plasma glucose, RR=risk ratio, SBP=systolic blood pressure, SGLT2= Sodium-glucose co-transporter 2, TC=total cholesterol, TG=triglyceride, TZD=thiazolidinedione, Vo_{2MAX}=regional fat distribution, WHO=World Health Organization

Additional Evidence

Dose Simplification
One small study by Aoki et al. concluded that the effects of alpha-glucosidase inhibitors on glycosylated hemoglobin (HbA_{1c}) were similar to those who took it prior to meals (as recommended) and those who took it after meals. Thirty-one type 2 diabetic patients who had never been treated with insulin injections or alpha-glucosidase inhibitors were randomized into two groups. One group took miglitol prior to meals, and the other group took miglitol after meals. After three months, the reduction in HbA_{1c} between the two groups was similar. The authors concluded that for those patients who could not remember to take their alpha-glucosidase inhibitor prior to meals could do so after their meal without a noticeable difference in HbA_{1c}.[49]

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 9. Relative Cost of the Alpha-Glucosidase Inhibitors

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Acarbose	tablet	Precose®*	$$$$	$
Miglitol	tablet	N/A	N/A	$$$

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

X. Conclusions

The alpha-glucosidase inhibitors are approved for use as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.[1-2] Acarbose and miglitol are available in a generic formulation.

The goal of treatment for type 2 diabetes is to control hyperglycemia and reduce the risk of long-term complications. A notable new theme in diabetes treatment guidelines is an emphasis on a complication-centric approach, beyond glucose levels, to frame decisions regarding first-line pharmacologic choices for the treatment

of persons with diabetes. Pharmacologic therapy should be guided by person-centered treatment factors, including comorbidities and treatment goals. In adults with type 2 diabetes and established/high risk of atherosclerotic cardiovascular disease, heart failure, and/or chronic kidney disease, the treatment regimen should include agents that reduce cardiorenal risk. Pharmacologic approaches that provide adequate efficacy to achieve and maintain treatment goals should be considered, such as metformin or other agents, including combination therapy.[3-6]
A variety of clinical trials have been conducted with the alpha-glucosidase inhibitors. A clinical trial directly comparing acarbose and miglitol does not evaluate glycemic control among type 2 diabetics; rather the results demonstrate that there is no significant difference between the two agents with regards to glucose variability during pre- and post-prandial periods.[29] The majority of the clinical trials have compared active treatment to placebo or compared combination therapy to monotherapy. In these studies, the more aggressive treatment regimens improved glycemic parameters to a greater extent than the less-intensive treatment regimens.[16-19,27-29,36-37,40,42-46] When comparing similar monotherapy treatment regimens, sulfonylureas have been shown to be more effective than the alpha-glucosidase inhibitors.[22,24]

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with the alpha-glucosidase inhibitors.[1,2]

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

Therefore, all brand products 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-glucosidase 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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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Amylinomimetics
AHFS Class 682003
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I. Overview

Diabetes mellitus is a chronic condition which results in hyperglycemia. It is differentiated into four main classes: 1) type 1 diabetes; 2) type 2 diabetes; 3) gestational diabetes; and 4) other types (drug- or chemical-induced, genetic defects in β-cell function or insulin action, and diseases of the exocrine pancreas). Type 2 diabetes is the most prevalent form of the disease in the United States. Inadequate glycemic control may lead to both acute and long-term complications, including microvascular and macrovascular events. There are a variety of oral and injectable antidiabetic agents currently available to treat diabetes. The antidiabetic agents are categorized into 12 different American Hospital Formulary Service (AHFS) classes, which differ with regards to their mechanism of action, efficacy, safety profiles, tolerability, and ease of use.

Pramlintide is the only amylinomimetic agent that is currently available. It is approved for use as an adjunctive treatment in patients with type 1 and type 2 diabetes mellitus who use mealtime insulin therapy and who have failed to achieve desired glucose control despite optimal insulin therapy.[1-3] Amylin is co-secreted with insulin by pancreatic beta cells in response to food intake. It affects postprandial glucose levels by slowing gastric emptying, suppressing glucagon secretion, and regulating food intake via modulation of appetite.[1] Patients with type 1 and type 2 diabetes have dysfunctional beta cells, which leads to a reduced secretion of insulin and amylin in response to food.[1] Pramlintide is a synthetic analog of human amylin, which has been shown to modulate gastric emptying, decrease postprandial glucagon concentrations in patients using insulin, and reduce caloric intake.[1-3]

The amylinomimetics 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 November 2021.

Table 1. Amylinomimetics Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Pramlintide	injection	SymlinPen®	none

PDL=Preferred Drug List

II. Evidence-Based Medicine and Current Treatment Guidelines

Current clinical guidelines are summarized in Table 2. Please note that guidelines addressing the treatment of type 1 and 2 diabetes are presented globally, addressing the role of various medication classes.

Table 2. Treatment Guidelines Using the Amylinomimetics

Clinical Guideline	Recommendation(s)
American Diabetes Association: **Standards of Care in Diabetes (2023)**[4]	Current criteria for the diagnosis of diabetes • The following are the criteria for a diagnosis of diabetes: glycosylated hemoglobin (HbA_{1c}) ≥6.5%, or a fasting plasma glucose (FPG) ≥126 mg/dL, or a two-hour plasma glucose ≥200 mg/dL during an oral glucose tolerance test or patients with classic symptoms of hyperglycemia, or classic symptoms of hyperglycemia or hyperglycemic crisis (random plasma glucose ≥200 mg/dL). Prevention or delay of type 2 diabetes • Refer adults with overweight/obesity at high risk of type 2 diabetes, as typified by the Diabetes Prevention Program (DPP), to an intensive lifestyle behavior change program to achieve and maintain a weight reduction of at least 7% of initial body weight through healthy reduced-calorie diet and ≥150 minutes/week of moderate-intensity physical activity.

Clinical Guideline	Recommendation(s)
	• A variety of eating patterns can be considered to prevent diabetes in individuals with prediabetes. • Metformin therapy for prevention of type 2 diabetes should be considered i in adults at high risk of type 2 diabetes, as typified by the DPP, especially those aged 25 to 59 years with BMI ≥35 kg/m^2, higher FPG) (e.g., ≥110 mg/dL), and higher A1C (e.g., ≥6.0%), and in individuals with prior gestational diabetes mellitus (GDM). • Long-term use of metformin may be associated with biochemical vitamin B12 deficiency; consider periodic measurement of vitamin B12 levels in metformin-treated individuals, especially in those with anemia or peripheral neuropathy. Glycemic goals in adults • An A1C goal for many nonpregnant adults of <7% (53 mmol/mol) without significant hypoglycemia is appropriate. • If using ambulatory glucose profile (AGP)/glucose management indicator (GMI) to assess glycemia, a parallel goal for many nonpregnant adults is time in range (TIR) of >70% with time below range (TBR) <4% and time <54 mg/dL <1%. For those with frailty or at high risk of hypoglycemia, a target of >50% TIR with <1% TBR is recommended. • On the basis of health care provider judgment and patient preference, achievement of lower A1C levels than the goal of 7% may be acceptable and even beneficial if it can be achieved safely without significant hypoglycemia or other adverse effects of treatment. • Less stringent A1C goals (such as <8% [64 mmol/mol]) may be appropriate for patients with limited life expectancy or where the harms of treatment are greater than the benefits. HCPs should consider deintensification of therapy if appropriate to reduce the risk of hypoglycemia in patients with inappropriate stringent A1C targets. Pharmacologic therapy for type 1 diabetes • Most individuals with type 1 diabetes should be treated with multiple dose insulin injections (three to four injections per day of basal and pre-prandial insulin) or continuous subcutaneous (SC) insulin infusion therapy. • Most patients should use rapid-acting insulin analogs to reduce hypoglycemia risk. • Patients with type 1 diabetes should receive education on how to match prandial insulin doses to carbohydrate intake, premeal blood glucose, and anticipated physical activity. Pharmacologic therapy for type 2 diabetes • Healthy lifestyle behaviors, diabetes self-management education and support, avoidance of clinical inertia, and social determinants of health should be considered in the glucose-lowering management of type 2 diabetes. Pharmacologic therapy should be guided by person-centered treatment factors, including comorbidities and treatment goals. • In adults with type 2 diabetes and established/high risk of atherosclerotic cardiovascular disease, heart failure, and/or chronic kidney disease, the treatment regimen should include agents that reduce cardiorenal risk. • Pharmacologic approaches that provide adequate efficacy to achieve and maintain treatment goals should be considered, such as metformin or other agents, including combination therapy. • Weight management is an impactful component of glucose-lowering management in type 2 diabetes. The glucose-lowering treatment regimen should consider approaches that support weight management goals. • Metformin should be continued upon initiation of insulin therapy (unless contraindicated or not tolerated) for ongoing glycemic and metabolic benefits.

Clinical Guideline	Recommendation(s)
	• Early combination therapy can be considered in some individuals at treatment initiation to extend the time to treatment failure. • The early introduction of insulin should be considered if there is evidence of ongoing catabolism (weight loss), if symptoms of hyperglycemia are present, or when A1C levels (>10% [86 mmol/mol]) or blood glucose levels (≥300 mg/dL [16.7 mmol/L]) are very high. • A person-centered approach should guide the choice of pharmacologic agents. Consider the effects on cardiovascular and renal comorbidities, efficacy, hypoglycemia risk, impact on weight, cost and access, risk for side effects, and individual preferences. • Among individuals with type 2 diabetes who have established atherosclerotic cardiovascular disease or indicators of high cardiovascular risk, established kidney disease, or heart failure, a sodium–glucose cotransporter 2 inhibitor and/or glucagon-like peptide 1 receptor agonist with demonstrated cardiovascular disease benefit is recommended as part of the glucose-lowering regimen and comprehensive cardiovascular risk reduction, independent of A1C and in consideration of person-specific factors. • In adults with type 2 diabetes, a glucagon-like peptide 1 receptor agonist is preferred to insulin when possible. • If insulin is used, combination therapy with a glucagon-like peptide 1 receptor agonist is recommended for greater efficacy, durability of treatment effect, and weight and hypoglycemia benefit. • Recommendation for treatment intensification for individuals not meeting treatment goals should not be delayed. • Medication regimen and medication-taking behavior should be reevaluated at regular intervals (every three to six months) and adjusted as needed to incorporate specific factors that impact choice of treatment. • Clinicians should be aware of the potential for over-basalization with insulin therapy. Clinical signals that may prompt evaluation of over-basalization include basal dose more than ~0.5 units/kg/day, high bedtime–morning or post-preprandial glucose differential, hypoglycemia (aware or unaware), and high glycemic variability. Indication of over-basalization should prompt reevaluation to further individualize therapy.
American Diabetes Association/ European Association for the Study of Diabetes: **Management of Hyperglycemia in Type 2 Diabetes. A consensus report by the American Diabetes Association and the European Association for the Study of Diabetes (2022)**[5]	Consensus recommendations • All people with type 2 diabetes should be offered access to ongoing diabetes self-management education and support programs. • Providers and health care systems should prioritize the delivery of person-centered care. • Optimizing medication adherence should be specifically considered when selecting glucose-lowering medications. • Medical nutrition therapy focused on identifying healthy dietary habits that are feasible and sustainable is recommended in support of reaching metabolic and weight goals. • Physical activity improves glycemic control and should be an essential component of type 2 diabetes management. • Adults with type 2 diabetes should engage in physical activity regularly (>150 min/week of moderate- to vigorous-intensity aerobic activity) and be encouraged to reduce sedentary time and break up sitting time with frequent activity breaks. • Aerobic activity should be supplemented with two to three resistance, flexibility, and/or balance training sessions/week. Balance training sessions are particularly encouraged for older individuals or those with limited mobility/poor physical function. • Metabolic surgery should be considered as a treatment option in adults with type 2 diabetes who are appropriate surgical candidates with a BMI ≥40.0 kg/m^2 (BMI

Clinical Guideline	Recommendation(s)
	≥37.5 kg/m^2 in people of Asian ancestry) or a BMI of 35.0 to 39.9 kg/m^2 (32.5 to 37.4 kg/m^2 in people of Asian ancestry) who do not achieve durable weight loss and improvement in comorbidities (including hyperglycemia) with nonsurgical methods. • In people with established CVD, a GLP-1 RA with proven benefit should be used to reduce MACE, or an SGLT2i with proven benefit should be used to reduce MACE and HF and improve kidney outcomes. • In people with CKD and an eGFR ≥20 ml/min per 1.73 m^2 and a urinary albumin/creatinine ratio >3.0 mg/mmol (>30 mg/g), an SGLT2i with proven benefit should be initiated to reduce MACE and HF and improve kidney outcomes. Indications and eGFR thresholds may vary by region. If such treatment is not tolerated or is contraindicated, a GLP-1 RA with proven cardiovascular outcome benefit could be considered to reduce MACE and should be continued until kidney replacement therapy is indicated. • In people with HF, SGLT2i should be used because they improve HF and kidney outcomes. • In individuals without established CVD but with multiple cardiovascular risk factors (such as age ≥55 years, obesity, hypertension, smoking, dyslipidemia, or albuminuria), a GLP-1 RA with proven benefit could be used to reduce MACE, or an SGLT2i with proven benefit could be used to reduce MACE and HF and improve kidney outcomes. • In people with HF, CKD, established CVD, or multiple risk factors for CVD, the decision to use a GLP-1 RA or SGLT2i with proven benefit should be independent of background use of metformin. • SGLT2i and GLP-1 RA reduce MACE, which is likely to be independent of baseline HbA1c. In people with HF, CKD, established CVD, or multiple risk factors for CVD, the decision to use a GLP-1 RA or an SGLT2i with proven benefit should be independent of baseline HbA1c. • In general, selection of medications to improve cardiovascular and kidney outcomes should not differ for older people. • In younger people with diabetes (<40 years), consider early combination therapy. • In women with reproductive potential, counseling regarding contraception and taking care to avoid exposure to medications that may adversely affect a fetus are important.
American Association of Clinical Endocrinologists/ American College of Endocrinology: **Clinical Practice Guidelines for Developing a Diabetes Mellitus Comprehensive Care Plan (2022)**[6]	<u>Antihyperglycemic Pharmacotherapy for Persons with Type 2 Diabetes</u> • Individualized pharmacotherapy for persons with T2D should be prescribed based on evidence for benefit that includes glucose lowering, avoidance of hypoglycemia and weight gain, and reduction of cardio-renal risk. • Persons with T2D and their health care professionals should use patient-centered shared decision-making to agree on therapy targets and treatments as well as a regimen for glucose monitoring (i.e., BGM, structured BGM, or CGM). • Glycemic targets include A1C, BGM, and, for those using CGM, achievement of CGM targets such as time in range (TIR), percentage in low and very low range, time above range, and glycemic variability. Nonglycemic targets include avoidance of hypoglycemia, control of BP, lipids, other CVD risk factors, and achieving and maintaining a healthy body weight. • Independent of glycemic control, targets, or treatment, if there is established or high risk for ASCVD, HF, and/or CKD, clinicians should prescribe a GLP-1 RA or an SGLT2i with proven efficacy for the specific condition(s) of the person with T2D being treated. • DM therapy should be individualized based on level of glycemia and the presence of comorbidities, complications, and access. Metformin is often the preferred initial therapy. Other agents may be appropriate as first line or in addition to

Clinical Guideline	Recommendation(s)
	metformin to reduce BG and/or to address specific comorbidities (such as ASCVD, HF, CKD, obesity, NAFLD), independent of glucose-lowering effects. • For some recently diagnosed individuals with T2D and more severe hyperglycemia (A1C ≥7.5%), unlikely to attain the A1C target with a single agent, early combination pharmacotherapy should be considered, usually to include metformin plus another agent that does not cause hypoglycemia, especially a GLP-1 RA, SGLT2i, or dipeptidyl peptidase 4 (DPP-4) inhibitor. • For newly diagnosed persons with T2D and an entry A1C >9.0% and/or ≥1.5% above target, one should initiate, along with lifestyle modifications, dual- or possibly triple-combination pharmacotherapy usually including metformin. Basal insulin along with noninsulin therapy is recommended if there are significant signs or symptoms of hyperglycemia, especially including catabolism (e.g., weight loss) or a very high A1C >10% (86 mmol/mol) or BG levels (≥300 mg/dL [16.7 mmol/L]). • Clinicians should discuss with persons with T2D the likelihood that most persons with T2D ultimately require a combination of multiple complementary antihyperglycemic agents, in addition to lifestyle interventions, to attain and maintain optimal glycemic control. • The DM care team should assess medication adherence and safety and glycemic control in persons with T2D quarterly or more frequently as needed. Subsequent visits will depend upon the metabolic targets achieved and the stability of metabolic control. • Persons with T2D who start on metformin should continue it unless intolerance or contraindications occur. When intensification of antihyperglycemic treatment is needed, other agents should be added to metformin. • Most persons with T2D who require intensification of antihyperglycemic therapy with a GLP-1 RA or insulin should initially be prescribed a GLP-1 RA. If further intensification is required, one should prescribe a basal insulin or a switch to a fixed-ratio combination of a basal insulin and a GLP-1 RA (insulin glargine U100 + lixisenatide [GlarLixi] or insulin degludec + liraglutide [IdegLira]). • Insulin should be prescribed for persons with T2D when noninsulin antihyperglycemic therapy fails to achieve target glycemic control or when a person has symptomatic hyperglycemia. • Long-acting basal insulin analogs are the recommended initial choice of insulin therapy for persons with T2D. The insulin analogs glargine (U100 or U300), degludec (U100 or U200), or detemir are preferred over intermediate-acting Neutral Protamine Hagedorn (NPH) insulin because analog insulins have demonstrated less hypoglycemia in some studies. Glargine U300 and degludec can be associated with less hypoglycemia than glargine U100 or detemir. • Many persons with T2D receiving basal insulin and not at goal A1C can have significantly improved glycemia by the addition of a GLP-1 RA or being switched to a fixed-ratio combination basal insulin–GLP-1 RA (GlarLixi or IdegLira). One of these changes should be considered before adding a meal-time insulin for postprandial glycemic control. • When control of postprandial hyperglycemia is needed and a basal insulin and a GLP-1 RA are already being used, preference should be given to rapid-acting insulins (the analogs lispro, aspart, and glulisine or the rapid-acting inhaled human insulin powder) over regular human insulin. The former have a more consistent and a more rapid onset and offset of action with less risk of hypoglycemia. • Ultra-rapid-acting insulins (faster-acting insulin aspart, lispro aabc, and [human insulin] inhalation powder) may allow a decrease in the time between insulin administration and food intake and reduce the postprandial peak of PG as compared with rapid-acting insulins. The significance of this on long-term complications is unknown.

Clinical Guideline	Recommendation(s)
	• Basal-bolus insulin regimens or continuous subcutaneous insulin infusion (CSII) (i.e., insulin pump) allow for adjustment of insulin doses according to carbohydrate intake and activity levels and are recommended for intensive insulin therapy in persons with T2D. • Premixed insulin formulations (fixed combinations of shorter- and longer-acting components) of human or analog insulin may be considered for persons with T2D who have consistent dietary and exercise patterns and in whom adherence to more intensive insulin regimens is problematic. However, these preparations have reduced dosage flexibility and may increase the risk of hypoglycemia compared with basal insulin or basal-bolus regimens. • In persons with T2D who are treated with basal-bolus insulin therapy, adding a GLP-1 RA, or switching to a fixed-ratio combination of a GLP-1 RA and a basal insulin, or adding an SGLT2i or pramlintide (less commonly used) may be able to reduce postprandial hyperglycemia, A1C, and weight. GlP-1 RAs may also allow reduction or discontinuation of bolus insulin in some individuals. <u>How should insulin therapy be used for management of persons with type 1 diabetes?</u> • Insulin must be used to treat all persons with T1D. • Physiologic insulin replacement regimens, which provide both basal and prandial (meal-related or bolus) insulin, are recommended for most persons with T1D. • Achievement of glucose targets using either MDI of insulin or CSII, is needed to prevent development of life-threatening crises, such as acute hyperglycemic crises (DKA and hyperglycemic hyperosmolar state) and catabolic state. • A multi-component self-management DM education program is recommended for persons with T1D. Ideally, this is provided by a professional with expertise (i.e., certified diabetes care and education specialist) in the topics of healthy lifestyle, insulin technique including prandial insulin dosing guided by carbohydrate counting and diet adjustments for special situations, such as physical activity and prolonged fasting. Instruction is also needed in how to deal with sick days and prevention of DKA and hypoglycemia, and other relevant issues. Due to changes in DM self-management practices and each individual's medical history, personal and cultural background, and educational needs, specific education topics may need to be repeated at regular intervals. • The ideal insulin regimen should be personalized to an individual's needs and glycemic targets, attempting to better emulate physiological insulin replacement to maintain near normoglycemia, to prevent the development and progression of DM complications, while minimizing hypoglycemia and providing flexibility for specific daily life situations/scenarios such as: exercise, sleep, acute illness, psychological stress, etc. • Insulin regimens usually should involve the use of insulin analogs for most persons with T1D and include the following approaches: o MDI, which usually involve 1 to 2 subcutaneous injections daily of basal insulin to suppress ketogenesis and gluconeogenesis and to control glycemia between meals and overnight, and subcutaneous injections of prandial insulin or use of inhaled insulin before each meal to control meal-related glycemic excursions. CGM is the preferred method of glucose monitoring for all individuals with T1D. o Insulin pump therapy (CSII) provides constant/continuous infusion of fast-acting insulin driven by mechanical force and delivered via a cannula inserted under the skin. CSII can improve (or enhance) glycemic control and should be an option for insulin delivery for appropriate persons with DM. Ideally, these individuals should also use CGM as stated in R13.6.a. o Automated insulin delivery systems (AIDs), which include an insulin pump, an integrated CGM, and computer software algorithm, aim to better emulate physiological insulin replacement and achieve glycemic targets. This technology is recommended for many persons with T1D since its use

Clinical Guideline	Recommendation(s)
	has been shown to increase TIR while often reducing hypoglycemia or at least without causing increased hypoglycemia. ○ Open-loop (use of a pump and sensor which do not communicate) and sensor-augmented pump (SAP) systems: (CGM communicates with pump facilitating needed adjustments to basal rate; temporary interruption of insulin delivery when glucose levels are low or forecast to be low within 30 min). Insulin pump with a CGM or an SAP is recommended to manage persons with DM treated with intensive insulin management who prefer not to use AIDs or have no access to them. How should diabetes mellitus in pregnancy be managed? • For women with GDM, the following treatment goals are recommended: preprandial glucose concentration ≤95 mg/dL and either a 1-h post-meal glucose ≤140 mg/dL or a 2-h post-meal glucose ≤120 mg/dL to decrease adverse fetal outcomes. • All women with preexisting DM (T1D, T2D, or previous GDM) need access to preconception care and counseling to ensure adequate nutrition, healthy weight, and glucose control before conception, during pregnancy, and in the postpartum period. • Rapid-acting insulin analogs (insulin-lispro, insulin-aspart) should be used to treat postprandial hyperglycemia in pregnant women. • Options for basal insulin include long-acting insulin (e.g., NPH, detemir, or glargine) or rapid-acting insulin via a CSII. Regular insulin, although not recommended as first-line therapy, is acceptable to use in managing pregnant women with DM when rapid-acting insulin analogs are not available. • Insulin is the preferred therapeutic choice for pregnant women with GDM or T2D, but metformin has been given a category B for pregnancy with accumulating clinical evidence of metformin's safety during the first trimester and beyond. Metformin has been shown to improve pregnancy and fetal outcomes except for increased rates of infants with SGA and later onset of obesity. The prescriber should discuss the potential risks and benefits of oral agent therapy during pregnancy as well as the need for longer-term outcome studies.
American Association of Clinical Endocrinologists/ American College of Endocrinology: **Consensus Statement on the Comprehensive Type 2 Diabetes Management Algorithm (2023)**[7]	Principles underlying the algorithm • Lifestyle modification underlies all therapy. • Maintain or achieve optimal weight. • Choice of antihyperglycemic therapy reflects glycemic targets, atherosclerotic cardiovascular disease (ASCVD), congestive heart failure (CHF), chronic kidney disease (CKD), overweight/obesity, and nonalcoholic fatty liver disease (NAFLD). • Choice of therapy includes ease of use and access. • Optimal hemoglobin A1c (A1C) is ≤6.5% or as close to normal as is safe and achievable for most patients. • Individualize all glycemic targets (A1C, glucose management indicator [GMI], time in range [TIR], fasting blood glucose [FBG], and PPG). • Get to goal as soon as possible (adjust ≤3 months). • Avoid hypoglycemia. Hypoglycemia, defined as blood glucose (BG) <70 mg/dL, is associated with an increased risk for adverse outcomes including mortality. • CGM is highly recommended to assist persons with diabetes in reaching goals safely. • Comorbidities must be managed for comprehensive care. Algorithm summative information

Clinical Guideline	Recommendation(s)
	• The algorithm is intended as a more concise document than the guideline, providing easily accessible, visual guidance for decision-making in the clinic setting. • In this 2023 algorithm, there continues to be an emphasis on lifestyle modification and treatment of overweight/obesity as key pillars of the management of prediabetes and DM. • The importance of appropriate management of the atherosclerotic risk factors of dyslipidemia and hypertension is highlighted. • One notable new theme is an obvious emphasis on a complication-centric approach, beyond glucose levels, to frame decisions regarding first-line pharmacologic choices for the treatment of persons with diabetes. • The algorithm is divided into discrete graphic sections that outline the principles for management of T2D and guide management of adiposity-based chronic disease (ABCD), prediabetes, and atherosclerotic risk factors of dyslipidemia and hypertension. In addition, the algorithms for antihyperglycemic agents include both complication-centric and glucose-centric approaches, and there is direction for insulin initiation and titration. Tables summarizing the benefits and risks of antihyperglycemic medications (updated) and weight-loss pharmacotherapy (new) are provided.

American Academy of Pediatrics: **Management of Newly Diagnosed Type 2 Diabetes Mellitus (T2DM) in Children and Adolescents (2013)[8]**	• Clinicians must ensure that insulin therapy is initiated for children and adolescents with T2DM who are ketotic or in diabetic ketoacidosis and in whom the distinction between types 1 and 2 diabetes mellitus is unclear and, in usual cases, should initiate insulin therapy for patients.
	  ○ Who have random venous or plasma blood glucose (BG) concentrations ≥250 mg/dL.
	  ○ Whose HbA_{1c} is >9%.
	• In all other instances, clinicians should initiate a lifestyle modification program, including nutrition and physical activity, and start metformin as first-line therapy for children and adolescents at the time of diagnosis of T2DM.
	• Monitoring of HbA_{1c} concentrations is recommended every three months and intensifying treatment is recommended if treatment goals for finger-stick BG and HbA_{1c} concentrations are not being met.
	• Advise patients to monitor finger-stick BG concentrations in patients who:
	  ○ Are taking insulin or other medications with a risk of hypoglycemia; or
	  ○ Are initiating or changing their diabetes treatment regimen; or
	  ○ Have not met treatment goals; or
	  ○ Have intercurrent illnesses.
	• Incorporate the Academy of Nutrition and Dietetics' *Pediatric Weight Management Evidence-Based Nutrition Practice Guidelines* in dietary or nutrition counseling of patients with T2DM at the time of diagnosis and as part of ongoing management.
	• Encourage children and adolescents with T2DM to engage in moderate-to-vigorous exercise for at least 60 minutes daily and to limit nonacademic "screen time" to less than two hours a day.

American Diabetes Association: **Type 1 Diabetes in Children and Adolescents: A Position Statement by the American Diabetes Association (2018)[9]**	<u>Blood Glucose Management: Monitoring and Treatment</u> • Most children with type 1 diabetes should be treated with intensive insulin regimens via either multiple daily injections of prandial insulin and basal insulin or continuous subcutaneous insulin infusion. • An HbA_{1c} target of <7.5% should be considered in most children and adolescents but should be individualized based on the needs and situation of the patient and family. • Children and adolescents with type 1 diabetes should have blood glucose levels monitored up to six to ten times/day including premeal, pre-bedtime, and as needed

Clinical Guideline	Recommendation(s)
	for safety (e.g., exercise, driving, illness, or the presence of symptoms of hypoglycemia). • Continuous blood glucose monitoring should be considered in all children and adolescents whether using insulin injections or an insulin pump. • In pediatric patients with type 1 diabetes automated insulin delivery systems can improve glycemic control and reduce hypoglycemia. <u>Lifestyle Management</u> • Individualized medical nutrition therapy is recommended for children and adolescents with type 1 diabetes. • Monitoring carbohydrate intake, whether by carbohydrate counting or experience-based estimation, is key to achieving optimal glycemic control. • Exercise if recommended for all children and adolescents with type 1 diabetes. The suggested goal is 60 minutes of moderate to vigorous aerobic activity daily with muscle-strengthening and bone-strengthening activities three times a week. • Children and adolescents with type 1 diabetes should be educated about prevention and management of potential hypoglycemia during and after exercise. • Strategies to prevent hypoglycemia during exercise, after exercise, and overnight following exercise include reducing prandial insulin dosing for the meal/snack preceding exercise, increasing carbohydrate intake, eating bedtime snacks, using continuous blood glucose monitoring, and/or reducing basal insulin doses. <u>Behavioral Aspects of Self-Management</u> • Children and adolescents with diabetes should be assessed for psychosocial issues and family stresses that could impact diabetes management at diagnosis and routine follow-up. • Consider including children in consent processes as early as cognitive development indicates understanding of health consequences of behavior. • Offer adolescents time by themselves with their care provider(s) starting at age 12 years, or when developmentally appropriate. <u>Complications and Comorbidities</u> • Diabetic Ketoacidosis o All individuals with type 1 diabetes should have access to an uninterrupted supply of insulin. Lack of access and insulin omissions are major causes of diabetic ketoacidosis. o Patients with type 1 diabetes should have continuous access to medical support for sick-day management. • Hypoglycemia o The recommended treatment of hypoglycemia (blood glucose <70 mg/dL) in conscious patients is 15 g of glucose, although any form of carbohydrate can be used. If hypoglycemia continues after 15 minutes, treatment should be repeated. Once blood glucose has returned to normal patients should consider consuming a meal/snack and/or reduce insulin. o All individuals with type 1 diabetes should be prescribed glucagon and families/caregivers should be educated on administration. o Treatment regimens should be reevaluated in those with hypoglycemia unawareness or one or more episodes of severe hypoglycemia. • Diabetic Kidney Disease o Annual screening for albuminuria with a random spot urine sample for albumin-to-creatinine ratio should be considered at puberty or at age >10 years, whichever is earlier, once the child has had diabetes for 5 years. o An angiotensin-converting-enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB), titrated to normalization of albumin excretion, may be considered when elevated urinary albumin-to-creatinine ratio is documented.

Clinical Guideline	Recommendation(s)
	• Retinopathy o An initial dilated and comprehensive eye examination is recommended at age 10 years or after puberty has started, whichever is earlier, once the patient has had diabetes for three to five years. o Annual routine follow-up is recommended but may be given every two years based on the advice of an eye care professional. • Neuropathy o Consider an annual comprehensive foot exam for adolescents at the start of puberty or at age 10 years, whichever is earlier, once the patient has had type 1 diabetes for 5 years. • Hypertension o Children and adolescents with type 1 diabetes should have blood pressure monitored at each visit. Elevated blood pressure should be confirmed on three separate days. o Initial treatment of high-normal blood pressure should include dietary modification and increased exercise. Pharmacologic treatment should be considered if blood pressure is not controlled after three to six months. o In patients with conformed hypertension pharmacologic treatment should be added to lifestyle modification at diagnosis. o ACE inhibitors and ARBs should be considered for initial treatment. • Dyslipidemia o A fasting lipid profile should be taken in children ≥10 years of age or older after the diagnosis of diabetes. Obtain a fasting lipid profile in children 10 years of age or older as soon as convenient after the diagnosis of diabetes o If lipids are abnormal, initial therapy should consist of optimizing glucose control and medical nutrition therapy using a Step 2 American Heart Association diet that restricts saturated fat to 7% of total calories and dietary cholesterol to 200 mg/day. o If lipids remain abnormal after six months of lifestyle intervention, consider adding a statin in children at least 10 years of age.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the amylinomimetics 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 Amylinomimetics[1]

Indication	Pramlintide
Type 1 diabetes, as an adjunct treatment in patients who use mealtime insulin therapy and who have failed to achieve desired glucose control despite optimal insulin therapy	✔
Type 2 diabetes, as an adjunct treatment in patients who use mealtime insulin therapy and who have failed to achieve desired glucose control despite optimal insulin therapy	✔

IV. Pharmacokinetics

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

Table 4. Pharmacokinetic Parameters of the Amylinomimetics[1-3]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Half-Life (hours)

Pramlintide	30 to 40	Not extensively protein bound	Renal	0.50 to 0.83

V. Drug Interactions

There are no significant drug interactions reported with the amylinomimetics.[1-3] Due to its effects on gastric emptying, pramlintide should not be considered for patients taking drugs that alter gastrointestinal motility (e.g., anticholinergic agents) and agents that slow the intestinal absorption of nutrients (e.g., alpha-glucosidase inhibitors).[1] Pramlintide has the potential to delay the absorption of concomitantly administered oral medications. When the rapid onset of a concomitant administered oral agent is a critical determinant of effectiveness, the agent should be administered at least one hour prior to or two hours after pramlintide injection.[1]

VI. Adverse Drug Events

The most common adverse drug events reported with the amylinomimetics are listed in Table 5. The boxed warning for pramlintide is listed in Table 6. When used alone, pramlintide does not cause hypoglycemia; however, when co-administered with insulin, there is an increased risk of insulin-induced severe hypoglycemia. Severe hypoglycemia occurs within the first three hours following administration of pramlintide.

Table 5. Adverse Drug Events (%) Reported with the Amylinomimetics[1-3]

Adverse Event	Pramlintide*
Central Nervous System	
Dizziness	2 to 6
Fatigue	3 to 7
Headache	5 to 13
Gastrointestinal	
Abdominal pain	2 to 8
Anorexia	0 to 17
Nausea	28 to 48
Vomiting	7 to 11
Respiratory	
Coughing	2 to 6
Pharyngitis	3 to 5
Other	
Allergic reaction	<1 to 6
Arthralgia	2 to 7
Inflicted injury	8 to 14
Severe hypoglycemia (medically assisted)	0.4 to 7.3
Severe hypoglycemia (patient-ascertained)	0.6 to 16.8

*In combination with insulin therapy.

Table 6. Boxed Warning for the Amylinomimetics[1-3]

WARNING
Pramlintide use with insulin and has been associated with an increased risk of insulin-induced severe hypoglycemia, particularly in patients with type 1 diabetes. When severe hypoglycemia associated with pramlintide use occurs, it is seen within three hours following a pramlintide injection. If severe hypoglycemia occurs while operating a motor vehicle, heavy machinery, or while engaging in other high-risk activities, serious injuries may occur. Appropriate patient selection, careful patient instruction, and insulin dose adjustments are critical elements for reducing this risk.

VII. Dosing and Administration

The usual dosing regimens for the amylinomimetics are listed in Table 7.

Table 7. Usual Dosing Regimens for the Amylinomimetics[1-3]

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
Pramlintide	Type 1 diabetes, as an adjunct treatment in patients who use mealtime insulin therapy and who have failed to achieve desired glucose control despite optimal insulin therapy: Multi-dose pen: initial, 15 µg SC immediately prior to major meals; maintenance, 30 to 60 µg SC immediately prior to major meals Type 2 diabetes, as an adjunct treatment in patients who use mealtime insulin therapy and who have failed to achieve desired glucose control despite optimal insulin therapy: Multi-dose pen: initial, 60 µg SC immediately prior to major meals; maintenance, 60 to 120 µg SC immediately prior to major meals	Safety and efficacy in children have not been established.	Pen injector: 2700 µg/ 2.7 mL 1500 µg/ 1.5 mL

SC=subcutaneous

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the amylinomimetics are summarized in Table 8.

Table 8. Comparative Clinical Trials with the Amylinomimetics

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Type 1 Diabetes				
Edelman et al.[10] (2006) Pramlintide 15 to 60 µg with meals and insulin (existing regimen) vs placebo and insulin (existing regimen)	DB, MC, PC, RCT Type 1 diabetic patients <18 years of age with an HbA_{1c} 7.5 to 9.0%, intensely or continuously treated with insulin for the past year, and with no severe hypoglycemic event over the preceding 6 months	N=296 29 weeks	Primary: Safety Secondary: Change from baseline in HbA_{1c}, PPG concentrations, insulin, and weight; tolerability	Primary: Both treatments resulted in a similar number of nonsevere hypoglycemic events. The event rate per patient years was 0.57 with pramlintide compared to 0.30 with placebo (P<0.05). Secondary: Baseline HbA_{1c} was 8.1% with both treatments and at week 29 had decreased comparably (-0.50; 95% CI, -0.61 to -0.33 vs -0.50%; 95% CI, -0.63 to -0.35; P value not reported). Among pramlintide-treated patients, a significantly greater number were able to achieve a PPG concentration of 9.9 mmol/L at breakfast (68 vs 51%), lunch (71 vs 61%), and dinner (70 vs 58%; P<0.0001 for each meal). At week 29 the total insulin dose with pramlintide decreased by -12% compared to an increase of 1% with placebo. Between weeks 0 through 29, the reduction in body weight was significant with pramlintide compared to placebo (-1.3 vs 1.2 kg; P<0.0001). Reduced appetite, vomiting, and sinusitis occurred at twice the level with pramlintide compared to placebo (P<0.01).
Whitehouse et al.[11] (2002) Pramlintide 30 to 60 µg QID and insulin (existing regimen) vs	DB, PC, RCT Type 1 diabetic patients	N=480 52 weeks	Primary: Change from baseline HbA_{1c} Secondary: Change from baseline HbA_{1c} and body weight at	Primary: Significantly greater reductions in HbA_{1c} were observed with pramlintide (-0.39%) compared to placebo (-0.12%; P=0.0071) at 52 weeks. Secondary: Significantly greater reductions in HbA_{1c} with pramlintide were achieved at weeks 13 (-0.67 vs -0.16%; P<0.0001), 26 (-0.58 vs -0.18%; P=0.0001), and 52 (-0.39 vs -0.12%; P=0.0071).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo and insulin (existing regimen)			weeks 13, 26, and 52	Pramlintide-treated patients had sustained reductions in body weight that were significantly different compared to placebo-treated patients (P<0.001) from week 13 onward (data reported in graphical form only). The most commonly reported side effects with pramlintide were nausea (46.5 vs 21.9%; P values not reported) and anorexia (17.7 vs 2.1%; P values not reported). Withdrawal due to adverse event(s) occurred in 31 (12.8%) and 19 (8.0%) pramlintide- and placebo-treated patients.
Ratner et al.[12] (2004) Pramlintide 60 µg TID, 60 µg QID, or 90 µg TID and insulin (existing regimen) vs placebo and insulin (existing regimen)	DB, PC, RCT Type 1 diabetics	N=651 52 weeks	Primary: Change from baseline HbA_{1c} at week 26 Secondary: Change from baseline HbA_{1c} at week 52, proportion of patients achieving HbA_{1c} <7.0%, safety	Primary: Significantly greater reductions in HbA_{1c} were achieved with pramlintide 60 µg TID compared to placebo (-0.41 vs -0.18%; P=0.012) after 26 weeks. In addition, significantly greater reductions in HbA_{1c} were achieved with pramlintide 60 µg QID compared to placebo (-0.39 vs -0.18%; P=0.013). Secondary: Significantly greater reductions in HbA_{1c} were achieved with pramlintide 60 µg TID compared to placebo (-0.29 vs -0.04%; P=0.011) after 52 weeks. In addition, significantly greater reductions in HbA_{1c} were achieved with pramlintide 60 µg QID compared to placebo (-0.34 vs -0.04%; P=0.001). A threefold greater proportion of pramlintide-treated patients achieved HbA_{1c} <7.0% compared to placebo treated patients (P value not reported; data was reported in graphical form only). Pramlintide 90 µg was excluded from the analysis when results from a separate trial indicated the dose had an adverse tolerability profile. Patients originally randomized to this treatment continued to receive 90 µg to preserve the trial design. During the first four weeks of therapy, pramlintide-treated patients had a fourfold increase in severe hypoglycemic event rate compared to placebo-treated subjects (3.78 vs 0.87 events/year; no P value reported). The most commonly reported adverse event with pramlintide was nausea. Withdrawal due to adverse event(s) occurred in 38 (22.1%) patients receiving pramlintide 90 µg TID, 22 (13.7%) patients receiving

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				pramlintide 60 µg QID, 32 (19.5%) patients receiving pramlintide 60 µg TID, and six (3.9%) patients receiving placebo.
Marrero et al.[13] (2007) Pramlintide 15 to 60 µg with meals and insulin (existing regimen) vs placebo and insulin (existing regimen)	Post hoc analysis Type 1 diabetic patients who completed a 29 week DB, noninferiority, dose-finding pramlintide trial	N=266 29 weeks	Primary: Patient response to satisfaction questionnaire Secondary: Not reported	Primary: For the following topics the survey ratings favored pramlintide: Study medication (1) "made my blood glucose control more even or predictable," (2) "provided me with more flexibility in what I can eat," (3) "made it easier to control my weight," and (4) "made it easier to control my appetite" (P<0.05 for all). There was no difference between treatments in the response to the following statements: Study medication (1) "made it easier to avoid low blood sugar reactions (hypoglycemia)" and (2) "I would like to continue taking the study medication" (P value not significant). Secondary: Not reported
Ratner et al.[14] (2005) Pramlintide and insulin (existing regimen) vs placebo and insulin (existing regimen)	MA (3 trials) Type 1 diabetic patients with HbA_{1c} 7.0 to 8.5%	N=477 26 weeks	Primary: Change from baseline in HbA_{1c} and body weight, adverse events (hypoglycemia) Secondary: Not reported	Primary: Significant baseline reductions in HbA_{1c} (-0.3%) and body weight (-1.8 kg) at endpoint were achieved with pramlintide (P<0.0009 for both). The risk of severe hypoglycemia was 1.40 with pramlintide compared to 1.86 with placebo. Secondary: Not reported
Heptulla et al.[15] (2009) Pramlintide 3 to 5 µg /hour as a basal dose and insulin infusion (existing regimen was reduced by 30%)	RCT Adolescents with type 1 diabetes mellitus on insulin pump therapy	N=13 24 hours	Primary: PPG, glucagon, and insulin concentrations Secondary: Not reported	Primary: Postprandial hyperglycemia was reduced by 26% with pramlintide compared to placebo (P<0.008). Postprandial glucagon concentrations were suppressed with pramlintide compared to placebo (P<0.003). The plasma insulin concentrations were unchanged. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs insulin infusion (existing regimen)				Not reported
Type 2 Diabetes				
Singh-Franco et al.[16] (2011) Pramlintide 120 to 150 µg SC BID or TID with meals	MA (8 trials) Type 2 diabetic patients (4 trials) and obese patients without diabetes (4 trials)	N=1,616 6 to 52 weeks	Primary: Change from baseline in HbA_{1c} Secondary: Likelihood of achieving HbA_{1c} ≤7.0%; change from baseline in FPG, PPG, and weight	Primary: Pooled analysis revealed that compared to placebo, pramlintide was associated with a baseline reduction in HbA_{1c} of -0.33% (P=0.0004). Secondary: After 52 weeks, pramlintide-treated patients were 1.52 times (95% CI, 0.83 to 2.78) more likely to achieve an HbA_{1c} ≤7.0% compared to placebo treated patients; however, this difference was not significant (P=0.18). Treatment with pramlintide was associated with a reduction from baseline in FPG of -6.34 mg/dL (95% CI, -24.96 to 12.28) over 24 weeks of treatment, but the difference was not significant (P=0.50). Treatment with pramlintide was associated with a reduction from baseline in PPG of -7.20 mg/dL (95% CI, -40.12 to 25.75) over 24 weeks of treatment, but the difference was not significant (P=0.67). Pramlintide was associated with a significant change in body weight in patients with type 2 diabetes compared to placebo (-2.21 kg; P<0.000001).
Karl et al.[17] (2007) Pramlintide 120 µg before meals and insulin (existing regimen)	MC, OL Type 2 diabetics >18 years of age currently receiving insulin therapy with or without oral antidiabetics, and HbA_{1c} >7.0 to <11.0%	N=166 12 months (all results reported at 6 months)	Primary: Change from baseline in HbA_{1c}, FPG, PPG, body weight, and insulin; safety Secondary: Not reported	Primary: Pramlintide resulted in significant HbA_{1c} reductions at months three and six (-0.66 and -0.56%; P<0.05). At some point during the initial six months after initiating therapy, 28.1% of the patients who had a baseline HbA_{1c} >7.0% achieved an HbA_{1c} <7.0%. Compared to baseline, both fasting and PPG concentrations were significantly reduced (P<0.05). Significant baseline reductions in weight were noted at months three and six (-2.3 and -2.8 kg; P<0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				At months three and six, mealtime and total insulin doses remained significantly lower compared to baseline (P<0.05). Nausea (29.5%), vomiting (7.2%), and diarrhea (5.4%) were the most commonly reported adverse events. There was an overall incidence of 12% for hypoglycemia, with two patients experiencing severe hypoglycemia during the six month treatment period. Secondary: Not reported
Riddle et al.[18] (2007) Pramlintide 60 µg SC BID or TID with meals, titrated to 120 µg SC vs placebo All patients also received existing insulin regimens.	DB, MC, PC, RCT Type 2 diabetics 25 to 75 years of age not achieving adequate glycemic control with insulin glargine (no mealtime insulin), with or without oral antidiabetic therapy, and an HbA_{1c} >7.0 to 10.5% and BMI 25 to 45 kg/m^2	N=212 16 weeks	Primary: Change from baseline HbA_{1c} at week 16, proportion of patients meeting all of the following prespecified criteria at week 16: HbA_{1c} ≤7.0% or an HbA_{1c} baseline reduction ≥0.5%, mean daily PPG increments ≤40 mg/dL, no weight gain, and no severe hypoglycemia Secondary: Individual components of the composite endpoint; proportion of	Primary: Pramlintide-treated patients experienced significantly greater baseline reductions in HbA_{1c} at week 16 compared to placebo –treated patients (-0.70 vs -0.36%; P<0.05). At week 16, significantly more pramlintide-treated patients achieved the composite endpoint compared to placebo-treated patients (25 vs 7%; P<0.001). Secondary: The proportion of patients who achieved an HbA_{1c} ≤7.0% or who had a reduction in HbA_{1c} ≥0.5% was not different between pramlintide and placebo (54 vs 45%; P value not reported). Significantly more pramlintide-treated patients achieved mean PPG increments ≤40 mg/dL (P<0.0001) and did not experience weight gain (P<0.0001) compared to placebo-treated patients. Compared to placebo-treated patients, more pramlintide-treated patients achieved both HbA_{1c} and PPG components (P<0.005), more patients reached the HbA_{1c} goal without weight gain (P<0.0001), and more patients had well controlled PPG without weight gain (P<0.0001). The proportion of patients achieving an HbA_{1c} ≤7.0 or ≤6.5% was 23 and 11% with pramlintide compared to 13 and 4% with placebo, respectively (P values not reported).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			patients achieving HbA_{1c} ≤7.0 or ≤6.5%; changes from baseline to each time point in HbA_{1c}, seven-point glucose profiles, PPG increments, FPG, weight, and insulin glargine dose	The insulin glargine dosage increased steadily throughout the trial. The mean increase in insulin glargine dosage at week 16 was 11.7±1.9 and 13.1±1.6 units with pramlintide and placebo, respectively (P value not reported). The average change from baseline in FPG was -28.3 and -12.0 mg/dL at week 16 with pramlintide and placebo, respectively (P value not reported). At week 16, PPG was significantly decreased from baseline with pramlintide compared to placebo (-24.4 vs -0.4 mg/dL; P<0.0001). By week 16, pramlintide was associated with weight loss compared to weight gain with placebo (-1.6 vs 0.7 kg; P<0.0001) By the end of treatment, 68% of pramlintide-treated patients had lost weight compared to approximately 35% of placebo-treated patients (P<0.0001).
Hollander et al.[19] (2003) Pramlintide 60, 90, or 120 µg SC BID and insulin (existing regimen) vs placebo and insulin (existing regimen) Data for patients randomized to pramlintide 60 µg SC BID are not reported.	DB, MC, PC, PG, RCT Type 2 diabetics >18 years of age requiring insulin therapy for ≥ 6 months prior to trial initiation with an HbA_{1c} ≥8.0%, and without hypoglycemia in the 2 weeks preceding the trial	N=656 12 months	Primary: Change from baseline in HbA_{1c} at week 26 Secondary: Absolute change in HbA_{1c} at other time points, proportion of patients who achieved an HbA_{1c} <7.0 or <8.0%	Primary: After 26 weeks, pramlintide 120 µg was associated with a significant reduction in HbA_{1c} compared to placebo (-0.68; P<0.05), but no difference in the baseline reduction of HbA_{1c} was reported between the pramlintide 90 µg and placebo (-0.54%; P value not reported). Secondary: After 52 weeks, pramlintide 120 µg was associated with a significant baseline reduction in HbA_{1c} compared to placebo (-0.62; P<0.05), but no difference in the baseline reduction of HbA_{1c} was reported between pramlintide 90 µg and placebo (-0.35%; P value not reported). More patients receiving pramlintide (either dose) achieved an HbA_{1c} <7.0% compared to patients receiving placebo (9.4 and 12.2 vs 4.1%, respectively; P value not reported). Similarly, 42.4, 45.7, and 27.6% of patients receiving pramlintide 90 µg, pramlintide 120 µg, and placebo, respectively, achieved an HbA_{1c} <8.0% (P value not reported).
Ratner et al.[20] (2002)	DB, PC, RCT Type 2 diabetic patients	N=538 52 weeks	Primary: Change in baseline HbA_{1c} and body	Primary: Significantly greater reductions in HbA_{1c} were achieved with pramlintide 75 µg compared to placebo (-0.9%; P=0.0004) after 13 weeks. In addition,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Pramlintide 30 to 150 µg TID and insulin (existing regimen) vs placebo and insulin (existing regimen)			weight at weeks 13, 26, and 52 Secondary: Proportion of patients achieving HbA_{1c} <7.0 or 8.0%, relative change of insulin use, safety	HbA_{1c} was significantly lower for the majority of the study periods with the exception of week 52 (P value not reported). Significantly greater reductions in HbA_{1c} were achieved with pramlintide 150 µg compared to placebo (-1.0%; P=0.0002). After 13 weeks, HbA_{1c} remained significantly lower for the rest of the trial (-0.6%; P=0.0068). Reductions in HbA_{1c} with pramlintide 30 µg were not different compared to placebo at any point during the trial. Significant baseline reductions (P<0.05) in body weight were achieved with all pramlintide doses throughout the trial when compared to placebo. Secondary: The proportions of patients achieving an HbA_{1c} <7.0% were 12.7, 13.4, and 19.2% in patients receiving pramlintide 30, 75, and 150 µg compared to 11.1% in patients receiving placebo (P values not reported). The proportions of patients achieving an HbA_{1c} <8.0% were 45.1, 46.4, and 54.0% in patients receiving pramlintide 30, 75, and 150 µg compared to 37.6% in patients receiving placebo (P values not reported). Insulin use increased with all treatments. With pramlintide, insulin use increased by 7.9 to 10.9%, while insulin use increased by 15.4% with placebo (P values not reported). The most commonly reported side effect with pramlintide was nausea.
Hollander et al.[21] (2003) Pramlintide 120 µg BID and insulin (existing regimen) vs	Post hoc analysis Type 2 diabetic patients who completed a 26 or 52 week, DB, PC, RCT	N=186 26 and 52 weeks	Primary: Change in baseline HbA_{1c}, body weight, insulin use, and the rate of severe hypoglycemia at week 26; safety Secondary:	Primary: At week 26, the difference in HbA_{1c} baseline reduction with pramlintide compared to placebo was- 0.43% (P<0.0009). The proportion of patients who achieved an HbA_{1c} <7.0% at week 26 was 14% in the pramlintide group compared to 2% in the placebo group (P value was not reported). At week 26, the difference in weight baseline reduction with pramlintide compared to placebo was 2 kg (P<0.0003).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo and insulin (existing regimen)			Not reported	No significant change in insulin dose or the number of insulin injections was noted between the treatments (P value not reported). At week 26, no significant difference was noted between the treatments in rates of severe hypoglycemia as reported in event rate per subject year (0.13 vs 0.19; P value not reported). No serious adverse events were reported with either treatment. Secondary: Not reported
Maggs et al.[22] (2003) Pramlintide 120 µg BID or pramlintide 150 µg TID and insulin (existing regimen) vs placebo and insulin (existing regimen)	Post hoc analysis Type 2 diabetic patients who completed a 52 week, DB, PC, RCT	N=410 52 weeks	Primary: Change in baseline in HbA_{1c} and weight at week 52, safety Secondary: Not reported	Primary: A significantly greater baseline reduction in HbA_{1c} was achieved with pramlintide compared to placebo at week 52 (P<0.0001). This result was seen across the following ethnic groups: African Americans (-0.7%), Caucasians (-0.5%), and Hispanics (-0.3%). A significant baseline reduction in body weight was achieved with pramlintide compared to placebo at week 52 (-2.6 kg; P<0.0001). Nausea was more common with pramlintide, and hypoglycemia was reported to a similar extent with both treatments. Secondary: Not reported
Hollander et al. [23] (2004) Pramlintide 120 µg BID and insulin (existing regimen) vs placebo and insulin (existing regimen)	Post hoc analysis Type 2 diabetic patients who completed a 26 or 52 week, DB, PC, RCT	N=498 26 and 52 weeks	Primary: Change in baseline HbA_{1c}, insulin dose, and body weight Secondary: Not reported	Primary: At week 26, mean baseline reductions in HbA_{1c} with pramlintide compared to placebo (-0.59 vs -0.18%; P<0.0001). There was no difference in the change in total daily insulin requirements between the two treatments. At week 26, pramlintide-treated patients achieved a significant baseline reduction in weight compared to placebo (-1.5 vs 0.3 kg; P<0.0001). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Riddle et al.[24] (2009) Pramlintide 120 µg prior to meals and basal insulin (QD to BID) vs rapid-acting insulin analogs 5 units before meals (titrated) and basal insulin (QD to BID)	MC, OL Type 2 diabetic patients who were inadequately controlled using basal insulin and prior oral antihyperglycemic agents	N=113 24 weeks	Primary: Proportion of patients achieving an HbA_{1c} ≤7.0% Secondary: Individual components of the composite end point, insulin dose, HbA_{1c}, change in HbA_{1c}, proportion of patients reaching HbA_{1c} ≤6.5%, FPG, PPG increments, changes in weight, changes in waist circumference, and adverse events including the incidence, severity, and time courses of hypoglycemia and nausea	Primary: Thirty percent of pramlintide-treated patients achieved an HbA_{1c} ≤7% compared to 11% of the patients receiving rapid-acting insulin analogs (P=0.018) with a similar dose of basal insulin. Secondary: Mean HbA_{1c} at 24 weeks was 7.2% with addition of pramlintide and 7.0% with addition of a rapid acting insulin analog. The least squares mean reduction of HbA_{1c} from baseline was -1.1% for pramlintide and -1.3% for rapid acting insulin analogs (P=0.46 between groups). HbA_{1c} ≤6.5% at 24 weeks was achieved by 29% of patients treated with pramlintide and by 34% of patients treated with a rapid-acting insulin analog (P=0.68 between groups). At week 24, mean weights were 106 kg (pramlintide) versus 109 kg (rapid-acting insulin analog). Least squares mean changes in weight from baseline were 0.0kg (pramlintide) versus 4.7 kg (rapid-acting insulin analog; P<0.0001). Differences in waist measurements were consistent with weight differences. Waist circumferences at week 24 were 115 cm and 120 cm for the pramlintide and rapid-acting insulin analog groups, respectively. Least squares mean changes in waist circumference from baseline were -0.6 cm and 2.2 cm, respectively (P=0.016) Similar basal insulin titration in both treatment arms resulted in similar mean FPG concentrations at week 24: 122 mg/dl (pramlintide) and 123 mg/dl (rapid-acting insulin analog) The least squares mean change of FPG from baseline was -31 mg/dl (pramlintide) and -34 mg/dl (rapid-acting insulin analog; P=0.65). An FPG concentration <100 mg/dl was achieved at week 24 by 30% of pramlintide-treated and 27% of rapid-acting insulin analog-treated patients (P=0.83).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				PPG increments were similar between study groups at week 24. No significant difference in the least squares mean change in postprandial increment from baseline to week 24 was found between treatment groups (-17 mg/dl [pramlintide] vs -27 mg/dl [rapid-acting insulin analog]; P=0.17). The most common adverse events were hypoglycemia and nausea. Mild or moderate hypoglycemia occurred more frequently than nausea in both study groups and was observed in more patients treated with rapid acting insulin analog (82%) than with pramlintide (55%). Hypoglycemic events occurred more frequently in the pramlintide treatment group in the first 4 weeks but were more common in the rapid acting insulin analog treatment group from 18 to 24 weeks. Nausea was reported only in the pramlintide group (21%), most often early in treatment and declined over time.

Drug regimen abbreviations: BID=twice daily, QD=once daily, QID=four times daily, SC=subcutaneous, TID=three times daily
Study abbreviations: DB=double-blind, MA=meta-analysis, MC=multicenter, OL=open label, PC=placebo-controlled, PG=parallel-group, RCT=randomized controlled trial
Miscellaneous abbreviation: BMI=body mass index, CI=confidence interval, FPG=fasting plasma glucose, HbA_{1c}=glycosylated hemoglobin, PPG=post-prandial glucose

Additional Evidence

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

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

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

IX. Cost

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

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

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

Rx=prescription

Table 9. Relative Cost of the Amylinomimetics

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Pramlintide	injection	SymlinPen®	$$$$$	N/A

N/A=Not available

X. Conclusions

Pramlintide is the only amylinomimetic agent that is currently available. It is approved for use as an adjunctive treatment in patients with type 1 and type 2 diabetes mellitus who use mealtime insulin therapy and who have failed to achieve desired glucose control despite optimal insulin therapy.[1-3] It is not available in a generic formulation.

The goal of treatment for type 2 diabetes is to control hyperglycemia and reduce the risk of long-term complications. A notable new theme in diabetes treatment guidelines is an emphasis on a complication-centric approach, beyond glucose levels, to frame decisions regarding first-line pharmacologic choices for the treatment of persons with diabetes. Pharmacologic therapy should be guided by person-centered treatment factors, including comorbidities and treatment goals. In adults with type 2 diabetes and established/high risk of atherosclerotic cardiovascular disease, heart failure, and/or chronic kidney disease, the treatment regimen should include agents that reduce cardiorenal risk. Pharmacologic approaches that provide adequate efficacy to achieve and maintain treatment goals should be considered, such as metformin or other agents, including combination therapy.[4-7] In

general, current clinical guidelines do not support the use of amylin analogs in the management of type 2 diabetes.[4-9]

For the treatment of type 1 diabetes, the American Diabetes Association recommends the use of multiple dose insulin injections or continuous subcutaneous insulin infusion therapy. The addition of pramlintide to intensive insulin therapy may be considered to enhance glycemic control and to assist with weight management.[4]

Several clinical trials have been conducted with pramlintide in patients with type 1 and type 2 diabetes mellitus.[10-12,15,18-20] Data from clinical trials demonstrate that treatment with pramlintide is associated with significant baseline reductions in HbA_{1c} compared to treatment with placebo in type 1 and 2 diabetics already receiving insulin.[10-24] Furthermore, treatment with pramlintide is associated with significant baseline reductions in fasting plasma glucose levels, post-prandial glucose levels, insulin use, and body weight.[10-24] However, compared to other available antidiabetic agents, pramlintide is associated with modest HbA_{1c} lowering ability, and its use is often limited by adverse events.[5-7]

Pramlintide does not cause hypoglycemia when used alone; however, it is intended to be coadministered with insulin therapy. In this setting, pramlintide increases the risk of insulin-induced severe hypoglycemia, especially in patients with type 1 diabetes mellitus.[1] To minimize this risk, patients must be carefully selected, proper education must be provided, and glucose levels must be carefully monitored.[1] Therapy should only be considered in patients with insulin-using type 1or type 2 diabetes who fulfill the following criteria: 1) have failed to achieve adequate glycemic control despite individualized insulin management; and 2) are receiving ongoing care under the guidance of a healthcare professional skilled in the use of insulin and supported by the services of diabetes educator(s).[1]

There is insufficient evidence to support that one brand amylinomimetic is safer or more efficacious than another within its given indication. Since pramlintide is only approved for use as an adjunctive treatment in patients with type 1 and type 2 diabetes mellitus, it should be managed through the existing medical justification portion of the prior authorization process.

Therefore, all brand products 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 amylinomimetic 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 Biguanides
AHFS Class 682004
November 8, 2023

I. Overview

Diabetes mellitus is a chronic condition which results in hyperglycemia. It is differentiated into four main classes: 1) type 1 diabetes; 2) type 2 diabetes; 3) gestational diabetes; and 4) other types (drug- or chemical-induced, genetic defects in β-cell function or insulin action, and diseases of the exocrine pancreas). Type 2 diabetes is the most prevalent form of the disease in the United States. Inadequate glycemic control may lead to both acute and long-term complications, including microvascular and macrovascular events. There are a variety of oral and injectable antidiabetic agents currently available to treat diabetes. The antidiabetic agents are categorized into 12 different American Hospital Formulary Service (AHFS) classes, which differ with regards to their mechanism of action, efficacy, safety profiles, tolerability, and ease of use.

Metformin is the only biguanide currently available and it is approved for use as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Insulin secretion remains unchanged; however, fasting insulin levels and day-long plasma insulin response may decrease.[1-5]

The biguanides that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Both the immediate-release and sustained-release tablets are available in a generic formulation. This class was last reviewed in November 2021.

Table 1. Biguanides Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Metformin	extended-release suspension, extended-release tablet, solution, tablet	Glumetza ER®*, Riomet®*, Riomet ER®	metformin, metformin extended-release

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

II. Evidence-Based Medicine and Current Treatment Guidelines

Current clinical guidelines are summarized in Table 2. Please note that guidelines addressing the treatment of type 2 diabetes are presented globally, addressing the role of various medication classes.

Table 2. Treatment Guidelines Using the Biguanides

Clinical Guideline	Recommendation(s)
American Diabetes Association: **Standards of Care in Diabetes (2023)**[6]	Current criteria for the diagnosis of diabetes • The following are the criteria for a diagnosis of diabetes: glycosylated hemoglobin (HbA_{1c}) ≥6.5%, or a fasting plasma glucose (FPG) ≥126 mg/dL, or a two-hour plasma glucose ≥200 mg/dL during an oral glucose tolerance test or patients with classic symptoms of hyperglycemia, or classic symptoms of hyperglycemia or hyperglycemic crisis (random plasma glucose ≥200 mg/dL). Prevention or delay of type 2 diabetes • Refer adults with overweight/obesity at high risk of type 2 diabetes, as typified by the Diabetes Prevention Program (DPP), to an intensive lifestyle behavior change program to achieve and maintain a weight reduction of at least 7% of initial body

Clinical Guideline	Recommendation(s)
	weight through healthy reduced-calorie diet and ≥150 minutes/week of moderate-intensity physical activity. • A variety of eating patterns can be considered to prevent diabetes in individuals with prediabetes. • Metformin therapy for prevention of type 2 diabetes should be considered in adults at high risk of type 2 diabetes, as typified by the DPP, especially those aged 25 to 59 years with BMI ≥35 kg/m^2, higher FPG) (e.g., ≥110 mg/dL), and higher A1C (e.g., ≥6.0%), and in individuals with prior gestational diabetes mellitus (GDM). • Long-term use of metformin may be associated with biochemical vitamin B12 deficiency; consider periodic measurement of vitamin B12 levels in metformin-treated individuals, especially in those with anemia or peripheral neuropathy. Glycemic goals in adults • An A1C goal for many nonpregnant adults of <7% (53 mmol/mol) without significant hypoglycemia is appropriate. • If using ambulatory glucose profile (AGP)/glucose management indicator (GMI) to assess glycemia, a parallel goal for many nonpregnant adults is time in range (TIR) of >70% with time below range (TBR) <4% and time <54 mg/dL <1%. For those with frailty or at high risk of hypoglycemia, a target of >50% TIR with <1% TBR is recommended. • On the basis of health care provider judgment and patient preference, achievement of lower A1C levels than the goal of 7% may be acceptable and even beneficial if it can be achieved safely without significant hypoglycemia or other adverse effects of treatment. • Less stringent A1C goals (such as <8% [64 mmol/mol]) may be appropriate for patients with limited life expectancy or where the harms of treatment are greater than the benefits. HCPs should consider deintensification of therapy if appropriate to reduce the risk of hypoglycemia in patients with inappropriate stringent A1C targets. Pharmacologic therapy for type 1 diabetes • Most individuals with type 1 diabetes should be treated with multiple dose insulin injections (three to four injections per day of basal and pre-prandial insulin) or continuous subcutaneous (SC) insulin infusion therapy. • Most patients should use rapid-acting insulin analogs to reduce hypoglycemia risk. • Patients with type 1 diabetes should receive education on how to match prandial insulin doses to carbohydrate intake, premeal blood glucose, and anticipated physical activity. Pharmacologic therapy for type 2 diabetes • Healthy lifestyle behaviors, diabetes self-management education and support, avoidance of clinical inertia, and social determinants of health should be considered in the glucose-lowering management of type 2 diabetes. Pharmacologic therapy should be guided by person-centered treatment factors, including comorbidities and treatment goals. • In adults with type 2 diabetes and established/high risk of atherosclerotic cardiovascular disease, heart failure, and/or chronic kidney disease, the treatment regimen should include agents that reduce cardiorenal risk. • Pharmacologic approaches that provide adequate efficacy to achieve and maintain treatment goals should be considered, such as metformin or other agents, including combination therapy. • Weight management is an impactful component of glucose-lowering management in type 2 diabetes. The glucose-lowering treatment regimen should consider approaches that support weight management goals.

Clinical Guideline	Recommendation(s)
	• Metformin should be continued upon initiation of insulin therapy (unless contraindicated or not tolerated) for ongoing glycemic and metabolic benefits. • Early combination therapy can be considered in some individuals at treatment initiation to extend the time to treatment failure. • The early introduction of insulin should be considered if there is evidence of ongoing catabolism (weight loss), if symptoms of hyperglycemia are present, or when A1C levels (>10% [86 mmol/mol]) or blood glucose levels (≥300 mg/dL [16.7 mmol/L]) are very high. • A person-centered approach should guide the choice of pharmacologic agents. Consider the effects on cardiovascular and renal comorbidities, efficacy, hypoglycemia risk, impact on weight, cost and access, risk for side effects, and individual preferences. • Among individuals with type 2 diabetes who have established atherosclerotic cardiovascular disease or indicators of high cardiovascular risk, established kidney disease, or heart failure, a sodium–glucose cotransporter 2 inhibitor and/or glucagon-like peptide 1 receptor agonist with demonstrated cardiovascular disease benefit is recommended as part of the glucose-lowering regimen and comprehensive cardiovascular risk reduction, independent of A1C and in consideration of person-specific factors. • In adults with type 2 diabetes, a glucagon-like peptide 1 receptor agonist is preferred to insulin when possible. • If insulin is used, combination therapy with a glucagon-like peptide 1 receptor agonist is recommended for greater efficacy, durability of treatment effect, and weight and hypoglycemia benefit. • Recommendation for treatment intensification for individuals not meeting treatment goals should not be delayed. • Medication regimen and medication-taking behavior should be reevaluated at regular intervals (every three to six months) and adjusted as needed to incorporate specific factors that impact choice of treatment. • Clinicians should be aware of the potential for over-basalization with insulin therapy. Clinical signals that may prompt evaluation of over-basalization include basal dose more than ~0.5 units/kg/day, high bedtime–morning or post-preprandial glucose differential, hypoglycemia (aware or unaware), and high glycemic variability. Indication of over-basalization should prompt reevaluation to further individualize therapy.
American Diabetes Association/ European Association for the Study of Diabetes: **Management of Hyperglycemia in Type 2 Diabetes. A consensus report by the American Diabetes Association and the European Association for the Study of Diabetes (2022)**[7]	Consensus recommendations • All people with type 2 diabetes should be offered access to ongoing diabetes self-management education and support programs. • Providers and health care systems should prioritize the delivery of person-centered care. • Optimizing medication adherence should be specifically considered when selecting glucose-lowering medications. • Medical nutrition therapy focused on identifying healthy dietary habits that are feasible and sustainable is recommended in support of reaching metabolic and weight goals. • Physical activity improves glycemic control and should be an essential component of type 2 diabetes management. • Adults with type 2 diabetes should engage in physical activity regularly (>150 min/week of moderate- to vigorous-intensity aerobic activity) and be encouraged to reduce sedentary time and break up sitting time with frequent activity breaks. • Aerobic activity should be supplemented with two to three resistance, flexibility, and/or balance training sessions/week. Balance training sessions are particularly encouraged for older individuals or those with limited mobility/poor physical function.

Clinical Guideline	Recommendation(s)
	• Metabolic surgery should be considered as a treatment option in adults with type 2 diabetes who are appropriate surgical candidates with a BMI ≥40.0 kg/m^2 (BMI ≥37.5 kg/m^2 in people of Asian ancestry) or a BMI of 35.0 to 39.9 kg/m^2 (32.5 to 37.4 kg/m^2 in people of Asian ancestry) who do not achieve durable weight loss and improvement in comorbidities (including hyperglycemia) with nonsurgical methods. • In people with established CVD, a GLP-1 RA with proven benefit should be used to reduce MACE, or an SGLT2i with proven benefit should be used to reduce MACE and HF and improve kidney outcomes. • In people with CKD and an eGFR ≥20 ml/min per 1.73 m^2 and a urinary albumin/creatinine ratio >3.0 mg/mmol (>30 mg/g), an SGLT2i with proven benefit should be initiated to reduce MACE and HF and improve kidney outcomes. Indications and eGFR thresholds may vary by region. If such treatment is not tolerated or is contraindicated, a GLP-1 RA with proven cardiovascular outcome benefit could be considered to reduce MACE and should be continued until kidney replacement therapy is indicated. • In people with HF, SGLT2i should be used because they improve HF and kidney outcomes. • In individuals without established CVD but with multiple cardiovascular risk factors (such as age ≥55 years, obesity, hypertension, smoking, dyslipidemia, or albuminuria), a GLP-1 RA with proven benefit could be used to reduce MACE, or an SGLT2i with proven benefit could be used to reduce MACE and HF and improve kidney outcomes. • In people with HF, CKD, established CVD, or multiple risk factors for CVD, the decision to use a GLP-1 RA or SGLT2i with proven benefit should be independent of background use of metformin. • SGLT2i and GLP-1 RA reduce MACE, which is likely to be independent of baseline HbA1c. In people with HF, CKD, established CVD, or multiple risk factors for CVD, the decision to use a GLP-1 RA or an SGLT2i with proven benefit should be independent of baseline HbA1c. • In general, selection of medications to improve cardiovascular and kidney outcomes should not differ for older people. • In younger people with diabetes (<40 years), consider early combination therapy. • In women with reproductive potential, counseling regarding contraception and taking care to avoid exposure to medications that may adversely affect a fetus are important.
American Association of Clinical Endocrinologists/ American College of Endocrinology: **Clinical Practice Guidelines for Developing a Diabetes Mellitus Comprehensive Care Plan (2022)**[8]	<u>Antihyperglycemic Pharmacotherapy for Persons with Type 2 Diabetes</u> • Individualized pharmacotherapy for persons with T2D should be prescribed based on evidence for benefit that includes glucose lowering, avoidance of hypoglycemia and weight gain, and reduction of cardio-renal risk. • Persons with T2D and their health care professionals should use patient-centered shared decision-making to agree on therapy targets and treatments as well as a regimen for glucose monitoring (i.e., BGM, structured BGM, or CGM). • Glycemic targets include A1C, BGM, and, for those using CGM, achievement of CGM targets such as time in range (TIR), percentage in low and very low range, time above range, and glycemic variability. Nonglycemic targets include avoidance of hypoglycemia, control of BP, lipids, other CVD risk factors, and achieving and maintaining a healthy body weight. • Independent of glycemic control, targets, or treatment, if there is established or high risk for ASCVD, HF, and/or CKD, clinicians should prescribe a GLP-1 RA or an SGLT2i with proven efficacy for the specific condition(s) of the person with T2D being treated. • DM therapy should be individualized based on level of glycemia and the presence of comorbidities, complications, and access. Metformin is often the preferred

Clinical Guideline	Recommendation(s)
	initial therapy. Other agents may be appropriate as first line or in addition to metformin to reduce BG and/or to address specific comorbidities (such as ASCVD, HF, CKD, obesity, NAFLD), independent of glucose-lowering effects. • For some recently diagnosed individuals with T2D and more severe hyperglycemia (A1C ≥7.5%), unlikely to attain the A1C target with a single agent, early combination pharmacotherapy should be considered, usually to include metformin plus another agent that does not cause hypoglycemia, especially a GLP-1 RA, SGLT2i, or dipeptidyl peptidase 4 (DPP-4) inhibitor. • For newly diagnosed persons with T2D and an entry A1C >9.0% and/or ≥1.5% above target, one should initiate, along with lifestyle modifications, dual- or possibly triple-combination pharmacotherapy usually including metformin. Basal insulin along with noninsulin therapy is recommended if there are significant signs or symptoms of hyperglycemia, especially including catabolism (e.g., weight loss) or a very high A1C >10% (86 mmol/mol) or BG levels (≥300 mg/dL [16.7 mmol/L]). • Clinicians should discuss with persons with T2D the likelihood that most persons with T2D ultimately require a combination of multiple complementary antihyperglycemic agents, in addition to lifestyle interventions, to attain and maintain optimal glycemic control. • The DM care team should assess medication adherence and safety and glycemic control in persons with T2D quarterly or more frequently as needed. Subsequent visits will depend upon the metabolic targets achieved and the stability of metabolic control. • Persons with T2D who start on metformin should continue it unless intolerance or contraindications occur. When intensification of antihyperglycemic treatment is needed, other agents should be added to metformin. • Most persons with T2D who require intensification of antihyperglycemic therapy with a GLP-1 RA or insulin should initially be prescribed a GLP-1 RA. If further intensification is required, one should prescribe a basal insulin or a switch to a fixed-ratio combination of a basal insulin and a GLP-1 RA (insulin glargine U100 + lixisenatide [GlarLixi] or insulin degludec + liraglutide [IdegLira]). • Insulin should be prescribed for persons with T2D when noninsulin antihyperglycemic therapy fails to achieve target glycemic control or when a person has symptomatic hyperglycemia. • Long-acting basal insulin analogs are the recommended initial choice of insulin therapy for persons with T2D. The insulin analogs glargine (U100 or U300), degludec (U100 or U200), or detemir are preferred over intermediate-acting Neutral Protamine Hagedorn (NPH) insulin because analog insulins have demonstrated less hypoglycemia in some studies. Glargine U300 and degludec can be associated with less hypoglycemia than glargine U100 or detemir. • Many persons with T2D receiving basal insulin and not at goal A1C can have significantly improved glycemia by the addition of a GLP-1 RA or being switched to a fixed-ratio combination basal insulin–GLP-1 RA (GlarLixi or IdegLira). One of these changes should be considered before adding a meal-time insulin for postprandial glycemic control. • When control of postprandial hyperglycemia is needed and a basal insulin and a GLP-1 RA are already being used, preference should be given to rapid-acting insulins (the analogs lispro, aspart, and glulisine or the rapid-acting inhaled human insulin powder) over regular human insulin. The former have a more consistent and a more rapid onset and offset of action with less risk of hypoglycemia. • Ultra-rapid-acting insulins (faster-acting insulin aspart, lispro aabc, and [human insulin] inhalation powder) may allow a decrease in the time between insulin administration and food intake and reduce the postprandial peak of PG as compared with rapid-acting insulins. The significance of this on long-term complications is unknown.

Clinical Guideline	Recommendation(s)
	• Basal-bolus insulin regimens or continuous subcutaneous insulin infusion (CSII) (i.e., insulin pump) allow for adjustment of insulin doses according to carbohydrate intake and activity levels and are recommended for intensive insulin therapy in persons with T2D. • Premixed insulin formulations (fixed combinations of shorter- and longer-acting components) of human or analog insulin may be considered for persons with T2D who have consistent dietary and exercise patterns and in whom adherence to more intensive insulin regimens is problematic. However, these preparations have reduced dosage flexibility and may increase the risk of hypoglycemia compared with basal insulin or basal-bolus regimens. • In persons with T2D who are treated with basal-bolus insulin therapy, adding a GLP-1 RA, or switching to a fixed-ratio combination of a GLP-1 RA and a basal insulin, or adding an SGLT2i or pramlintide (less commonly used) may be able to reduce postprandial hyperglycemia, A1C, and weight. GLP-1 RAs may also allow reduction or discontinuation of bolus insulin in some individuals. <u>How should insulin therapy be used for management of persons with type 1 diabetes?</u> • Insulin must be used to treat all persons with T1D. • Physiologic insulin replacement regimens, which provide both basal and prandial (meal-related or bolus) insulin, are recommended for most persons with T1D. • Achievement of glucose targets using either MDI of insulin or CSII, is needed to prevent development of life-threatening crises, such as acute hyperglycemic crises (DKA and hyperglycemic hyperosmolar state) and catabolic state. • A multi-component self-management DM education program is recommended for persons with T1D. Ideally, this is provided by a professional with expertise (i.e., certified diabetes care and education specialist) in the topics of healthy lifestyle, insulin technique including prandial insulin dosing guided by carbohydrate counting and diet adjustments for special situations, such as physical activity and prolonged fasting. Instruction is also needed in how to deal with sick days and prevention of DKA and hypoglycemia, and other relevant issues. Due to changes in DM self-management practices and each individual's medical history, personal and cultural background, and educational needs, specific education topics may need to be repeated at regular intervals. • The ideal insulin regimen should be personalized to an individual's needs and glycemic targets, attempting to better emulate physiological insulin replacement to maintain near normoglycemia, to prevent the development and progression of DM complications, while minimizing hypoglycemia and providing flexibility for specific daily life situations/scenarios such as: exercise, sleep, acute illness, psychological stress, etc. • Insulin regimens usually should involve the use of insulin analogs for most persons with T1D and include the following approaches: o MDI, which usually involve 1 to 2 subcutaneous injections daily of basal insulin to suppress ketogenesis and gluconeogenesis and to control glycemia between meals and overnight, and subcutaneous injections of prandial insulin or use of inhaled insulin before each meal to control meal-related glycemic excursions. CGM is the preferred method of glucose monitoring for all individuals with T1D. o Insulin pump therapy (CSII) provides constant/continuous infusion of fast-acting insulin driven by mechanical force and delivered via a cannula inserted under the skin. CSII can improve (or enhance) glycemic control and should be an option for insulin delivery for appropriate persons with DM. Ideally, these individuals should also use CGM as stated in R13.6.a. o Automated insulin delivery systems (AIDs), which include an insulin pump, an integrated CGM, and computer software algorithm, aim to better emulate physiological insulin replacement and achieve glycemic targets. This technology is recommended for many persons with T1D since its use

Clinical Guideline	Recommendation(s)
	has been shown to increase TIR while often reducing hypoglycemia or at least without causing increased hypoglycemia. ○ Open-loop (use of a pump and sensor which do not communicate) and sensor-augmented pump (SAP) systems: (CGM communicates with pump facilitating needed adjustments to basal rate; temporary interruption of insulin delivery when glucose levels are low or forecast to be low within 30 min). Insulin pump with a CGM or an SAP is recommended to manage persons with DM treated with intensive insulin management who prefer not to use AIDs or have no access to them. How should diabetes mellitus in pregnancy be managed? • For women with GDM, the following treatment goals are recommended: preprandial glucose concentration ≤95 mg/dL and either a 1-h post-meal glucose ≤140 mg/dL or a 2-h post-meal glucose ≤120 mg/dL to decrease adverse fetal outcomes. • All women with preexisting DM (T1D, T2D, or previous GDM) need access to preconception care and counseling to ensure adequate nutrition, healthy weight, and glucose control before conception, during pregnancy, and in the postpartum period. • Rapid-acting insulin analogs (insulin-lispro, insulin-aspart) should be used to treat postprandial hyperglycemia in pregnant women. • Options for basal insulin include long-acting insulin (e.g., NPH, detemir, or glargine) or rapid-acting insulin via a CSII. Regular insulin, although not recommended as first-line therapy, is acceptable to use in managing pregnant women with DM when rapid-acting insulin analogs are not available. • Insulin is the preferred therapeutic choice for pregnant women with GDM or T2D, but metformin has been given a category B for pregnancy with accumulating clinical evidence of metformin's safety during the first trimester and beyond. Metformin has been shown to improve pregnancy and fetal outcomes except for increased rates of infants with SGA and later onset of obesity. The prescriber should discuss the potential risks and benefits of oral agent therapy during pregnancy as well as the need for longer-term outcome studies.
American Association of Clinical Endocrinologists/ American College of Endocrinology: **Consensus Statement on the Comprehensive Type 2 Diabetes Management Algorithm (2023)**[9]	Principles underlying the algorithm • Lifestyle modification underlies all therapy. • Maintain or achieve optimal weight. • Choice of antihyperglycemic therapy reflects glycemic targets, atherosclerotic cardiovascular disease (ASCVD), congestive heart failure (CHF), chronic kidney disease (CKD), overweight/obesity, and nonalcoholic fatty liver disease (NAFLD). • Choice of therapy includes ease of use and access. • Optimal hemoglobin A1c (A1C) is ≤6.5% or as close to normal as is safe and achievable for most patients. • Individualize all glycemic targets (A1C, glucose management indicator [GMI], time in range [TIR], fasting blood glucose [FBG], and PPG). • Get to goal as soon as possible (adjust ≤3 months). • Avoid hypoglycemia. Hypoglycemia, defined as blood glucose (BG) <70 mg/dL, is associated with an increased risk for adverse outcomes including mortality. • CGM is highly recommended to assist persons with diabetes in reaching goals safely. • Comorbidities must be managed for comprehensive care. Algorithm summative information • The algorithm is intended as a more concise document than the guideline, providing easily accessible, visual guidance for decision-making in the clinic setting.

Clinical Guideline	Recommendation(s)
	• In this 2023 algorithm, there continues to be an emphasis on lifestyle modification and treatment of overweight/obesity as key pillars of the management of prediabetes and DM. • The importance of appropriate management of the atherosclerotic risk factors of dyslipidemia and hypertension is highlighted. • One notable new theme is an obvious emphasis on a complication-centric approach, beyond glucose levels, to frame decisions regarding first-line pharmacologic choices for the treatment of persons with diabetes. • The algorithm is divided into discrete graphic sections that outline the principles for management of T2D and guide management of adiposity-based chronic disease (ABCD), prediabetes, and atherosclerotic risk factors of dyslipidemia and hypertension. In addition, the algorithms for antihyperglycemic agents include both complication-centric and glucose-centric approaches, and there is direction for insulin initiation and titration. Tables summarizing the benefits and risks of antihyperglycemic medications (updated) and weight-loss pharmacotherapy (new) are provided.

American Academy of Pediatrics: **Management of Newly Diagnosed Type 2 Diabetes Mellitus (T2DM) in Children and Adolescents (2013)[10]**	• Clinicians must ensure that insulin therapy is initiated for children and adolescents with T2DM who are ketotic or in diabetic ketoacidosis and in whom the distinction between types 1 and 2 diabetes mellitus is unclear and, in usual cases, should initiate insulin therapy for patients.
	  ○ Who have random venous or plasma blood glucose (BG) concentrations ≥250 mg/dL.
	  ○ Whose HbA_{1c} is >9%.
	• In all other instances, clinicians should initiate a lifestyle modification program, including nutrition and physical activity, and start metformin as first-line therapy for children and adolescents at the time of diagnosis of T2DM.
	• Monitoring of HbA_{1c} concentrations is recommended every three months and intensifying treatment is recommended if treatment goals for finger-stick BG and HbA_{1c} concentrations are not being met.
	• Advise patients to monitor finger-stick BG concentrations in patients who:
	  ○ Are taking insulin or other medications with a risk of hypoglycemia; or
	  ○ Are initiating or changing their diabetes treatment regimen; or
	  ○ Have not met treatment goals; or
	  ○ Have intercurrent illnesses.
	• Incorporate the Academy of Nutrition and Dietetics' *Pediatric Weight Management Evidence-Based Nutrition Practice Guidelines* in dietary or nutrition counseling of patients with T2DM at the time of diagnosis and as part of ongoing management.
	• Encourage children and adolescents with T2DM to engage in moderate-to-vigorous exercise for at least 60 minutes daily and to limit nonacademic "screen time" to less than two hours a day.

American Diabetes Association: **Type 1 Diabetes in Children and Adolescents: A Position Statement by the American Diabetes Association (2018)[11]**	<u>Blood Glucose Management: Monitoring and Treatment</u> • Most children with type 1 diabetes should be treated with intensive insulin regimens via either multiple daily injections of prandial insulin and basal insulin or continuous subcutaneous insulin infusion. • An HbA_{1c} target of <7.5% should be considered in most children and adolescents but should be individualized based on the needs and situation of the patient and family. • Children and adolescents with type 1 diabetes should have blood glucose levels monitored up to six to ten times/day including premeal, pre-bedtime, and as needed for safety (e.g., exercise, driving, illness, or the presence of symptoms of hypoglycemia). • Continuous blood glucose monitoring should be considered in all children and adolescents whether using insulin injections or an insulin pump.

Clinical Guideline	Recommendation(s)
	• In pediatric patients with type 1 diabetes automated insulin delivery systems can improve glycemic control and reduce hypoglycemia. <u>Lifestyle Management</u> • Individualized medical nutrition therapy is recommended for children and adolescents with type 1 diabetes. • Monitoring carbohydrate intake, whether by carbohydrate counting or experience-based estimation, is key to achieving optimal glycemic control. • Exercise if recommended for all children and adolescents with type 1 diabetes. The suggested goal is 60 minutes of moderate to vigorous aerobic activity daily with muscle-strengthening and bone-strengthening activities three times a week. • Children and adolescents with type 1 diabetes should be educated about prevention and management of potential hypoglycemia during and after exercise. • Strategies to prevent hypoglycemia during exercise, after exercise, and overnight following exercise include reducing prandial insulin dosing for the meal/snack preceding exercise, increasing carbohydrate intake, eating bedtime snacks, using continuous blood glucose monitoring, and/or reducing basal insulin doses. <u>Behavioral Aspects of Self-Management</u> • Children and adolescents with diabetes should be assessed for psychosocial issues and family stresses that could impact diabetes management at diagnosis and routine follow-up. • Consider including children in consent processes as early as cognitive development indicates understanding of health consequences of behavior. • Offer adolescents time by themselves with their care provider(s) starting at age 12 years, or when developmentally appropriate. <u>Complications and Comorbidities</u> • Diabetic Ketoacidosis o All individuals with type 1 diabetes should have access to an uninterrupted supply of insulin. Lack of access and insulin omissions are major causes of diabetic ketoacidosis. o Patients with type 1 diabetes should have continuous access to medical support for sick-day management. • Hypoglycemia o The recommended treatment of hypoglycemia (blood glucose <70 mg/dL) in conscious patients is 15 g of glucose, although any form of carbohydrate can be used. If hypoglycemia continues after 15 minutes, treatment should be repeated. Once blood glucose has returned to normal patients should consider consuming a meal/snack and/or reduce insulin. o All individuals with type 1 diabetes should be prescribed glucagon and families/caregivers should be educated on administration. o Treatment regimens should be reevaluated in those with hypoglycemia unawareness or one or more episodes of severe hypoglycemia. • Diabetic Kidney Disease o Annual screening for albuminuria with a random spot urine sample for albumin-to-creatinine ratio should be considered at puberty or at age >10 years, whichever is earlier, once the child has had diabetes for 5 years. o An angiotensin-converting-enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB), titrated to normalization of albumin excretion, may be considered when elevated urinary albumin-to-creatinine ratio is documented. • Retinopathy o An initial dilated and comprehensive eye examination is recommended at age 10 years or after puberty has started, whichever is earlier, once the patient has had diabetes for three to five years.

Clinical Guideline	Recommendation(s)
	○ Annual routine follow-up is recommended but may be given every two years based on the advice of an eye care professional. • Neuropathy ○ Consider an annual comprehensive foot exam for adolescents at the start of puberty or at age 10 years, whichever is earlier, once the patient has had type 1 diabetes for 5 years. • Hypertension ○ Children and adolescents with type 1 diabetes should have blood pressure monitored at each visit. Elevated blood pressure should be confirmed on three separate days. ○ Initial treatment of high-normal blood pressure should include dietary modification and increased exercise. Pharmacologic treatment should be considered if blood pressure is not controlled after three to six months. ○ In patients with conformed hypertension pharmacologic treatment should be added to lifestyle modification at diagnosis. ○ ACE inhibitors and ARBs should be considered for initial treatment. • Dyslipidemia ○ A fasting lipid profile should be taken in children ≥10 years of age or older after the diagnosis of diabetes. Obtain a fasting lipid profile in children 10 years of age or older as soon as convenient after the diagnosis of diabetes ○ If lipids are abnormal, initial therapy should consist of optimizing glucose control and medical nutrition therapy using a Step 2 American Heart Association diet that restricts saturated fat to 7% of total calories and dietary cholesterol to 200 mg/day. ○ If lipids remain abnormal after six months of lifestyle intervention, consider adding a statin in children at least 10 years of age.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the biguanides 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 Biguanides[1-3]

Indication	Metformin
Adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus	✔

IV. Pharmacokinetics

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

Table 4. Pharmacokinetic Parameters of the Biguanides[4]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Excretion (%)	Half-Life (hours)
Metformin	50 to 60†	Negligible (% not reported)	Renal (90)	1.5 to 6.2 (plasma) 17.6 (blood)

†Immediate-release formulations

V. Drug Interactions

Significant drug interactions with the biguanides are listed in Table 5.

Table 5. Significant Drug Interactions with the Biguanides[4]

Generic Name(s)	Interaction	Mechanism
Metformin	Iodinated contrast materials	Iodinated contrast materials-induced renal failure can interfere with the renal elimination of metformin; therefore, there is an increased risk of metformin-induced lactic acidosis.

VI. Adverse Drug Events

The most common adverse drug events reported with the biguanides are listed in Table 6. The boxed warning for metformin-containing products are listed in Table 7.

Table 6. Adverse Drug Events (%) Reported with the Biguanides[1-5]

Adverse Events	Metformin Immediate-Release Formulations	Metformin Sustained-Release Formulations
Cardiovascular		
Chest discomfort	-	1 to 5*
Hypertension	-	1 to 5*
Palpitations	1 to 5	-
Central Nervous System		
Asthenia	9.2	1 to 5*
Dizziness	-	1 to 5
Headache	5 to 6	4.7 to 5.0
Lightheadedness	1 to 5	-
Gastrointestinal		
Abdominal discomfort	6.4	-
Abdominal pain	-	1 to 5
Abnormal stools	1 to 5	1 to 5*
Constipation	-	1 to 5
Diarrhea	12 to 53	9.6 to 16.7
Distention abdomen	-	1 to 5
Dyspepsia/heartburn	-	1 to 5
Flatulence	12.1	1 to 5
Indigestion	7.1	-
Loose stools	-	1 to 5*
Nausea/vomiting	25.5	6.5 to 8.5
Respiratory		
Dyspnea	1 to 5	-
Rhinitis	-	4.2
Upper respiratory infection	-	1 to 5
Miscellaneous		
Accidental injury	-	5.6 to 7.3
Contusion	-	1 to 5*
Ear pain	-	1 to 5*
Flu syndrome	1 to 5	1 to 5*
Hypoglycemia	1 to 5	13.7*
Increased sweating	1 to 5	-
Infection	20.9	20.5, 1 to 5*
Myalgia	1 to 5	1 to 5*
Nail disorder	1 to 5	-
Rash	1 to 5	-

Adverse Events	Metformin Immediate-Release Formulations	Metformin Sustained-Release Formulations
Seasonal allergy	-	1 to 5*
Taste disorder	1 to 5	1 to 5
Toothache	-	1 to 5*
Tonsillitis	-	1 to 5*
Tremor	-	1 to 5*

- Event not reported
*Reported with Glumetza®

Table 7. Boxed Warning for metformin products[1-5]

WARNING
Postmarketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias. The onset of metformin-associated lactic acidosis is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, somnolence, and abdominal pain. Metformin-associated lactic acidosis was characterized by elevated blood lactate levels (>5 mmol/Liter), anion gap acidosis (without evidence of ketonuria or ketonemia), an increased lactate/pyruvate ratio; and metformin plasma levels generally >5 mcg/mL. Risk factors for metformin-associated lactic acidosis include renal impairment, concomitant use of certain drugs (e.g., carbonic anhydrase inhibitors such as topiramate), age 65 years old or greater, having a radiological study with contrast, surgery and other procedures, hypoxic states (e.g., acute congestive heart failure), excessive alcohol intake, and hepatic impairment. Steps to reduce the risk of and manage metformin-associated lactic acidosis in these high risk groups are provided. If metformin-associated lactic acidosis is suspected, immediately discontinue metformin and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended.

VII. Dosing and Administration

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

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

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Metformin	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus: Oral solution, tablet: initial, 500 mg BID or 850 mg QD; maintenance, 2,000 mg/day administered in divided doses; maximum, 2,550 mg/day Extended-release suspension, sustained-release tablet: initial, 500 mg QD; maximum, 2,000 mg QD	Adjunct to diet and exercise to improve glycemic control in children 10 to 16 years of age with type 2 diabetes mellitus: Oral solution, tablet: initial, 500 mg BID; maximum, 2,000 mg/day Extended-release suspension: initial, 500 mg QD; maximum, 2,000 mg QD	Extended-release suspension (Riomet ER®): 500 mg/5 mL Oral solution (Riomet®): 500 mg/5 mL Sustained-release tablet: 500 mg (Glumetza®) 750 mg 1,000 mg (Glumetza®) Tablet: 500 mg 850 mg 1,000 mg

BID=twice daily, QD=once daily

VIII. Effectiveness

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

Table 9. Comparative Clinical Trials with the Biguanides

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Type 2 Diabetes – Monotherapy				
Jones et al.[12] (2002) Metformin 1,000 to 2,000 mg daily vs placebo	DB, MC, PC, RCT Patients 8 to 16 years of age with type 2 diabetes, FPG 7.0 to 13.3 mmol/L, HbA_{1c} ≥7.0%, stimulated C-peptide ≥0.5 nmol/L, and BMI >50th percentile for age	N=82 16 weeks	Primary: Change in baseline FPG Secondary: Change in baseline HbA_{1c}, body weight, height, BMI, lipid stimulated C-peptide levels	Primary: Adjusted mean change from baseline in FPG for metformin was -2.4 mmol/L compared to 1.2 mmol/L for placebo (P<0.001). Secondary: Mean HbA_{1c} levels, adjusted for baseline levels, were significantly lower for metformin compared to placebo (7.5 vs 8.6%, respectively; P<0.001). Mean TC decreased from baseline in the metformin group (-0.25 mmol/L [-9.7 mg/dL]) compared to a slight increase in the placebo group (0.01 mmol/L [0.7 mg/dL]; P=0.043). Mean LDL-C decreased more with metformin (-0.11 mmol/L [-4.2 mg/dL] vs -0.10 mmol/L [4 mg/dL]; P=0.053). No between-group differences were seen in the mean adjusted changes in HDL-C or TGs. Mean weight changes and mean BMI changes from baseline were comparable between the treatment groups. There was no between-group difference seen in the adjusted mean stimulated C-peptide change from baseline (-0.2 nmol/L for both groups [-0.7 vs -0.6 ng/mL]). The most common reported adverse events were abdominal pain, diarrhea, nausea/vomiting, and headache. Patients receiving metformin experienced more abdominal pain (25%) vs placebo (12%) and more nausea/vomiting (17%) vs placebo (10%).
Bhansali et al.[13] (2005)	OL	N=40	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Month 1: After a lead-in period of 3 months on their usual metformin IR regimen, patients were evaluated (visit 0, baseline) and started on a specific brand of metformin IR at their usual dose, 1,000 to 2,000 mg daily, and continued on this regimen for 1 month until visit 1. Month 2: patients were evaluated (visit 1) and changed over to metformin ER as a single dose at dinner, at a dose 500 mg less than the baseline dose of metformin IR; they continued on this regimen for 1 month Month 3: patients were evaluated (visit 2) and changed over to metformin XR 1,000 to 2,000 mg daily at	Patients ≥40 years of age with type 2 diabetes, BMI ≥20 kg/m^2, HbA_{1c} ≤8.5%, and a fasting capillary glucose ≤120 mg/dL who had achieved moderate or good glycemic control with metformin IR alone or in combination with other antihyperglycemic agents	7 months (3 month lead-in and 4 month observation)	Changes in four-point glucose profile at each visit and in HbA_{1c} at the end of the study period, changes in weight and lipid profiles, compliance was assessed by reviewing the tablet counts conducted at each study visit and patients were asked to confirm their compliance with therapy at each visit (acceptable compliance was defined as >80% of expected study drug consumption) Secondary: Not reported	Mean fasting glucose was <120 mg/dL in 80, 63, 73, and 90% of patients at visits one, two, three, and four, respectively; these differences were not significant. Mean post-breakfast glucose was 149, 165 (P=0.009), 158 (P=0.159), and 159 mg/dL (P=0.111) at visits one, two, three, and four, respectively (P values are when compared to visit one). Mean post-lunch glucose was 130, 154 (P=0.003), 151 (P=0.012), and 138 mg/dL (P=0.076) at visits one, two, three, and four, respectively (P values are when compared to visit one). Mean post-dinner glucose was 138, 161 (P=0.020), 138 (P=0.967), and 128 mg/dL (P=0.264) at visits one, two, three, and four, respectively (P values are when compared to visit one). Mean PPG was 139, 160 (P=0.001), 149 (P=0.065), and 142 mg/dL (P=0.289) at visits one, two, three, and four, respectively (P values are when compared to visit one). Mean HbA_{1c} after three months of metformin ER (visit 4) was 6.3% compared to baseline HbA_{1c} of 6.9% with metformin IR (P=0.008). No other HbA_{1c} values were reported. Patients switched over to the ER formulation, once re-established at doses equivalent to their baseline metformin IR doses, and achieved glycemic control comparable to baseline levels. Mean weight at the end of three months of metformin ER (visit four) was 68.7±10.2 kg as compared to 69.6±10.8 kg at baseline (P=0.020). Lipid profile after three months of metformin XR was the following: mean TC (182±29 mg/dL), LDL-C (113±26 g/dL), HDL-C (45±8 mg/dL), and TG (119±55 mg/dL). These were not statistically significant from baseline. Two patients complained of diarrhea and one had loss of appetite and complained of diarrhea during the new metformin XR regimen.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
bedtime, keeping the dose the same as their baseline metformin IR dose; they continued on this regimen for 1 month Month 4: patients were evaluated (visit 3) and changed over to metformin XR 1,000 to 2,000 mg daily in two divided doses keeping the dose the same as baseline metformin IR dose; they continued on this regimen for 1 month Patients were evaluated at the end of the study (visit 4).				Secondary: Not reported
Blonde et al.[14] (2004) Metformin XR 500 to 2,500 mg daily vs metformin IR 500 to 2,500 mg daily	MC, RETRO Patients ≥17 years of age with type 2 diabetes who were started on metformin XR (Glucophage XR®), or switched from metformin IR or another oral antidiabetic agent to	N=468 1 year	Primary: Gastrointestinal tolerability and frequency of diarrhea for metformin XR compared to metformin IR during the first year of treatment Secondary:	Primary: Overall metformin XR vs metformin IR cohorts: The frequency of gastrointestinal events was similar between metformin XR and metformin IR (11.94 vs 11.39%, respectively; P=0.86). The RR of any gastrointestinal adverse event for metformin XR compared to metformin IR was 1.05 (95% CI, 0.62 to 1.78). The percentages of patients with individual gastrointestinal adverse events in the metformin XR and metformin IR groups, respectively were as follows: diarrhea (6.77 vs 7.59%), nausea (2.26 vs 3.80%), dyspepsia (1.61 vs 1.27%), abdominal pain (1.61 vs 0.63%), constipation (0.97 vs

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	metformin XR within the previous 2 years		Not reported	0.63%), vomiting (0.65 vs 0.63%), abdominal distention (0.32 vs 0.00%), fecal abnormality (0.32 vs 0.63%), blood in stools (0.00 vs 063%), and flatulence (0.00 vs 0.63%). Patients switched from metformin IR to metformin XR: Significantly more patients experienced a gastrointestinal adverse event during the first year of treatment with metformin IR (26.34%, 54/205; P=0.006) than after switching to metformin XR (11.71%, 24/205). The mean daily dose of metformin XR was 1,184 mg (range, 500 to 2,500 mg) during the first year of therapy and 1,047 mg (range, 500 to 2,550 mg) for the metformin IR groups. A significantly higher percentage of patients reported diarrhea (18.05%, 37/205) while taking metformin IR than after switching to metformin XR (8.29%, 17/205; P=0.0084). More patients reported nausea (2.93%), dyspepsia (3.41%), abdominal distention (2.44%), and flatulence (2.44%) while taking the metformin IR than after switching to metformin XR (1.95, 1.46, 0.49, and 0.0%, respectively); however, the differences were not significant. Patients new to metformin XR vs metformin IR: A greater percent of patients reported a gastrointestinal adverse event during the first year of treatment with metformin IR (19.83%, 72/363) than during the first year of therapy with metformin XR (9.23%, 6/65; P=0.0414). A greater percent of patients taking metformin IR reported diarrhea (13.5%, 49/363) as compared to the metformin XR group (3.08%, 2/65; P=0.0169). Secondary: Not reported
Fujioka et al.[15] (2003)	DB, MC, PG, RCT Patients to 27 to 77 years of age with	N=217 24 weeks	Primary: Change in baseline HbA_{1c} from baseline to week	Primary: Mean changes from baseline in HbA_{1c} values at week 12 were small and similar in the three treatment groups. At week 12, the mean change from

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Metformin XR (Glucophage XR®) 1,000 mg QD with the evening meal vs metformin XR 1,000 mg QD with the evening meal for 1 week, then increased to 1,500 mg QD vs continued metformin IR 500 mg BID Note: after 12 weeks, the daily dose of metformin could be increased by 500 mg in any group if HbA_{1c} was ≥8.0% at that time.	type 2 diabetes for >2 months to <10 years, HbA_{1c} ≤8.5%, FPG ≤200 mg/dL, and receiving metformin IR 500 mg BID for ≥8 weeks		12 with the switch from metformin IR to metformin XR Secondary: Change in baseline HbA_{1c} to week 24, changes in FPG, mean daily blood glucose concentrations, fructosamine, serum insulin levels, lipid levels, body weight, safety	baseline was 0.15% for metformin IR, 0.23% for metformin XR 1,000 mg, and 0.04% for metformin XR 1,500 mg. Secondary: The corresponding changes in HbA_{1c} values at week 24 were small and similar among the three treatment groups: 0.06% for metformin IR, 0.25% for metformin XR 1,000 mg, and 0.14% for metformin XR 1,500 mg. The distribution of HbA_{1c} values in the specified categories (<7.0, 7.0 to <8.0, and ≥8.0%, respectively) was not significant between the groups during the study. Mean FPG concentrations had also increased in all three treatment groups at week 12 and 24. The mean increases were smaller in the metformin XR groups compared to the metformin IR group. No clinically relevant significant changes from baseline were seen in HDL-C or TC levels in any treatment group. LDL-C decreased in all treatment groups, with a mean change of -4 mg/dL in the metformin IR group (95% CI, -9 to 1), and -6 mg/dL in both XR groups (1,000 mg XR, 95% CI, -11 to -1; 1,500 mg XR, 95% CI, -12 to 0). There were small increases from baseline in TG levels in patients receiving metformin IR (mean change, 1 mg/dL; 95% CI, -14 to 17). There were significant increases in TGs in patients receiving metformin XR. Patients in the 1,000 mg group had an increase of 34 mg/dL (95% CI, 15 to 53) and patients in the 1,500 mg group had an increase of 42 mg/dL (95% CI, 6 to 78). Mean daily blood glucose concentration, fructosamine, serum insulin levels, and body weight showed similar changes in each group. Twenty-five percent of patients in the metformin IR group, 29% of patients in the metformin XR 1,000 mg group, and 34% of patients in the metformin XR 1,500 mg group experienced adverse drug events (occurring in ≥3% of patients). Diarrhea, flatulence, abdominal pain, and nausea/vomiting were the most common adverse events reported among all groups combined. Three percent of metformin IR, 5% of metformin XR 1,000 mg, and 15% of metformin 1,500 mg patients experienced diarrhea. Flatulence was reported in 1% of metformin IR patients, 4% of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				metformin XR 1,000 mg patients, and 3% of metformin XR 1,500 mg patients. Abdominal pain was reported in 1% of metformin IR patients and metformin XR 1,500 mg patients and in 4% of metformin XR 1,000 mg patients. Nausea/vomiting were reported in 4% of metformin IR patients and 3% in both metformin XR groups. Headache was reported in 4% of metformin IR and metformin XR 1,000 mg patients. Dyspepsia/heartburn was reported in 6% of metformin IR and 3% of metformin XR 1,000 mg patients. The study was not statistically powered to detect differences in tolerability between the groups.
Schwartz et al.[16] (2006) Metformin XR 1,500 mg QD vs metformin XR 1,500 mg daily in 2 divided doses vs metformin XR 2,000 mg QD vs metformin IR 1,500 mg daily in 2 divided doses	AC, DB, MC, RCT Patients 18 to 79 years of age with type 2 diabetes, HbA_{1c} 7.0 to 12.0% (drug-naïve patients) or 6.5 to 10.0% (prior drug therapy patients), FPG 120 to 400 mg/dL (drug-naïve patients) or 120 to 250 mg/dL (prior drug therapy patients), C-peptide levels >1 ng/mL, and BMI 22 to 50 kg/m^2	N=750 24 weeks	Primary: Change in baseline HbA_{1c} Secondary: Change in baseline FPG, fructosamine, TC, HDL-C, LDL-C, and TG	Primary: Reductions in mean HbA_{1c} were significant by week 12 for all groups, continued to decline until week 20, and were maintained for the duration of the study. The change from baseline was significant for each group (P<0.001). Mean changes in HbA_{1c} from baseline to end point in all metformin XR groups were similar to the metformin IR groups. Mean changes in HbA_{1c} from baseline to end point in the two groups given 1,500 mg metformin XR (-0.73% and -0.74%) were not significantly different from the change in the metformin IR group (-0.70%), whereas the 2,000 mg metformin XR group showed a greater decrease in HbA_{1c} levels (-1.06%). Secondary: Reductions in mean FPG were significant in all groups by the end of week one, declined until week eight, and these levels were maintained until the end of the study. The change from baseline was significant for each group (P<0.001). The mean changes from baseline to end point within each of the metformin XR groups were comparable with or greater than that in the metformin IR group (P=0.051 for overall comparison among groups). Mean fructosamine levels decreased from baseline within all groups. There was a significant difference among groups for fructosamine levels at the end point, with the lowest level observed with the 2,000 mg once daily metformin XR group. TC, LDL-C, and HDL-C levels were similar at baseline and end point with all treatment groups, except for differences with treatment groups for

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				final LDL-C (P=0.015) and TG (P=0.030). The lowest mean concentrations for LDL-C and TG occurred with 2,000 mg QD metformin XR and metformin IR, respectively. Overall incidence of gastrointestinal adverse events was low and comparable among treatment groups during the first week of treatment. There was a higher incidence of nausea in the metformin IR group than in the metformin XR groups (P=0.05) during the first week. Overall incidence of adverse events considered possibly or probably related to the study drug was similar for all groups. The only events reported for >5% of patients in any group during the entire study were gastrointestinal (diarrhea, nausea, dyspepsia, upper abdominal pain).
Ji et al.[17] (2018) Metformin XR 500 to 2,000 mg daily (administered once daily) vs metformin IR 500 to 2,000 mg daily (administered in three divided doses)	MC, OL, PRO, RCT Treatment-naïve Chinese patients with T2DM	N=532 16 weeks	Primary: Change in HbA_{1c} from baseline and gastrointestinal (GI) tolerability Secondary: Proportion of patients achieving HbA_{1c} < 7%, GI tolerability across individual GI adverse events (frequencies of diarrhea, nausea, abdominal pain, abdominal distension, constipation, dyspepsia and flatulence) during the entire treatment period, and	Primary: Metformin XR was non-inferior to metformin IR for the primary efficacy endpoint in the per-protocol population (n=419). The HbA_{1c} least squares mean change was -1.61% and -1.58% in each group, respectively (least squares mean difference, 0.03; 95% CI, -0.10 to 0.17). Sensitivity analyses of the intent-to-treat population were performed and the results were consistent with the primary analysis. Metformin XR was not superior to metformin IR for overall GI adverse events incidence during the entire treatment period in the safety population. Sixty-two patients (23.8%) in the metformin IR group and 59 (22.3%) in the metformin XR group reported GI adverse events. The difference in incidence rate of overall GI adverse events was −1.52 (95% CI, −8.60 to 5.56; P=0.674); thus, the superiority criterion was not met for metformin XR vs metformin IR. Secondary: The percentage of patients who achieved the target of HbA_{1c} < 7% at week 16 was similar between groups in the intent-to-treat population (metformin IR, 68.50%; 95% CI, 62.60 to 74.06%; metformin XR, 69.80%; 95% CI, 63.90 to 75.28; P=0.742). Incidences of individual GI adverse events were similar between treatment groups, with diarrhea (metformin IR, 16.50%; metformin XR, 12.50%), abdominal distension (metformin IR, 6.10%;

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			incidence of hypoglycemia	metformin XR, 6.40%) and nausea (metformin IR, 6.10%; metformin XR, 4.50%) being the most frequently reported. No difference in incidence of hypoglycemia was noted between treatment groups. Incidence rates of hypoglycemia were 1.10% vs 3.00% (95% CI, 1.32 to 5.88%) in metformin IR and metformin XR groups, respectively. The difference in incidence rates between treatment groups was 1.88%. No significant differences were noted for reduction of mean FPG and PPG levels from baseline to endpoint between groups.
Aggarwal et al.[18] (2018) Metformin XR 2000 mg once daily vs metformin IR 1000 mg twice daily	DB, MC, PG, RCT Patients ≥18 years of age who had type 2 diabetes and inadequate glycemic control with diet and lifestyle advice alone (pharmacotherapy-naïve, defined as no prior pharmacotherapy for glucose lowering within 90 days prior to enrolment and no more than 14 days of glucose-lowering medication) and HbA_{1c} of 7.0 to 9.2%	N=539 24 weeks	Primary: Change in HbA_{1c} after 24 weeks Secondary: Change in FPG, mean daily glucose, and percentage of patients with HbA_{1c} <7.0%	Primary: The adjusted mean change in HbA_{1c} from baseline to week 24 was similar between treatment arms (metformin XR, −0.93%; metformin IR, −0.96%), resulting in a non-significant difference of 0.03% between groups (95% CI, −0.10 to 0.17). Secondary: Baseline adjusted changes in mean FPG and mean daily glucose levels, and percentage of patients with HbA_{1c} <7.0% were similar between treatment arms, as were changes in body weight, waist circumference and serum lipid profiles.
Pavo et al.[19] (2003) Metformin 850 to 2,550 mg daily	DB, MC, RCT Recently diagnosed (<12 months) type 2 diabetic patients	N=205 32 weeks	Primary: Change in HbA_{1c} from baseline Secondary:	Primary: Each treatment group had a significant reduction in HbA_{1c} from baseline (P<0.0001 for each group). The difference between pioglitazone and metformin was not significant (P=0.280).

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vs pioglitazone 30 to 45 mg daily	≥40 years of age, HbA_{1c} of 7.5 to 11.0%, and naïve to oral antihyperglycemic medications		Changes in FPG, fasting serum insulin, and insulin sensitivity	Secondary: Each treatment group had a significant reduction in FPG (P<0.0001 for each group). The difference between pioglitazone and metformin was not significant (P=0.620). Pioglitazone reduced fasting serum insulin significantly (P<0.0001). The change in fasting serum insulin was not significant for metformin (P=0.803). Pioglitazone was significantly more effective than metformin in improving indicators of insulin sensitivity, as determined by reduction of fasting serum insulin (P=0.003) and by analysis of HOMA-S (P=0.002).
Cryer et al.[20] (2005) Metformin 500 mg BID to 2,500 mg daily in 3 divided doses vs usual care	MC, OL, PG, RCT Type 2 diabetic patients ≥18 years of age with glycemia inadequately controlled with diet or a sulfonylurea	N=8,732 1 year	Primary: Incidence of serious adverse events, death, hospitalization Secondary: Plasma lactate levels after one year of treatment in a substudy	Primary: Serious adverse reactions were reported in 10.3% (95% CI, 9.6 to 11.1) of patients in the metformin group and by 11.0% (95% CI, 9.5 to 12.7) of patients in the usual care group (P=0.43), with similar pattern of serious adverse events between groups according to body system. Serious cardiovascular adverse events were the most common, which included coronary artery disease (1.0 vs 1.1%) for metformin vs usual care, respectively, chest pain (0.7 vs 1.0%), congestive heart failure (0.7 vs 0.6%), MI (0.7 vs 0.7%), and cerebrovascular accident (0.4 vs 0.7%). There was not an excess of serious adverse events observed in the metformin group in all patients regardless of age. The incidence of all-cause hospitalization, hospitalization for metabolic causes (other than lactic acidosis), and all-cause mortality did not differ between metformin and usual care in the overall population (P=0.229, P=1.0, P=0.596, respectively) or in patients ≥65 years old (P=0.178, P=1.0, P=0.878, respectively), or in younger patients (P=0.945, P=0.835, P=0.21, respectively). There were no patients that were hospitalized or that died from lactic acidosis. Secondary: Mean plasma lactate was 1.7±0.6 mmol/L in the metformin group and 1.6±0.6 mmol/L in the usual care group after 12 months of therapy (P=0.137). Plasma lactate >3 mmol/L occurred in 4% of metformin

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				patients and 1% in the usual care group. There was no significant difference between the groups.
Gottschalk et al.[21] (2007) Metformin 500 to 1,000 mg BID vs glimepiride 1 to 8 mg QD	AC, MC, PG, SB, RCT Pediatric subjects 8 to 17 years of age with type 2 diabetes (HbA_{1c} >7.1 and <12.0%) with inadequate control despite treatment with either diet and exercise alone for at least 2 weeks prior to randomization or diet and exercise combined with 3 months of ongoing or previous oral antidiabetic monotherapy	N=285 24 weeks	Primary: Mean change in HbA_{1c} from baseline to week 24 Secondary: Mean change in HbA_{1c} from baseline to week 12, proportion of patients achieving an HbA_{1c} <7.0% at week 24, mean change in fasting self-monitoring of blood glucose from baseline to weeks four, eight, 12, 18, and 24, mean changes in serum lipid concentrations from baseline to week 24 and changes in BMI, safety, adverse events, hypoglycemic episodes and vital signs	Primary: Significant reductions from baseline HbA_{1c} were seen in both the glimepiride (−0.54%; P=0.001) and metformin (−0.71%; P=0.0002) groups. No significant differences were observed between groups in reductions in HbA_{1c}. Secondary: Significant reductions in the adjusted mean change from baseline HbA_{1c} to week 12 were –0.69 and –0.76% in patients receiving glimepiride and metformin, respectively (P<0.05). A total of 42.4 and 48.1% of patients in the glimepiride and metformin groups, respectively, achieved HbA_{1c} <7.0% at week 24 (P=0.347). Significant reductions were seen in fasting self-monitoring of blood glucose levels from baseline to weeks 18 and 24 in patients receiving metformin (P<0.05) but no similar reductions were reported in the glimepiride group. There were no significant differences between the glimepiride and metformin groups in the mean change from baseline in any of the serum lipid concentrations. Significant between-group differences were observed in the mean change from baseline BMI to week 24. Values were 0.26 and 0.33 kg/m^2 in patients receiving glimepiride and metformin, respectively (P=0.003). No deaths occurred during the study. The proportions of patients experiencing ≥1 adverse event were comparable between both treatment groups, with the most common adverse events being hyperglycemia, upper abdominal pain, diarrhea, nausea and headache. Two patients experienced serious adverse events that were considered possibly related to treatment: one patient in the glimepiride group had hyperglycemia, diabetic ketoacidosis and increased serum osmolarity and one patient in the metformin group had a non-hypoglycemic convulsion.

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				The incidence of clinically relevant hypoglycemia was similar in both groups (P=0.554). No clinically significant differences in vital signs were seen between treatment groups.
Hong et al.[22] (2013) SPREAD-DIMCAD Metformin 0.75 to 1.5 grams daily vs glipizide 15 to 30 mg daily	DB, MC, PC, RCT Patients 80 years of age or below with coronary artery disease (CAD) and type 2 diabetes	N=304 3 years	Primary: Composite of recurrent cardiovascular events (myocardial infarction [MI], nonfatal stroke, arterial revascularization, death) Secondary: New or worsening angina, new or worsening heart failure, new critical cardiac arrhythmia, and new peripheral vascular events.	Primary: A total of 103 composite primary end points occurred in 91 during the whole study period: 60 events in the glipizide group (14 deaths from any causes [including 11 deaths from cardiovascular events and 3 from sudden death; autopsies were not performed to confirm the 3 patients' precise causes of death], 6 nonfatal myocardial infarctions, 15 nonfatal strokes, and 25 arterial revascularizations), as compared with 43 events in the metformin group (7 deaths from any causes [all were deaths from cardiovascular events], 5 nonfatal myocardial infarctions, 10 nonfatal strokes, and 21 arterial revascularizations). As compared with the patients treated with glipizide, the HR for the composite cardiovascular events for metformin treatment was 0.54 (95% CI 0.30 to 0.90; P=0.026) after adjustment for the duration of diabetes, duration of CAD, age, sex, and smoking history at baseline. No significant difference in the mortality rate between the two groups was found (P=0.55). Secondary: During the study drug administration, the following secondary end points occurred: • new or worsening heart failure: 10 (6.8%) patients in the glipizide group and 9 (5.8%) patients in the metformin group (adjusted HR, 0.82; 95% CI, 0.31 to 2.13; P=0.677) • new critical cardiac arrhythmia: 27 (18.2%) patients in the glipizide group and 30 (19.2%) patients in the metformin group (HR, 1.01; CI, 0.60 to 1.72; P=0.958) • new or worsening angina: 71 (48%) patients in the glipizide group and 77 (49.4%) patients in the metformin group (HR, 1.07; CI, 0.77 to 1.48; P=0.696) • new peripheral vascular events: 6 (4.1%) patients in the glipizide group and 1 (0.6%) patient in the metformin group (HR, 0.13; CI, 0.02 to 1.08; P=0.059)

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				Furthermore, the two groups did not differ significantly with respect to the number of patients who reported one or more hypoglycemic attacks during study drug administration.
Lund et al.[23] (2008) Repaglinide 2 mg TID for 4 months vs metformin 1,000 mg BID for 4 months	DD, XO Non-obese (BMI ≤27 kg/m^2), insulin-naïve patients with type 2 diabetes mellitus	N=96 8 months with 1 month washout	Primary: Cardiovascular disease biomarkers and metabolic regulation Secondary: Not reported	Primary: Levels of TNF-α, plasminogen activator inhibitor-1 antigen, tissue-type plasminogen activator antigen, von Willebrand factor, soluble intercellular adhesion molecule-1 and soluble E-selectin were significantly lower during metformin treatment compared with repaglinide treatments. Amadori albumin and heart rate were higher during metformin compared with repaglinide. Both treatment groups experienced similar levels of interleukin-6, fibrinogen, soluble vascular cell adhesion molecule-1, asymmetric dimethylarginine and advanced glycation end products as well as glycemic levels and 24 hour BP. Secondary: Not reported
Lund et al.[24] (2008) Repaglinide 2 mg TID for 4 months vs metformin 1,000 mg BID for 4 months	DD, XO Non-obese (BMI ≤27 kg/m^2), insulin-naïve patients with type 2 diabetes mellitus	N=192 8 months with 1 month washout	Primary: Postprandial metabolism with blood sampling 0 to six hours postprandially Secondary: Not reported	Primary: Both treatment groups equally changed fasting levels and total AUC for plasma glucose, TGs and FFA. The metformin treatment group obtained lower fasting levels and AUC of TC, LDL-C, and non-HDL-C and serum insulin compared with repaglinide. After adjusting for fasting levels, AUC differences still remained significant. Secondary: Not reported
Fang et al.[25] (2014) Repaglinide vs	OL, PG, RCT Chinese drug-naive patients aged 20 to 90 years with newly diagnosed type 2	N=60 15 weeks	Primary: Change in HbA_{1c} from baseline Secondary:	Primary: At week 15, mean changes in HbA_{1c} from baseline were -1.8±1.5% in the repaglinide group (P<0.01) and -1.6±1.5% in the metformin group (P<0.01). No significant difference was found with regard to change in HbA_{1c} level between the two groups (P=0.739).

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metformin	diabetes mellitus with a BMI of 18.5 to 30 kg/m^2 and with an HbA_{1c} <10.0%		Changes in glycemic variability, insulin sensitivity, β-cell function	Secondary: No significant differences in secondary outcomes were found between the groups.
Sullivan et al.[26] (2011) FIELD Metformin vs sulfonylurea vs diet alone	PRO Patients with type 2 diabetes	N=6,005 5 years	Primary: Cardiovascular disease outcomes Secondary: Hypoglycemic therapy	Primary: Patients receiving monotherapy with either metformin or a sulfonylurea appeared to be at greater risk of cardiovascular disease compared to those on diet alone, but results were only significant for the sulfonylurea group, ranging from 42% higher risk of coronary revascularization to a doubled risk of coronary heart disease death. However, adjustment for the duration and intensity of diabetes and the severity of other cardiovascular risk factors abolished the significance of this effect. Total revascularization and total mortality were significantly higher in the sulfonylurea group compared to the metformin group, but all differences became non-significant on adjustment. Secondary: Use of oral hypoglycemic agents increased progressively as the trial proceeded. Over five years, treatment with diet alone decreased from 31 to 15%, and dual therapy with metformin plus a sulfonylurea increased from 29 to 36%. Insulin therapy was introduced at a rate of 4% per year. Metformin monotherapy declined from 21 to 18% but the sulfonylurea monotherapy rate declined from 20 to 12%. Patients on sulfonylurea monotherapy were more likely to progress to dual therapy.
Kahn et al.[27] (2006) Metformin 500 to 1,000 mg BID vs rosiglitazone 4 mg QD to 4 mg BID vs	DB, MC, RCT Recently diagnosed (within 3 years) type 2 diabetic patients between 30 to 75 years of age who had not received previous pharmacologic treatment, with FPG levels ranging from	N=4,360 4 to 6 years (median treatment durations 3.3 years for glyburide and 4 years for rosiglitazone and metformin)	Primary: Time from randomization to treatment failure (defined as FPG >180 mg/dL on consecutive testing after at least six weeks of treatment at the maximum tolerated dose)	Primary: At five years, 15% of patients receiving rosiglitazone, 21% of those on metformin, and 34% of those on glyburide had failed monotherapy. This represents a risk reduction of 32% for rosiglitazone as compared with metformin and 63% for rosiglitazone as compared with glyburide (P<0.001 for both comparisons). Secondary: Progression to a confirmed FPG ≥140 mg/dL was seen in 79 of 511 patients in the rosiglitazone group as compared with 127 of 520 patients in the metformin group (P=0.002) and 160 of 480 patients in the glyburide group (P<0.001).

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glyburide 2.5 to 7.5 mg BID	126 to 180 mg/dL while their only treatment was lifestyle management		Secondary: Time from randomization to a confirmed FPG >140 mg/dL after at least six weeks of treatment at the maximum tolerated dose (for patients who entered the study with FPG ≤140 mg/dL); FPG, HbA_{1c}, weight, measures of insulin sensitivity, β-cell function, and adverse events	At the four-year evaluation, 40% of the patients in the rosiglitazone group achieved an HbA_{1c} <7.0% compared with 36% of the patients in the metformin group (P=0.03) and 26% of the patients in the glyburide group (P<0.001). The annual rate of β-cell function decline after six months was greatest in the glyburide group (6.1% decreased), followed by the metformin group (3.1% decreased) and rosiglitazone group (2.0% decreased) (P<0.001 for rosiglitazone vs glyburide and P=0.02 for rosiglitazone vs metformin). Over a period of five years, the mean weight increased in the rosiglitazone group but decreased in the metformin group. In the glyburide group, weight gain occurred in the first year then remained stable. Treatment with glyburide was associated with lower risk of cardiovascular events (including congestive heart failure) than was seen in the rosiglitazone and metformin groups (P<0.05). Rosiglitazone was associated with more weight gain and edema than either metformin or glyburide, but fewer gastrointestinal events were reported with rosiglitazone compared to metformin and fewer hypoglycemic events were seen with rosiglitazone compared to with glyburide (P<0.001 for all comparisons).
Aschner et al.[28] (2010) Metformin 1,000 mg BID vs sitagliptin 100 mg QD	AC, DB, RCT Patients 18 to 78 years of age with type 2 diabetes mellitus who were treatment naïve with an HbA_{1c} of 6.5 to 9.0%	N=1,050 24 weeks	Primary: Change in HbA_{1c} from baseline Secondary: Proportions of patients with HbA_{1c} <7.0% or <6.5%, change in FPG, fasting serum insulin, fasting serum proinsulin, and lipid parameters	Primary: In the per protocol population, the change in HbA_{1c} (least squares mean) from baseline at week 24 was -0.43% in the sitagliptin group and -0.57% in the metformin group (difference, 0.14%; 95% CI, 0.06 to 0.21), which demonstrated the non-inferiority of sitagliptin to metformin. In the full analysis set, the HbA_{1c} change from baseline at week 24 was -0.38% (95% CI, -0.43 to -0.32) in the sitagliptin group and -0.55% (95% CI, -0.61 to -0.50) in the metformin group (difference, 0.18%; 95% CI, 0.10 to 0.25), which demonstrated the non-inferiority of sitagliptin to metformin. Secondary:

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				The proportion of patients with an HbA_{1c} <7.0% at week 24 was greater with metformin (76%) compared with sitagliptin (69%; difference, -7.1%; 95% CI, -12.9 to -1.2). The proportion of patients with an HbA_{1c} <6.5% was not statistically different between the metformin (39%) and sitagliptin (34%) groups (difference, -5.6%; 95% CI, -11.8 to 0.8). The change from baseline in FPG was greater with metformin (-19.4 mg/dL compared with sitagliptin (-11.5 mg/dL). The reduction in fasting proinsulin was greater in the metformin group, which resulted in a larger reduction in the proinsulin/insulin ratio at week 24. Both treatments produced similar increases in β-cell function and reductions in insulin resistance over 24 weeks. HDL-C was improved with both treatments. TGs were slightly reduced with sitagliptin. Small increases in TC were observed for each group, with a slightly greater increase for sitagliptin. Modest increases in LDL-C and non-HDL-C were observed with sitagliptin, but not metformin over 24 weeks. The incidence of drug-related adverse events was lower in the sitagliptin group than in the metformin group. The incidence of gastrointestinal adverse events overall was lower in the sitagliptin group compared with the metformin group (11.6 vs 20.7%, respectively). Hypoglycemia occurred at a low rate in both groups (1.7% with sitagliptin and 3.3% with metformin; P=0.116). Body weight was reduced from baseline in both the sitagliptin (-0.6 kg) and metformin (-1.9 kg; P<0.001).
Nichols et al.[29] (2007) Metformin vs	MC, OS, RETRO Patients who initiated metformin, sulfonylurea, insulin or TZDs between	N=9,546 ≥12 months	Primary: Weight changes Secondary: Not reported	Primary: Patients treated with metformin lost an average of 2.4 kg, sulfonylurea-treated patients gained 1.8 kg, insulin-treated patients gained 3.3 kg, and thiazolidinedione-treated patients gained 5.0 kg. All comparisons with metformin were statistically significant.

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sulfonylurea vs insulin vs TZDs	1996 and 2002 and continued use of that drug for at least 12 months without adding other therapies			Secondary: Not reported
Russell-Jones et al.[33] (2012) DRUATION-4 Exenatide ER 2 mg SC once weekly vs metformin 2,000 mg/day vs pioglitazone 45 mg/day vs sitagliptin 100 mg/day	DB, DD, MC, PG, RCT Drug-naïve (patients excluded if treated with any antihyperglycemic drug for >7 days within 3 months of screening) adult type 2 diabetics with HbA_{1c} 7.1 to 11.0%, BMI 23 to 45 kg/m^2, and stable weight	N=820 26 weeks	Primary: Change in baseline HbA_{1c} Secondary: Proportion of patients achieving HbA_{1c} <7.0 and ≤6.5%, fasting serum glucose, seven-point self-monitored glucose concentrations, weight, lipid profile, insulin profile, safety and tolerability, patient-reported QOL	Primary: Decreases in HbA_{1c} were -1.53±0.07, -1.48±0.07, -1.63±0.08, and -1.15±0.08% with exenatide ER, metformin (P=0.620 vs exenatide ER), pioglitazone (P=0.328 vs exenatide ER), and sitagliptin (P<0.001 vs exenatide ER). The HbA_{1c} at trial end was 6.94±0.07, 6.99±0.07, 6.84±0.08, and 7.32±0.08% with exenatide ER, metformin, pioglitazone, and sitagliptin, respectively. Secondary: Similar proportions of patients receiving exenatide ER and metformin achieved HbA_{1c} <7.0% (63 vs 55%; P value not reported). A significantly greater proportion of patients receiving exenatide ER achieved HbA_{1c} <7.0% compared to patients receiving sitagliptin (63 vs 43%; P<0.001), and ≤6.5% compared to patients receiving metformin (49 vs 36%; P=0.004) and sitagliptin, respectively (49 vs 26%; P<0.001). Decreases in fasting serum glucose at weeks 16 and 26 were significantly greater with exenatide ER compared to sitagliptin (P<0.001 for both). There were no differences observed with exenatide ER compared to metformin (P=0.155 at week 26) and pioglitazone (P=0.153 at week 26). Seven-point self-monitored glucose concentrations demonstrated similar decreases with exenatide ER, metformin, and pioglitazone. Exenatide ER demonstrated greater decreases at all time points compared to sitagliptin. Mean decreases in post-meal excursions after 26 weeks were similar among all treatments.

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				Decreases in weight were significantly greater with exenatide ER compared to pioglitazone and sitagliptin by weeks four and eight, and the effect was sustained through 26 weeks (P≤0.003 for all). There was no difference between exenatide ER and metformin after 26 weeks (-2.0 vs -2.0 kg; P=0.892). No clinically significant changes in serum lipids were observed with any treatment. Mean HOMA-B was significantly improved with exenatide ER compared to metformin, pioglitazone, and sitagliptin (P<0.001 for all). HOMA-S significantly improved with metformin and pioglitazone compared to exenatide ER (P<0.001 for both), and the change with exenatide ER was similar to sitagliptin (P=0.329). Serious adverse events were reported in 1.6, 5.3, 5.5, and 1.8% of patients receiving exenatide ER, metformin, pioglitazone, and sitagliptin, respectively. No serious adverse event was reported by more than one patient. Treatment-emergent adverse events reported by at least five percent of patients in any group included headache (highest with metformin), diarrhea (highest with metformin), injection site nodule (highest with exenatide ER), nasopharyngitis (highest with sitagliptin), nausea (highest with exenatide ER), dyspepsia (highest with exenatide ER), constipation (highest with exenatide ER), back pain (highest with metformin), arthralgia (highest with exenatide ER), hypertension (highest with pioglitazone), and peripheral edema (highest with pioglitazone). No major hypoglycemia was reported. One patient receiving sitagliptin with elevated lipase at screening experienced moderate chronic pancreatitis after eight days and discontinued from study treatment. All treatments resulted in improvements in perceived treatment satisfaction, weight-related quality of life, and binge eating behavior. All treatments, except pioglitazone, resulted in significant improvements in health status. Significant improvements in weight-related quality of life, binge eating behavior, and health status were reported with exenatide ER compared to pioglitazone (P values not reported).
Simpson et al.[31]	RETRO	N=5,95	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2006) First-generation sulfonylurea vs glyburide vs metformin	New users of one oral diabetic agent	~4.6 years	Mortality Secondary: Not reported	An increased risk of death was associated with higher daily doses of first-generation sulfonylureas (adjusted HR, 2.1; 95% CI, 1.0 to 4.7) and glyburide (HR, 1.3; 95% CI, 1.2 to 1.4) compared to metformin (HR, 0.8; 95% CI, 0.7 to 1.1). Secondary: Not reported
Bolen et al.[32] (2007) Biguanides vs meglitinides vs TZDs vs α-glucosidase inhibitors vs second-generation sulfonylureas	MA (Analysis of 216 controlled trials and cohort studies, and 2 SR) Patients with type 2 diabetes	N=136 (articles on intermediate outcomes) N=167 (articles on adverse events) N=68 (articles on microvascular outcomes and mortality) Duration varied	Primary: Intermediate outcomes: HbA_{1c}, body weight, BP, lipid panels, all-cause mortality, cardiovascular morbidity and mortality, microvascular outcomes Secondary: Adverse events: hypoglycemia, gastrointestinal problems, congestive heart failure, edema or hypervolemia, lactic acidosis, elevated liver enzymes, allergic reactions requiring hospitalization,	Primary: Results from clinical trials showed that most oral agents including TZDs, metformin, and repaglinide improved glycemic control to the same degree as sulfonylureas (absolute decrease in HbA_{1c} level of about 1%). Nateglinide and α-glucosidase inhibitors have slightly weaker effects, on the basis of indirect comparisons of placebo-controlled trials. TZDs were the only class with beneficial effect on HDL-C (mean relative increase, 3 to 5 mg/dL) but a harmful effect on LDL-C (mean relative increase, 10 mg/dL) compared to other oral agents. Metformin decreased LDL-C levels by about 10 mg/dL, whereas other oral agents had no effects on LDL-C. TZDs, second-generation sulfonylureas, and metformin had similarly minimal effects on SBP. Most agents except metformin increased body weight by 1 to 5 kg. In the ADOPT (A Diabetes Outcome Progression Trial), the incidence of cardiovascular events was lower with glyburide compared to rosiglitazone or metformin (1.8, 3.4, and 3.2%, respectively; $P<0.05$). In the RECORD study (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of glycemia in Diabetes), rosiglitazone plus metformin or a sulfonylurea compared to metformin plus a sulfonylurea had a HR of

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			other serious adverse events	1.08 (95% CI, 0.89 to 1.31) for the primary end point of hospitalization or death from cardiovascular disease. The HR was driven by more congestive heart failure in the rosiglitazone plus metformin group compared to the control group of metformin plus sulfonylurea (absolute risk, 1.7 vs 0.8%, respectively). Too few comparisons were made to draw firm comparative conclusions on microvascular outcomes. Secondary: According to several RCTs and some OS trials, sulfonylureas and repaglinide were associated with greater risk for hypoglycemia. In many RCTs, TZDs were associated with a higher risk for edema than sulfonylureas or metformin (absolute risk difference, 2 to 21%). In cohort studies, TZDs were associated with higher risk for congestive heart failure although absolute risks were small (1 to 3%) and higher risk for mild anemia yet produced similarly low rates of elevated aminotransferase levels (<1%) compared to sulfonylureas and metformin. In many trials and a few OS trials, metformin was associated with greater risk for gastrointestinal problems compared to other oral diabetes agents. According to a SR of 176 comparative trials, lactic acidosis events were similar between metformin and other oral diabetes agents.
Saenz et al.[33] (2005) Metformin monotherapy vs placebo, sulfonylureas, TZDs, meglitinides, α-glucosidase	MA (29 RCTs) Adult patients with type 2 diabetes	N=5,259 ≥3 months	Primary: Incidence of any diabetes-related outcomes (sudden death, death from hyperglycemia or hypoglycemia, fatal or nonfatal MI, angina, heart failure, stroke, renal failure, amputation [of at	Primary: Obese patients receiving metformin showed a greater benefit than chlorpropamide, glibenclamide*, or insulin for any diabetes-related outcomes (P=0.009) and for all-cause mortality (P=0.03). Obese patients receiving metformin showed a greater benefit than overweight patients on conventional treatment (diet) for any diabetes-related outcomes (P=0.004), diabetes-related death (P=0.03), all cause mortality (P=0.01), and MI (P=0.02). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
inhibitors, diet, any other oral antidiabetic intervention, insulin			least one digit], vitreous hemorrhage, retinopathy requiring photocoagulation, blindness in one eye, or cataract extraction); diabetes-related death (death from MI, stroke, peripheral vascular disease, renal disease, hypo-glycemia or hyperglycemia, and sudden death); all-cause mortality Secondary: Changes in HbA_{1c}, FPG, quality of life, weight, BMI, lipids, insulin, C-peptide, BP, micro-albuminuria, glomerular filtration rate, renal plasma flow	Patients receiving metformin monotherapy showed a significant benefit for glycemic control, weight, dyslipidemia, and DBP. Metformin presents a strong benefit for HbA_{1c} when compared to diet and placebo. Additionally, metformin showed a moderate benefit for glycemic control, LDL-C, and BMI or weight when compared to sulfonylureas.
Monami et al.[34] (2008) Metformin vs	MA Patients with type 2 diabetes mellitus	N=7,890 (27 RCT) Variable duration	Primary: Reduction in HbA_{1c} at 16 to 36 months Secondary: Not reported	Primary: Combining the results of different placebo-controlled trials, sulfonylurea, α-glucosidase inhibitors, and TZDs led to a reduction in HbA_{1c} by -0.85% (95% CI, 0.78 to 0.94], -0.61% (95% CI, 0.55 to 0.67), and -0.42% (95% CI, 0.40 to 0.44), respectively when combined with metformin.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
sulfonylureas, α-glucosidase inhibitors, TZDs, glinides, GLP-1 agonists				In direct comparisons, sulfonylureas led to a greater reduction in HbA_{1c} (0.17%; 95% CI, 0.16 to 0.18; P<0.05) than TZDs. Differences between sulfonylureas and α-glucosidase inhibitors, and between α-glucosidase inhibitors and TZDs, were not statistically significant. Secondary: Not reported
Amori et al.[35] (2007) Incretin-based therapies (exenatide, liraglutide, sitagliptin, and vildagliptin†) vs non-incretin-based therapy (placebo or hypoglycemic agent)	MA (29 RCTs) Type 2 diabetics	N=12,996 Duration varied (12 to 52 weeks)	Primary: Change in baseline HbA_{1c} Secondary: FPG, proportion of patients achieving an HbA_{1c} <7.0%	Primary: Pooled analysis of trials comparing GLP-1 analogues to placebo demonstrated a significant difference in the decrease in HbA_{1c} favoring GLP-1 analogues (WMD, -0.97; 95% CI, -1.13 to -0.81). Specifically, no difference in the HbA_{1c} was found in OL, non-inferiority trials between exenatide and insulin glargine or biphasic aspart (WMD, -0.06; 95% CI, -0.22 to 0.10). Liraglutide demonstrated similar HbA_{1c} efficacy compared to OL glimepiride titrated to glycemic goals or DB maximum dose metformin (data not reported). Secondary: Compared to placebo, FPG was significantly decreased with GLP-1 analogues (WMD, -27 mg/dL; 95% CI, -33 to -21). Exenatide-treated patients were more likely to achieve an HbA_{1c} <7.0% compared to placebo treated patients (45 vs 10%, respectively; RR, 4.2; 95% CI, 3.2 to 5.5), while no difference in the proportions of patients achieving this goal was observed between exenatide and insulin therapy in non-inferiority trials (39 vs 35%, respectively; RR, 1.1; 95% CI, 0.8 to 1.5). Data with liraglutide were not reported.
Frederich et al.[36] (2010) Saxagliptin 2.5 to 10 mg QD vs	SR Inadequately controlled type 2 diabetics	N=4,607 16 to 116 weeks	Primary: Composite of cardiovascular events, cardiovascular death, MI, and stroke Secondary:	Primary: There were 38 (1.1%) cardiovascular events with saxagliptin compared to 23 (1.8%) with the comparator drugs (RR, 0.59; 95% CI, 0.35 to 1.00). There were 23 (0.7%) cardiovascular deaths, MIs, and stroke events with saxagliptin compared to 18 (1.4%) with the comparator drugs (RR, 0.44; 95% CI, 0.24 to 0.82). There were seven (0.2%) cardiovascular deaths with saxagliptin compared to 10 (0.8%) with comparator drugs (RR, 0.24; 95% CI, 0.09 to 0.63).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
glyburide, metformin, or placebo			Not reported	Secondary: Not reported
Singh et al.[37] (2011) TZDs (pioglitazone, rosiglitazone) vs placebo, sulfonylurea, or metformin	MA, SR (13 RCTs) Type 2 diabetics	N=17,627 1 to 5.5 years (follow-up)	Primary: Any pneumonia or lower respiratory tract infection reported as an adverse event, pneumonia or lower respiratory tract infection reported as a serious adverse event Secondary: Not reported	Primary: TZDs are associated with a significantly increased risk for any pneumonia or lower respiratory tract infection compared to control (130/8,163 vs 100/9,464; RR, 1.40; 95% CI, 1.08 to 1.82; P=0.01). In addition TZDs were associated with a significantly increased risk of serious pneumonia or lower respiratory tract infection compared to control (111/7,391 vs 87/8,692; RR, 1.39; 95% CI, 1.05 to 1.83; P=0.02). Secondary: Not reported
Louisa et al.[38] (2011) TZDs (pioglitazone, rosiglitazone) vs placebo or other hypoglycemic agents	MA (37 RCTs) Type 2 diabetics	N=3,000 >3 months	Primary: Glycemic outcomes Secondary: Change in baseline BMI, lipid profile, BP, high-sensitivity CRP, and insulin sensitizing effect; cardiovascular and clinical endpoints	Primary: Both pioglitazone (WMD, -0.12%; 95% CI, -0.38 to -0.16) and rosiglitazone (WMD, -0.47%; 95% CI, -0.62 to -0.33) significantly decreased HbA_{1c}. Pioglitazone only demonstrated a significant decrease compared to placebo, while rosiglitazone significantly decreased HbA_{1c} compared to placebo and a sulfonylurea. Both pioglitazone (WMD, -9.16 mg/dL; 95% CI, -15.60 to -2.72) and rosiglitazone (WMD, -16.10 mg/dL; 95% CI, -22.20 to -10.01) significantly decreased FPG compared to control. Pioglitazone demonstrated a significant decrease compared to placebo, metformin, and voglibose†, while rosiglitazone significantly decreased FPG compared to placebo, metformin, and a sulfonylurea. Secondary: Pioglitazone and rosiglitazone had similar effects on BMI (pioglitazone: WMD, 0.57; 95% CI, 0.34 to 0.80 and rosiglitazone: WMD, 0.72; 95% CI, 0.29 to 1.14).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Pioglitazone demonstrated a neutral effect of LDL-C (WMD, 3.89 mg/dL; 95% CI, -0.04 to 7.83) and TC (WMD, 2.30 mg/dL; 95% CI, -3.81 to 8.41). Rosiglitazone significantly increased LDL-C (WMD, 11.30 mg/dL; 95% CI, 7.80 to 14.79) and TC (WMD, 7.34 mg/dL; 95% CI, 2.34 to 12.31). Both agents had favorable effects on HDL-C and TGs. Pioglitazone produced a small decrease in DBP and SBP, while rosiglitazone demonstrated a neutral effect. In 13 trials, pioglitazone demonstrated a neutral effect on high sensitivity CRP, while rosiglitazone demonstrated a small improvement in high sensitivity CRP. Consistent increase in adiponectin and improvement in HOMA-IR were observed with both pioglitazone and rosiglitazone. Four trials evaluated cardiovascular events as secondary endpoints. There were significant decreases in major cardiac events with both pioglitazone vs control (RR, 0.24; 95% CI, 0.09 to 0.63) and rosiglitazone vs control (RR, 0.41; 95% CI, 0.19 to 0.87).
Richter et al.[39] (2006) Pioglitazone monotherapy (16 trials) vs acarbose (1 trial), metformin (4 trials), placebo (4 trials), repaglinide (1 trial), rosiglitazone (1 trial), or a sulfonylurea (8 trials) or	MA of DB (15) or OL (4) RCTs (last search conducted in August 2006, included PROactive Study), PG Adults with type 2 diabetes, trial duration of at least 24 weeks	22 trials N=6,200 randomized to pioglitazone treatment (total N not reported) 24 weeks to 34.5 months	Primary: Patient-oriented outcomes including mortality, morbidity, adverse effects Secondary: Health-related quality of life, HbA_{1c}	Primary: Only one trial (PROactive Study) evaluated mortality and morbidity as an end point. The primary composite end point (time from randomization to all-cause mortality, nonfatal MI, stroke, acute coronary syndrome, endovascular or surgical intervention on the coronary or leg arteries, or amputation above the ankle) did not show statistically significant differences between the pioglitazone and placebo group (HR, 0.90; 95% CI, 0.80 to 1.02; P=0.095). Time to the first event of the composite end point of death from any cause, MI and stroke indicated a statistically significant difference between pioglitazone and placebo (HR, 0.84; 95% CI, 0.72 to 0.98; P=0.027). The individual components of the primary composite end point did not disclose statistically significant differences between the intervention and control groups. Significantly more patients developed heart failure

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
pioglitazone combination therapy vs a similar combination with another compound (9 trials including 2 trials vs rosiglitazone) Some studies had more than 1 treatment arm.				requiring hospitalization following administration of pioglitazone (6 vs 4% on placebo; P=0.007). The percentage of overall and serious adverse events was comparable between the intervention and control groups. Six trials reported a more pronounced (sometimes dose-related) decrease of hemoglobin after pioglitazone intake in comparison to other active compounds or placebo; hemoglobin reductions ranged between -0.50 and- 0.75 g/dL. Fifteen trials evaluated body weight and observed an increase up to 3.9 kg after pioglitazone treatment; seven trials described a rise in BMI up to 1.5 kg/m^2. Eleven of the 22 included trials showed data on hypoglycemic episodes: compared to the active monotherapy control, pioglitazone treatment resulted in somewhat lower rates of hypoglycemia (P value not reported). The RR for development of edema with pioglitazone compared to the control was 2.86 (95% CI, 2.14 to 3.18; P<0.00001) when results from 18 trials were pooled. Secondary: No study investigated health-related quality of life. Active glucose-lowering compounds like metformin, glibenclamide*, gliclazide† or glimepiride resulted in similar reductions of HbA_{1c} compared to pioglitazone treatment (P values not reported).
Lincoff et al.[40] (2007) Pioglitazone monotherapy vs metformin (1 trial), placebo (4 trials), sulfonylureas (6 trials) or rosiglitazone (1 trial) or	DB, MA, RCT with placebo or active comparator Adult patients with type 2 diabetes and inadequate glycemic control	N=16,390 (19 trials) 4 months to 3.5 years	Primary: Composite of death from any cause, MI or stroke Secondary: Incidence of serious heart failure	Primary: Death, MI, or stroke occurred in 375 of 8,554 patients (4.4%) receiving pioglitazone and 450 of 7,836 patients (5.7%) receiving control therapy (HR, 0.82; 95% CI, 0.72 to 0.94; P=0.005). Individual components of the primary end point were reduced with pioglitazone treatment with varying degrees of statistical significance (death: HR, 0.92; P=0.38, MI: HR, 0.81; P=0.08, death and MI: HR, 0.85; P=0.04, and stroke: HR, 0.80; P=0.09). Progressive separation of time-to-event curves became apparent after approximately one year of therapy. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
pioglitazone combination therapy (7 trials) with insulin, metformin, or sulfonylureas vs active comparator or placebo				Serious heart failure was reported in 2.3% of the pioglitazone-treated patients and 1.8% of the control treated patients (HR, 1.41; 95% CI, 1.14 to 1.76; P=0.002). The composite of serious heart failure and death was not significantly increased among patients receiving pioglitazone (HR, 1.11; 95% CI, 0.96 to 1.29; P=0.17).
Lago et al.[41] (2007) Pioglitazone 15 to 45 mg/day (2 trials) or rosiglitazone 4 to 8 mg/day (5 trials) vs placebo (4 trials), glibenclamide* (1 trial), glimepiride (1 trial), metformin (1 trial), or metformin plus nonspecified sulfonylurea (1 trial) Doses of comparators were not specified and 1 trial had 2 control groups.	MA of DB, RCTs of TZDs that reported risk estimates or frequency data for congestive heart failure and cardiovascular death Patients with prediabetes or type 2 diabetes (with and without cardiovascular disease), mean age 59.2 years, mean BMI 31 kg/m^2, mean baseline HbA_{1c} 7.72%	7 trials N=20,191 29.7 months (range, 12 to 48 months)	Primary: Development of congestive heart failure, risk of cardiovascular death Secondary: Not reported	Primary: Three hundred and sixty of 20,191 patients who had either prediabetes or type 2 diabetes had congestive heart failure events (214 with TZDs and 146 with comparators). The overall event rate for congestive heart failure was 2.3% for patients receiving TZDs and 1.4% in the comparator group. Patients given pioglitazone (RR, 1.32; 95% CI, 1.04 to 1.68; P=0.02) or rosiglitazone (RR, 2.18; 95% CI, 1.44 to 3.32; P=0.0003) had increased risk for development of congestive heart failure across a wide background of cardiac risk compared to the control agent (combined RR, 1.72; 95% CI, 1.21 to 2.42; P=0.002). The risk for congestive heart failure did not differ for rosiglitazone and pioglitazone (RR, 1.74; 95% CI, 0.97 to 3.14; P=0.07). The overall event rate for cardiovascular death was 0.7% in both groups. The risk of cardiovascular death was not increased with pioglitazone (RR, 1.01; 95% CI, 0.51 to 2.01; P=0.98), rosiglitazone (RR, 0.91; 95% CI, 0.63 to 1.32; P=0.63) or both TZDs (combined RR, 0.93; 95% CI, 0.67 to 1.29; P=0.68). The risk of cardiovascular death did not differ between both drug groups (RR, 1.01; 95% CI, 0.73 to 1.40; P=0.96). Secondary: Not reported
Mannucci et al.[42] (2008) Pioglitazone vs	MA (94 trials) Patients treated with pioglitazone (with or without type 2 diabetes)	N=21,180 Variable duration	Primary: All-cause mortality, non-fatal coronary event (defined as MI, unstable angina or coronary re-	Primary: In PROactive, pioglitazone treatment was not associated with a significant reduction in all-cause mortality (P value not reported). In non-diabetic patients, only one death was observed occurring among pioglitazone-treated patients.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
active comparators, placebo, no treatment			vascularization), non-fatal chronic heart failure requiring hospitalization Secondary: Not reported	In type 2 diabetic patients (excluding PROactive), the total number of deaths reported was 17 and 39 in the pioglitazone and comparator groups, respectively (RR, 0.41; 95% CI, 0.23 to 0.72). When analyzing all trials, no significant reduction of mortality was observed with pioglitazone. Comparing different agents, pioglitazone was associated with a lower mortality rate compared to sulfonylureas. There was no significant difference in all-cause mortality with metformin, rosiglitazone, glitazars, or placebo. When trials with zero events were included in the analysis, no significant difference was observed with sulfonylureas (RR, 0.22; 95% CI, 0.05 to 1.03), metformin (RR, 0.66; 95% CI 0.19 to 2.34), rosiglitazone (RR, 0.49; 95% CI, 0.04 to 5.36), glitazars (RR, 0.42; 95% CI, 0.11 to 1.61), or placebo (RR, 0.16; 95% CI, 0.02 to 1.45). In PROactive, pioglitazone significantly reduced the incidence of non-fatal coronary events (P value not reported). In non-diabetic subjects, only two non-fatal coronary events occurred and one case of heart failure in pioglitazone group were reported. In type 2 diabetes, 44 and 50 non-fatal coronary events were observed in pioglitazone and comparator groups, respectively (RR, 0.82; 95% CI, 0.55 to 1.23). Combining trials with at least one event, the difference between pioglitazone and comparators was not statistically significant. In PROactive, pioglitazone was associated with an increased risk for chronic heart failure. In the other 40 trials reporting data on non-fatal heart failure requiring hospitalization, 58 cases were reported in pioglitazone-treated subjects and 39 in controls (RR ,1.32; 95% CI, 0.88 to 1.98). Combining the results of all trials with at least one event except PROactive, the overall difference between pioglitazone and comparators was not significant (P value not reported). When adding PROactive or

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				excluding trials vs dual PPARα/γ agonists pioglitazone was associated with a significant increase of risk for chronic heart failure. In comparison with different agents, pioglitazone was associated with an increased risk of chronic heart failure in PC trials, while differences with sulfonylureas or glitazars did not reach significance. Secondary: Not reported
Nagajothi et al.[43] (2008) Pioglitazone vs active comparators (metformin and/or sulfonylurea) or placebo	MA (5 trials) Patients treated with pioglitazone	N=not reported Duration varied	Primary: MI Secondary: Stroke, revascularization, total mortality, cardiovascular mortality	Primary: The RR for MI was 0.86 (95% CI, 0.69 to 1.07; P=0.17). Secondary: The RR for stroke was 0.79 (95% CI, 0.61 to 1.02; P=0.07). The RR for total mortality was 0.94 (95% CI, 0.78 to 1.15; P=0.56). The RR for coronary revascularization was 0.40 (95% CI, 0.13 to 1.23; P=0.11. The RR for cardiovascular mortality was 0.92 (95% CI, 0.73 to 1.16; P=0.47).
Karter et al.[44] (2005) Patients initiated pioglitazone (15.2%), sulfonylureas (25.3%), metformin (50.9%), and insulin (8.6%) alone, or in addition to pre-existing therapies	Cohort study of all patients in the Kaiser Permanente Medical Care Program with type 2 diabetes (Kaiser Permanente Northern California Diabetes Registry) who initiated any new diabetes pharmacotherapy between October 1999 and November 2001	N=23,440 10.2 months (mean)	Primary: Time-to-incident admission to hospital for congestive heart failure Secondary: Not reported	Primary: Three hundred and twenty admissions for congestive heart failure were observed during the follow-up (mean, 10.2 months) after drug initiation. Relative to patients initiating sulfonylureas, there were no significant increases in the incidence of hospitalization for congestive heart failure in those initiating pioglitazone (HR, 1.28; 95% CI, 0.85 to 1.92). There was a significantly higher incidence among those initiating insulin (HR, 1.56; 95% CI, 1.00 to 2.45) and lower incidence among those initiating metformin (HR, 0.70; 95% CI, 0.49 to 0.99). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Singh et al.[45] (2007) Rosiglitazone vs control (placebo or other non-TZD oral hypoglycemic drug including glyburide or metformin)	MA of RCTs (available up to May 2007 and included ADOPT, DREAM and RECORD trials) of rosiglitazone of at least 12 months duration Study participants with impaired glucose tolerance or type 2 diabetes, studies monitored cardiovascular adverse events and provided numerical data on all adverse events	4 trials N=14,291 (n=6,421 rosiglitazone; n=7,870 control) 1 to 4 years	Primary: RR of MI, heart failure, and cardiovascular mortality Secondary: Not reported	Primary: Rosiglitazone significantly increased the risk of MI (94 vs 83; RR, 1.42; 95% CI, 1.06 to 1.91; P=0.02) and heart failure (102 vs 62; RR, 2.09; 95% CI, 1.52 to 2.88; P<0.001) compared to the control. There was no significant difference in the risk of cardiovascular mortality between the rosiglitazone and control group (59 vs 72; RR, 0.90; 95% CI, 0.63 to 1.26; P=0.53). Rosiglitazone had no effect on all-cause mortality (146 vs 180; RR, 0.99; 95% CI, 0.80 to 1.23; P=0.92). Secondary: Not reported
Nissen et al.[46] (2007) Rosiglitazone monotherapy or combination therapy vs placebo or active comparators (including gliclazide†, glimepiride, glipizide, glyburide, insulin, and metformin)	MA of RCTs of more than 24 weeks that had outcome data for MI and death from cardiovascular causes (included ADOPT and DREAM trials) Mean age of participants was 56 years, mean baseline HbA_{1c} 8.2%	42 trials n=15,560 for rosiglitazone; n=12,283 for comparator 24 to 208 weeks	Primary: MI and death from cardiovascular causes Secondary: Not reported	Primary: Rosiglitazone was associated with a significant increase in the risk of MI compared to the control agent (OR, 1.43; 95% CI, 1.03 to 1.98; P=0.03). Compared to the control agent, rosiglitazone was associated with a trend toward increased cardiovascular death (OR, 1.64; 95% CI, 0.98 to 2.74; P=0.06). Although not a prespecified end point, the OR for death from any cause with rosiglitazone was 1.18 (95% CI, 0.89 to 1.55; P=0.24). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Richter et al.[47] (2007) Rosiglitazone monotherapy (10 trials) vs glyburide (2 trials), metformin (3 trials), pioglitazone (1 trial), placebo (5 trials), or repaglinide (1 trial) or rosiglitazone combination therapy vs a similar combination with another compound (8 trials) Some studies had more than 1 treatment arm.	MA of DB (11) or OL (5) RCTs (last search conducted in April 2007, included the ADOPT trial), PG Adults with type 2 diabetes, trial duration of at least 24 weeks	18 trials N=3,888 randomized to rosiglitazone treatment (total N not reported) 24 weeks to 4 years (median 26 weeks)	Primary: Patient-oriented outcomes including mortality, morbidity, adverse effects Secondary: Health-related QOL, metabolic control (HbA_{1c})	Primary: No study included mortality as a primary or secondary end point. While not an initial primary or secondary study end point, the ADOPT trial reported that the all-cause mortality was 2.3% in the rosiglitazone group, 2.1% in the metformin group and 2.2% in the glyburide group (P values not reported in this reference). The ADOPT trial also reported comparable hospitalization rates for any cause between rosiglitazone (11.6%), metformin (11.8%), and glyburide (10.4%) groups (P values were not reported in this reference). Cardiovascular disease was increased in the rosiglitazone group compared to the glyburide group but not the metformin group with serious/total events reported in 3.4/4.3% and 1.8/2.8% of patients receiving rosiglitazone and glyburide, respectively (events were 3.2/4.0% with metformin; P values were not reported in this reference). Congestive heart failure was observed more frequently in patients receiving rosiglitazone (1.5%) than patients receiving glyburide (0.6%) but not metformin (1.3%; P values were not reported in this reference). The percentage of overall adverse events was comparable between the intervention and control groups (which included placebo arms); serious adverse events appeared to happen more often after rosiglitazone treatment (median of 6 vs 4% in the control groups; P value not reported). Median discontinuation rate following rosiglitazone administration was also higher than after control therapy (median of 7 vs 4%; P value not reported). Three studies reported a more pronounced (apparently dose-related) decrease of hemoglobin after rosiglitazone intake in comparison to other active compounds or placebo; hemoglobin reductions ranged between 0.5 and 1.0 g/dL. Eleven studies evaluated body weight and observed an increase up to 5.0 kg after rosiglitazone treatment; four studies described a rise in BMI up to 1.5 kg/m^2. Seven of the 18 included studies showed data on hypoglycemic episodes: compared to active monotherapy control, rosiglitazone treatment resulted in somewhat lower rates of hypoglycemia, especially when compared to sulfonylureas. Occurrence of edema was significantly raised when results of nine studies were pooled (OR, 2.27; 95% CI, 1.83 to 2.81; P<0.00001). The ADOPT trial reported a higher incidence of fractures in women receiving

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				rosiglitazone (9.30%) than metformin (5.08%; P<0.01) or glyburide (3.47%; P<0.01). Secondary: No study investigated health-related quality of life. Active glucose-lowering compounds like metformin, glibenclamide* or glimepiride resulted in similar reductions of HbA_{1c} compared to rosiglitazone treatment.
Kheirbek et al.[48] (2013) Hypoglycemic medications (metformin, glyburide, glipizide, rosiglitazone, acarbose, chlorpropamide, glimepiride, pioglitazone, tolazamide, repaglinide, troglitazone, insulin, and DPP-4 inhibitors) *Defined as any use of the medication independent of dose or days of use	OS, RETRO Veterans with diabetes cared for at a Veterans Administration Capital area medical center	N=17,773 Variable duration	Primary: All-cause mortality Secondary: Not reported	Primary: After adjustments were made for severity of illness and patient demographics, the remaining variance in mortality was explained by exposure to five medications, listed in order of impact on risk-adjusted mortality: glipizide (OR=1.566), glyburide (OR=1.804), rosiglitazone (OR=1.805), insulin (OR=2.382), and chlorpropamide (OR=3.026). None of the other medications (metformin, acarbose, glimepiride, pioglitazone, tolazamide, repaglinide, troglitazone, and DPP-4 inhibitors) were associated with excess mortality beyond what could be expected from the patients' severity of illness or demographic characteristics. Insulin, glyburide, glipizide, and rosiglitazone continued to be associated with statistically significant increased mortality after controlling for possible drug interactions. Secondary: Not reported
Type 2 Diabetes – Combination Therapy				
Halimi et al.[49] (2000) Metformin 850 mg BID to TID and	DB, PC, PG, RCT Patients 30 to 70 years of age with type 2 diabetes,	N=152 6 months	Primary: HbA_{1c} at trial end Secondary:	Primary: Mean difference in HbA_{1c} from baseline to trial end was -0.7±1.2% with acarbose compared to 0.2±1.3% with placebo (P=0.0001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
acarbose 50 to 100 mg TID vs metformin 850 mg BID to TID	BMI 25 to 35 kg/m^2, having poor glycemic control despite receiving metformin ≥2 months before the study start		Blood glucose, insulin profiles, TG	Patients were classified as responders if their HbA_{1c} values at trial end were <7.0% or had decreased by <15% relative to baseline. The total numbers of responders were 25 of 49 (42%) patients receiving acarbose and 12 of 70 (17%) patients receiving placebo (P=0.002). Secondary: Mean difference in the fasting blood glucose level from baseline to trial end was -1.0±2.8 mmol/L with acarbose compared to 1.3±2.8 mmol/L with placebo (P=0.0001). Mean difference in two-hour PPG level from baseline to trial end was -1.4±3.8 mmol/L with acarbose compared to 1.1±3.5 mmol/L with placebo (P=0.0001). Mean changes between acarbose compared to placebo for TG, fasting and postprandial serum insulin were not significant (P value not significant).
Phillips et al.[50] (2003) Metformin (usual dose) and acarbose 50 mg to 100 mg BID vs metformin (usual dose)	DB, MC, PC, PG, RCT Patients ≥40 years of age with type 2 diabetes for ≥6 months, BMI 25 to 35 kg/m^2, HbA_{1c} 7.0 to 10.0% at screening week and 6.8 to 10.2% at baseline, and inadequately controlled by metformin	N=83 24 weeks	Primary: Change in baseline HbA_{1c} Secondary: Change in baseline FPG	Primary: Mean HbA_{1c} increased with placebo from 7.82±0.83% at baseline to 8.10±1.06% at week 12 and 8.50±1.44% at trial end. The mean increase after 24 weeks was 0.68±1.17%, with a significant overall time effect (P=0.0001). With acarbose, mean HbA_{1c} decreased from 8.02±0.85% at baseline to 7.78±1.00% at week 12 (P=0.0261). At the trial end, mean HbA_{1c} increased to 7.97±1.10%. There was no significant overall time effect for acarbose (P value not reported). Adjusted least square means for the change in HbA_{1c} from baseline to trial end showed a decrease of 0.16±0.18% with acarbose compared to an increase of 0.86±0.16% with placebo. There was a significant difference between the treatment groups of 1.02% (95% CI, 0.543 to 1.497; P=0.0001). Secondary: Mean FPG levels increased with placebo from baseline (9.41 ±1.99 mmol/L) to week 4 (10.06 ±2.43 mmol/L) to trial end (10.77 ±3.39 mmol/L). The levels only changed slightly with acarbose.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Mean FPG increases were 1.36±2.88 mmol/L with placebo and 0.08±1.98 mmol/L with acarbose. The adjusted least square means showed increase at trial end with both treatments of 0.34±0.42 mmol/L with acarbose vs 1.48±0.39 mmol/L with placebo, with a significance of 1.132 mmol/L between the two treatments (95% CI, 0.056 to 2.208; P=0.0395).
Rosenstock et al.[51] (2016) Canagliflozin 100 mg and metformin XR (CANA100MET) vs Canagliflozin 300 mg and metformin XR (CANA300MET) vs Canagliflozin 100 mg (CANA 100) vs Canagliflozin 300 mg (CANA 300) vs metformin XR (MET)	DB, RCT Patients with drug-naïve type 2 diabetes from 18 to 75 years of age	N=1,186 26 weeks	Primary: Change in baseline HbA_{1c} Secondary: Noninferiority in HbA_{1c} lowering with canagliflozin monotherapy versus metformin; changes in FPG, body weight, and SBP; and proportion of patients achieving HbA_{1c} <7.0%	Primary: At week 26, reductions from baseline in HbA_{1c} were seen with CANA100/MET, CANA300/MET, CANA100, CANA300, and MET (–1.77, −1.78, –1.37, –1.42, and –1.30%, respectively), resulting in final mean HbA_{1c} values of 7.0, 7.0, 7.4, 7.3, and 7.4%, respectively. Reductions in HbA_{1c} with CANA100/MET and CANA300/MET were statistically significant versus MET (LS mean differences of –0.46% and –0.48%, respectively; P=0.001 for both) and versus CANA100 and CANA300 (LS mean differences of –0.40% and –0.36%, respectively; P=0.001 for both). Secondary: Noninferiority of HbA_{1c} lowering was also demonstrated with CANA100 and CANA300 versus MET (LS mean differences of –0.06% and –0.11%, respectively; noninferiority P=0.001 for both). At week 26, significant differences in the proportion of patients who achieved HbA_{1c} <7.0% were observed with CANA100/MET and CANA300/MET versus MET (P=0.027 and P=0.016, respectively); 49.6%, 56.8%, 38.8%, 42.8%, and 43.0% of patients achieved HbA_{1c} <7.0% with CANA100/MET, CANA300/MET, CANA100, CANA300, and MET, respectively. Dose-related reductions in FPG were observed with CANA100/MET and CANA300/MET that were greater compared with their respective monotherapies. At week 26, reductions in body weight from baseline were observed across groups (–3.2, –3.9, –2.8, –3.7, and –1.9 kg [−3.5%, –4.2%, –3.0%, –3.9%, and –2.1%] with CANA100/MET, CANA300/MET, CANA100, CANA300, and MET, respectively). CANA100/MET, CANA300/MET, CANA100, and CANA300 provided modest reductions in SBP compared with MET (–2.2, –1.7, –2.2, –2.4, and –0.3 mmHg, respectively). Reductions in SBP with CANA100/MET and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(Metformin XR doses were titrated)				CANA300/MET were not statistically significant versus MET (LS mean differences of –1.9 and –1.3 mmHg, respectively).
Lopez-Alvarenga et al.[52] (1999) Metformin 1,200 mg daily, chlorpropamide 500 mg daily, and acarbose 100 mg TID vs metformin 1,200 mg daily, chlorpropamide 500 mg daily, and NPH insulin at bedtime vs metformin 1,200 mg daily, chlorpropamide 500 mg daily, and placebo	DB, RCT, XO Patients with type 2 diabetes from 35 to 70 years of age with BMI 23 to 35 kg/m^2, with a FPG >8.8 mmol/L despite maximal doses of chlorpropamide and metformin for at least 2 months	N=46 42 weeks	Primary: Change in FPG from baseline, body weight, HbA_{1c}, fasting insulin, fasting C-peptide, intravenous glucose tolerance test (incremental area), glucose meal tests (incremental area) Secondary: Not reported	Primary: Changes in FPG from baseline were not significant for placebo (P=0.62), but were significant for acarbose (P=0.05) and insulin (P=0.003). Changes in HbA_{1c} from baseline were not significant for placebo (P=0.62) and acarbose (P=0.3), but were significant for insulin (P=0.008). Changes in body weight were not significant in any group (P=0.2 vs baseline). Changes in fasting insulin from baseline were not significant for placebo (P=0.38), but were significant for acarbose (P=0.03) and insulin (P=0.02). Changes in fasting C-peptide from baseline were not significant in any group, placebo (P=0.7), acarbose (P=0.5), and insulin (P=0.24). Changes in intravenous glucose tolerance test (incremental area) from baseline were not significant in any group, placebo (P=0.36), acarbose (P=0.91), and insulin (P=0.94). Changes in glucose meal tests (incremental area) from baseline were not significant for placebo (P=0.84) and insulin (P=0.08), but were for acarbose (P=0.02). Changes in insulin (incremental area) from baseline were not significant for any group, placebo (P=0.92), acarbose (P=0.3), and insulin (P=0.43). Thirty-seven percent of patients developed severe bloating during acarbose use. This was significant (P<0.05) compared to acarbose and placebo or insulin. Secondary: Not reported
Haak et al.[53] (2012)	DB, MC, PC, RCT	N=791	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Linagliptin 5 mg QD vs metformin 500 mg BID vs metformin 1,000 mg BID vs linagliptin 2.5 mg BID and metformin 500 mg BID vs linagliptin 2.5 mg BID and metformin 1,000 mg BID vs placebo	Patients 18 to 80 years of age with type 2 diabetes who were treatment-naïve (HbA_{1c} 7.5 to 11.0%) or who had received one other oral antidiabetic drug (HbA_{1c} 7.0 to 10.5%)	24 weeks	Change from baseline in HbA_{1c} at week 24 Secondary: Change from baseline in FPG, change from baseline in HbA_{1c} and FPG over time, proportion of patients requiring rescue therapy after failing to achieve pre-specified glycemic targets or discontinuing because of lack of efficacy, safety	After 24 weeks, the mean change in HbA_{1c} was 0.1% with placebo, -0.5% with linagliptin 5 mg QD, -0.6% with metformin 500 mg BID, -1.1% with metformin 1,000 mg BID, -1.2% with linagliptin plus metformin 500 mg, and -1.6% with linagliptin plus metformin 1,000 mg. The adjusted placebo-corrected mean changes in HbA_{1c} were -1.7% (95% CI, -2.0 to -1.4) for linagliptin plus metformin 1,000 mg; -1.3% (95% CI, -1.6 to -1.1) for linagliptin plus metformin 500 mg; -1.2% (95% CI, -1.5 to -0.9) for metformin 1,000 mg; -0.8% (95% CI, -1.0 to -0.5) for metformin 500 mg, and -0.6% (95% CI, -0.9 to -0.3) for linagliptin monotherapy (P<0.0001 for all). The mean treatment differences for linagliptin plus metformin 1,000 mg vs metformin and linagliptin monotherapy were -0.5% (95% CI, -0.7 to -0.3) and -1.1% (95% CI, -1.4 to -0.9), respectively. For linagliptin plus metformin 500 mg, the respective mean differences were -0.6% (95% CI, -0.8 to -0.4) and -0.8% (95% CI, -1.0 to -0.6; P<0.0001 for all). Secondary: The adjusted placebo-corrected mean changes in FPG from baseline were -3.3 mmol/L (95% CI, -4.0 to -2.6) and -2.4 mmol/L (95% CI, -3.1 to -1.7) in the linagliptin plus metformin 1,000 mg and linagliptin plus metformin 500 mg groups, respectively. This is compared to -2.3 mmol/L (95% CI, -3.0 to -1.7), -1.4 mmol/L (95% CI, -2.1 to -0.8) and -1.0 mmol/L (95% CI, -1.7 to -0.3) in the metformin 1,000 mg, metformin 500 mg, and linagliptin monotherapy groups, respectively (P<0.0001 for all). The proportion of patients requiring rescue therapy for inadequate glycemic control at week 24 was lower in the combination therapy groups (linagliptin plus metformin 1,000 mg, 4.3%; linagliptin plus metformin 500 mg, 7.3%) compared to either monotherapy alone (metformin 1,000 mg, 8.0%; metformin 500 mg, 13.5%; linagliptin, 11.1%). The proportion of patients reporting adverse events were comparable across the active treatment groups.
Haak et al.[54] (2013)	DB, MC, PC, RCT	N=566	Primary: Safety	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
linagliptin 2.5 mg plus metformin 500 mg (both twice daily) vs linagliptin 2.5 mg plus metformin 1000 mg (both twice daily) vs metformin 1000 mg twice daily monotherapy	Patients 18 to 80 years of age with type 2 diabetes who were treatment-naïve (HbA_{1c} 7.5 to 11.0%) or who had received one other oral antidiabetic drug (HbA_{1c} 7.0 to 10.5%) (extension study of Haak et al.)	54 weeks	Secondary: Change from baseline in HbA_{1c} and FPG, the percentages of patients who achieved target HbA_{1c} levels of < 7.0 or < 6.5%, the percentages of patients with a reduction in HbA_{1c} levels of ≥ 0.5%, and use of rescue therapy	The incidences of treatment-emergent AEs during the extension period were comparable across the groups, ranging between 66 and 77%. Most adverse events were of mild or moderate intensity, with the majority considered unrelated to study drug. Secondary: All three groups maintained the reduction in HbA_{1c} achieved at the end of the six-month trial, with changes of 0.12 ± 0.72%, 0.08 ± 0.74% and 0.13 ± 0.54%, for the metformin 1000 group, linagliptin 2.5 + metformin 500, and linagliptin 2.5 + metformin 1000 groups, respectively. The overall incidence of rescue medication use was lower in the linagliptin 2.5 + metformin 1000 treatment group (14.0%) than in the linagliptin 2.5 + metformin 500 (27.6%) and metformin 1000 (24.7%) treatment groups. During the extension study, there were no clinically meaningful changes in weight, with mean ±SD changes of –0.4 ± 2.7 kg, 0.2 ± 3.0 kg and –0.7 ± 3.2 kg in the metformin 1000, linagliptin 2.5 + metformin 500, and linagliptin 2.5 + metformin 1000 groups, respectively.
Standl et al.[55] (2001) Metformin 500 to 850 mg daily, miglitol 25 mg to 100 mg TID, and glibenclamide* 3.5 to 5 mg BID to QID vs metformin 500 to 850 mg daily and glibenclamide*	DB, MC, PC, PG, RCT Patients 30 to 70 years of age with type 2 diabetes for ≥3 years; HbA_{1c} ≥7.5 to ≤10.5%; BMI ≤35 kg/m^2; stable body weight over the previous 3 months; and inadequately controlled on combination therapy of diet,	N=154 24 weeks	Primary: Change in baseline HbA_{1c} Secondary: FPG, PPG, fasting and postprandial serum insulin, TG, urinary glucose	Primary: Miglitol produced a significant reduction in HbA_{1c} (-0.55%; P=0.04) and PPG (-2.6 mmol/L; P=0.0009) compared to placebo. Secondary: FPG decreased with miglitol and was almost unchanged with placebo; the difference was not significant (P=0.10). Fasting insulin levels were unchanged with both treatments throughout the trial, with no significant difference between them (P=0.79). Postprandial insulin decreased from baseline to trial end, but the difference between the groups was not significant (P=0.26). Postprandial TG decreased slightly with miglitol and remained unchanged with placebo, and the difference was not significant (P=0.47).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
3.5 to 5 mg BID to QID	glibenclamide* and metformin			
Van Gaal et al.[56] (2001) Metformin 500 mg TID or 850 mg BID to TID and miglitol 25 to 100 mg TID vs metformin 500 mg TID or 850 mg BID to TID	DB, MC, PC, PG, RCT Patients 30 to 75 years of age with type 2 diabetes for ≥1 year, HbA_{1c} ≥7.5 to ≤10.5%, BMI 23 to 40 kg/m^2, stable body weight over the previous 3 months, and whose diabetes was inadequately controlled by diet and metformin	N=152 32 weeks	Primary: Change in baseline HbA_{1c} Secondary: Change in FPG, PPG, serum insulin, fasting and one-hour postprandial TG levels	Primary: There was a significant decrease in HbA_{1c} with miglitol compared to placebo (-0.21 vs 0.22%; P=0.011). Secondary: PPG decreased with both treatments, but the reduction was more significant with miglitol (from 16.5±3.8 mmol/L at baseline to 13.8±5.0 mmol/L at trial end) compared to placebo (from 16.3±3.4 mmol/L at baseline to 15.7±3.8 mmol/L at trial end). The baseline adjusted means were 13.8 mmol/L with miglitol vs 15.8 mmol/L with placebo (P=0.0007). Fasting insulin levels decreased more with miglitol compared to placebo, the difference was not significant (P value not reported). FPG, fasting and postprandial TG levels showed a descriptive advantage for miglitol, but did not reach a statistical difference. Mean FPG levels fell more with miglitol (baseline, 11.5±2.7 mmol/L; end of treatment, 10.8±3.6 mmol/L) compared to placebo (baseline, 11.6±3.1 mmol/L; end of treatment, 11.5±3.4 mmol/L; difference of adjusted means; P=0.15). Fasting TG levels fell with miglitol (treatment effect, -16.3 mg/dL) compared to placebo (treatment effect, 3.77 mg/dL; P=0.26). Similar results were seen for postprandial TG.
Chiasson et al.[57] (2001) Metformin 500 mg TID and miglitol 100 mg TID vs metformin 500 mg TID vs	DB, MC, PC, RCT Patients >40 years of age with type 2 diabetes inadequately controlled by diet alone, HbA_{1c} 7.2 to 9.5%	N=324 36 weeks	Primary: Change in baseline HbA_{1c} Secondary: Change in baseline FPG and PPG, insulin levels, and TG	Primary: Mean change in HbA_{1c} from baseline was 0.38±0.12% with placebo, 0.02±0.10% with miglitol, -0.85±0.12% with metformin, and -1.39±0.11% with combination therapy. A reduction in mean placebo-subtracted HbA_{1c} of -1.78% was seen with combination therapy, and this was significantly different from metformin (-1.25%; P=0.002). Mean reductions in HbA_{1c} compared to placebo were -0.37% with miglitol, -1.25% with metformin, and -1.78% with combination therapy. The end of treatment mean HbA_{1c} was 8.5% with placebo, 8.2% with miglitol, 7.3% with metformin, and 6.9% with combination therapy. Significantly more patients (P=0.0014) receiving combination therapy (70.6%) were classified as responders (i.e., showed ≥15% reduction from

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
miglitol 100 mg TID vs placebo				baseline in HbA_{1c} or achieved an HbA_{1c} <7.0%) compared to metformin (45.5%). Secondary: Combination therapy resulted in better metabolic control compared to metformin for FPG (P=0.0025) and two-hour PPG AUC (P=0.0001). Changes in TG levels from baseline to trial end did not differ significantly between combination therapy compared to metformin, and showed no consistent trend (P value not reported).
DeFronzo et al.[58] (2009) Metformin (existing therapy) and saxagliptin 2.5, 5, or 10 mg QD vs metformin (existing therapy) and placebo	DB, PC, RCT Type 2 diabetics 18 to 77 years of age with inadequate glycemic control (HbA_{1c} ≥7.0 to ≤10.0%), receiving stable doses of metformin (≥1,500 to <2,550 mg/day) ≥8 weeks, fasting C-peptide concentration ≥1 ng/mL, and BMI ≤40 kg/m^2	N=743 24 weeks	Primary: Change in baseline HbA_{1c} Secondary: Change in baseline FPG and PPG $AUC_{0\text{-}3hr}$, proportion of patients achieving an HbA_{1c}<7.0%	Primary: Saxagliptin significantly decreased HbA_{1c} compared to placebo (-0.59, -0.69, and -0.58 vs 0.13%; P<0.0001 for all), with significance achieved after four weeks. Secondary: Saxagliptin significantly decreased FPG compared to placebo (-14.31, -22.03, and -20.50 vs 1.24 mg/dL; P<0.0001 for all). Similar results were observed with PPG $AUC_{0\text{-}3hr}$ (-8,891, -9,586, and -8,137 vs -3,291 [mg/minute]/[dL]; P<0.0001 for all). A significantly greater proportion of patients achieved an HbA_{1c} <7.0% with saxagliptin compared to placebo (37.1, 43.5, and 44.4 vs 16.6%; P<0.0001 for all).
Hermans et al.[59] (2012) PROMPT Fixed-dose metformin 1500 mg/day, plus either: Add-on saxagliptin 5 mg/day (SAXA-MET)	DB, RCT metformin-tolerant patients ≥18 years of age with type 2 diabetes and insufficient glycemic control on submaximal metformin therapy	N=286 24 weeks	Primary: Absolute change from baseline in HbA_{1c} Secondary: Proportion of patients achieving a therapeutic glycemic response,	Primary: Compared with baseline, an adjusted mean change in HbA_{1c} at Week 24 of -0.47% was observed in the SAXA-MET group and -0.38% in the MET-UP group. The difference in adjusted mean change from baseline HbA_{1c} between treatment groups was -0.10%, which was not statistically significant (P=0.260). Secondary: The proportion of patients achieving therapeutic glycemic response (HbA_{1c} <7%) at Week 24 was 43.8% (SAXA-MET) and 35.0% (MET-UP). In comparison, the proportion of patients achieving therapeutic

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vs metformin uptitration (MET-UP) to a max dose (2500 mg/day).			change from baseline in FPG, safety and tolerability	glycemic response (HbA_{1c} ≤6.5%) at Week 24 was 20.5% (SAXA-MET) and 16.8% (MET-UP). During the 24-week treatment period, 51.0% (75/147) of patients in the SAXA-MET group and 43.9% (61/139) in the MET-UP group experienced at least one adverse event.
Pfutzner et al.[60] (2011) Saxagliptin 5 and 10 mg QD plus metformin 500 mg/day vs saxagliptin 10 mg QD vs metformin 500 mg/day	AC, DB, ES, MC, RCT Type 2 diabetics 18 to 77 years of age, HbA_{1c} ≥8.0 to ≤12.0%, fasting C-peptide concentration ≥1 ng/mL, and BMI ≤40 kg/m^2	N=1,306 52 weeks (76 weeks total)	Primary: Change in baseline HbA_{1c} Secondary: Change in baseline body weight, proportion of patients achieving an HbA_{1c} <7.0 and ≤6.5%	Primary: Decreases in HbA_{1c} with saxagliptin 5 mg plus metformin were -2.31% (95% CI -2.44 to -2.18) and -2.33% (95% CI -2.46 to -2.20) with saxagliptin 10 mg plus metformin compared to -1.55 (95% CI, -1.70 to -1.40) and -1.79% (95% CI, -1.93 to -1.65) with saxagliptin and metformin monotherapies, respectively; P<0.0001 for combination therapy vs monotherapy). Secondary: Decreases in body weight were -1.2 kg with saxagliptin 5 mg plus metformin, -0.7 kg with saxagliptin 10 mg plus metformin, -0.3 kg with saxagliptin, and -1.0 kg with metformin (P values not reported). A greater proportion of patients achieved an HbA_{1c} <7.0% with saxagliptin 5 mg plus metformin and saxagliptin 10 mg plus metformin compared to saxagliptin and metformin (51.5 and 50.5 vs 25.0 and 34.7%, respectively; P values not reported). Similar results were observed with HbA_{1c} <6.5% (P values not reported).
Jadzinsky et al.[61] (2009) Metformin 500 to 2,000 mg daily and saxagliptin 5 mg QD vs metformin 500 to 2,000 mg daily and	AC, DB, MC, RCT Type 2 diabetics 18 to 77 years of age, HbA_{1c} ≥8.0 to ≤12.0%, fasting C-peptide concentration ≥1 ng/mL, and BMI ≤40 kg/m^2	N=1,306 24 weeks	Primary: Change in baseline HbA_{1c} Secondary: Change in baseline FPG and PPG $AUC_{0\text{-}3hr}$, proportion of patients achieving an HbA_{1c} <7.0 and ≤6.5%, proportion	Primary: Combination therapy significantly decreased HbA_{1c} compared to monotherapy with either saxagliptin or metformin (-2.5 and -2.5 vs -1.7 and -2.0%, respectively; P<0.0001 vs monotherapy for all). Secondary: Combination therapy significantly decreased FPG compared to monotherapy with either saxagliptin or metformin (P=0.0002 for saxagliptin 5 mg plus metformin vs saxagliptin and P<0.001 for saxagliptin 10 mg plus metformin vs saxagliptin and metformin). Similar results were observed for PPG $AUC_{0\text{-}3hr}$ (P<0.0001 for all vs monotherapy).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
saxagliptin 10 mg QD vs metformin 500 to 2,000 mg daily vs saxagliptin 10 mg QD			of patients requiring rescue for failing to achieve prespecified glycemic targets or discontinuing for lack of efficacy at 24 weeks	The proportion of patients achieving an HbA_{1c} <7.0% was significantly greater with combination therapy compared to monotherapy with either agent (60.3 and 59.7 vs 32.2 and 41.1%; P<0.0001 for all vs monotherapy). Similar results were observed for HbA_{1c} ≤6.5% (45.3 and 40.6 vs 20.3 and 29.0%; P<0.0001 for saxagliptin 5 mg plus metformin vs saxagliptin and metformin; P<0.0001 for saxagliptin 10 mg plus metformin vs saxagliptin, and P=0.0026 for saxagliptin 10 mg plus metformin vs metformin). At week 24, 7.5% of patients receiving saxagliptin 5 mg plus metformin and 21.2% of patients receiving saxagliptin 10 mg were discontinued or rescued for lack of glycemic control (P<0.0001). No significance was observed when saxagliptin 5 mg plus metformin was compared to metformin (P=0.2693). Similar results were observed with saxagliptin 10 mg plus metformin compared to either monotherapy (P<0.0001 vs saxagliptin 10 mg and P=0.0597 vs metformin).
Derosa et al.[62] (2010) Sitagliptin 100 mg QD vs metformin 850 mg BID All patients were receiving pioglitazone (15 or 30 mg/day).	DB, RCT Patients with type 2 diabetes, HbA_{1c} >7.5%, and receiving pioglitazone 30 mg/day	N=151 12 months	Primary: Body weight, BMI, HbA_{1c}, FPG, PPG, fasting plasma insulin, HOMA-IR, HOMA-B, fasting plasma proinsulin, proinsulin/fasting plasma insulin ratio, adiponectin, resistin, TNF-α, high sensitivity CRP Secondary: Not reported	Primary: A decrease in body weight and BMI were observed in patients receiving metformin, which was not observed in patients receiving sitagliptin. Significant decreases in HbA_{1c}, FPG, and PPG, and significant increases in HOMA-B were comparable between the two treatment groups. Fasting plasma insulin, fasting plasma proinsulin, proinsulin/fasting plasma insulin ratio, and HOMA-IR were decreased with both treatments. While values were lower with metformin, there were no significant differences observed between the two treatments. Sitagliptin achieved no significant changes in changes in adiponectin, resistin, TNF-α, compared to a significant increase in adiponectin and significant decreases in resistin and TNF-α achieved with metformin. High sensitivity CRP decreased significantly with both treatments, with no difference between them. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Not reported
Goldstein et al.[63] (2007) Sitagliptin 50 mg BID plus metformin 500 and 1,000 mg BID vs sitagliptin 100 mg QD vs metformin 500 and 1,000 mg BID vs placebo	DB, MC, PC, PG, RCT Type 2 diabetics 18 to 78 years of age and an HbA_{1c} of 7.5 to 11.0%	N=1,091 24 weeks	Primary: Change in baseline HbA_{1c} Secondary: Change in baseline FPG, fasting serum insulin, fasting serum proinsulin, lipid profiles, β cell function, insulin resistance; adverse events	Primary: Decreases in HbA_{1c} were significant with all active treatments as compared to placebo and for combination therapy compared to monotherapy (P<0.001). There was an additive effect seen in the combination treatment groups. The proportion of patients achieving an HbA_{1c} <7.0% was significantly greater with all active treatments compared to placebo (P<0.001). Secondary: Significant decreases in FPG were achieved between combination therapy and monotherapy, and between all active treatments compared to placebo (P<0.001). Data on fasting serum insulin and lipid profiles were not reported. Combination therapy demonstrated an additive effect, as compared to monotherapy, with regards to improvements in β cell function. HOMA-B increased with all active treatments compared to placebo (P<0.001). The combination therapy significantly increased HOMA-B compared to monotherapy (sitagliptin and low-dose metformin; P≤0.001). Significant improvements in the proinsulin:insulin ratio observed with all active treatments compared to placebo (P<0.05). Differences between combination therapy and monotherapy were also significant (P<0.05). The incidence of adverse events was similar between combination therapy and metformin. Gastrointestinal adverse events including diarrhea, nausea, abdominal pain, and vomiting were most frequently observed with metformin high-dose both as monotherapy and combination therapy. A low frequency of hypoglycemia was similar among all treatments (0.6 to 2.2%). No change in weight was observed with sitagliptin compared to all other active treatments, where there was a significant decrease in body weight (-0.6 to -1.3 kg; P<0.05) and placebo (-0.9 kg; P<0.01).
Reasner et al.[64] (2011)	DB, MC, PG, RCT	N=1,250	Primary:	Primary:

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Sitagliptin/ metformin 50/500 to 1,00 mg BID vs metformin 500 to 1,000 mg BID	Treatment-naïve type 2 diabetics 18 to 78 years of age, and an HbA_{1c} ≥7.5%	18 weeks	Change in baseline HbA_{1c} Secondary: Proportion of patients achieving an HbA_{1c} <7.0 and <6.5%, change in baseline FPG, proinsulin:insulin ratio, and β cell function	Combination therapy significantly decreased HbA_{1c} compared to metformin (-2.4 vs -1.8%; P<0.001). Secondary: A significantly greater proportion of patients receiving combination therapy achieved an HbA_{1c} <7.0% (49.2 vs 34.2%, respectively; P<0.001) and <6.5% (31.8 vs 16.0%, respectively; P<0.001) compared to patients receiving metformin. Combination therapy significantly decreased FPG compared to metformin (-3.8 vs -3.0 mg/dL; P<0.001). Combination therapy significantly decreased proinsulin:insulin ratio compared to metformin (-0.238 vs -0.186; P<0.05). Combination therapy significantly improved β cell function compared to metformin (P<0.05).
Raz et al.[65] (2008) Metformin 1,500 to 2,550 mg daily and sitagliptin 100 mg daily vs metformin 1,500 to 2,550 mg daily and placebo	DB, MC, PC, PG, RCT Type 2 diabetics 18 to 78 years of age, HbA_{1c} 7.0 to 10.0% receiving metformin or other oral antihyperglycemic agents as monotherapy or being treated with metformin in combination with other oral antihyperglycemic agents	N=190 30 weeks	Primary: Change in baseline HbA_{1c} at 18 weeks Secondary: Change in baseline FPG at 18 weeks, two-hour PPG at 18 weeks, and HbA_{1c} at 30 weeks; safety and tolerability	Primary: Sitagliptin significantly decreased HbA_{1c} compared to placebo (treatment difference, -1.0%; 95% CI, -1.4 to -0.7; P<0.001). Numerically greater decreases in HbA_{1c} were observed in patients with a higher baseline HbA_{1c}. A greater proportion of patients receiving sitagliptin achieved an HbA_{1c} <7.0% at weeks 18 and 30 compared to patients receiving placebo (13.7 and 22.1 vs 3.3 and 3.3%; P values not reported). Secondary: Sitagliptin significantly decreased FPG compared to placebo (treatment difference, -1.4 mmol/L; 95% CI, -2.1 to -0.7; P<0.001). Sitagliptin significantly decreased two-hour PPG compared to placebo (treatment difference, -3.0 mmol/L; 95% CI, -4.2 to -1.9; P<0.001). Sitagliptin significantly decreased HbA_{1c} compared to placebo at week 30 (treatment difference, -1.0%; 95% CI, -1.4 to -0.6; P<0.001). The incidence of adverse events was similar with both treatments. No serious adverse events or discontinuations due to clinical adverse events

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				were reported with sitagliptin. With placebo, there were six serious clinical adverse events that resulted in one death and two discontinuations. None of the adverse events were deemed to be drug-related. There were no differences between the two treatments in the incidences of hypoglycemia or gastrointestinal adverse events (abdominal pain, nausea, vomiting, and diarrhea). Over the 30 week period a small decrease in weight of 0.5 kg was observed with both treatments.
Derosa et al.[66] (2012) metformin + placebo vs metformin + sitagliptin All patients underwent a run-in period of 8±2 months of metformin monotherapy	DB, MC, PC, RCT Type 2 diabetic patients aged >18, drug-naïve, with poor glycemic control (HbA_{1c} level >8.0%), and overweight (body mass index [BMI] ≥25 and <30 kg/m2)	N=178 12 months	Primary: BMI, glycemic control, fasting plasma insulin (FPI), homeostasis model assessment insulin resistance index (HOMA-IR), homeostasis model assessment β-cell function index (HOMA-β), fasting plasma proinsulin (FPPr), proinsulin/fasting plasma insulin ratio (Pr/FPI ratio), C-peptide, glucagon, adiponectin (ADN), and high sensitivity-C reactive protein (Hs-CRP). Secondary: Not reported	Primary: A similar decrease of body weight and BMI was observed with both treatments at 12 months (P<0.05 for both), without any difference between the two groups. HbA_{1c} and PPG improved in both groups at six (P<0.05), nine (P< 0.01), and 12 months (P<0.001) with sitagliptin + metformin, and at nine (P<0.05) and 12 months (P<0.01) with placebo + metformin, even though sitagliptin + metformin were more effective than placebo + metformin in reducing HbA_{1c}, and PPG at 12 months (P<0.05). FPG obtained with sitagliptin + metformin was significantly lower compared to the value reached with placebo + metformin at 12 months (P<0.05). Most other parameters achieved favorable change from baseline but no significant difference between treatment groups. Sitagliptin + metformin resulted better than placebo + metformin in reducing HOMA-IR and glucagon at 12 months (P<0.05). Secondary: Not reported
Perez-Monteverde et al.[67] (2011)	DB, RCT	N=492 (Phase 1)	Primary: Change in baseline HbA_{1c}	Primary: At the end of Phase 1 (12 weeks), mean changes from baseline in HbA_{1c} were -1.0 and -0.9% with sitagliptin and pioglitazone. At the end of Phase

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Sitagliptin/ metformin vs pioglitazone 30 to 45 mg QD In Phase 1, patients were randomized to either sitagliptin 100 mg QD or pioglitazone 30 mg QD. In Phase 2, patients randomized to sitagliptin in Phase 1 were switched to sitagliptin/ metformin, and patients randomized to pioglitazone in Phase 1 were up titrated to 45 mg/day.	Patients with type 2 diabetes and HbA_{1c} 7.5 to 12.0%	12 weeks (Phase 1) plus 28 weeks (Phase 2)	Secondary: Change in baseline FPG and 2-hour PPG, proportion of patients achieving HbA_{1c} <7.0%, safety, body weight	2 (40 weeks), improvements in HbA_{1c} were greater with combination therapy compared to pioglitazone (-1.7 vs -1.4%; P=0.002). Secondary: At the end of Phase 1 (12 weeks), mean changes from baseline were -26.6 and -28.0 mg/dL for FPG and -52.8 and -50.1 mg/dL for two-hour PPG. At the end of Phase 2 (40 weeks), improvements in FPG and two-hour PPG were greater with combination therapy compared to pioglitazone (-45.8 vs -37.6 mg/dL; P=0.03 and -90.3 vs -69.1 mg/dL; P=0.001). Significantly more patients receiving combination therapy achieved an HbA_{1c} <7.0% (55.0 vs 40.5%; P=0.004). A numerically higher incidence of gastrointestinal adverse events and a significantly lower incidence of edema were observed with combination therapy compared to pioglitazone. The incidence of hypoglycemia was similarly low with both treatments. Body weight decreased with combination therapy and increased with pioglitazone (-1.1 vs 3.4 kg; P<0.001).
Wainstein et al.[68] (2012) Sitagliptin/ metformin 50/500 mg BID, titrated up to 50/1,000 mg BID vs	DB, RCT Treatment-naïve patients with type 2 diabetes HbA_{1c} 7.5 to 12.0%	N=517 32 weeks	Primary: Change from baseline HbA_{1c}, proportion of patients who achieved HbA_{1c} <7.0% Secondary:	Primary: The least squares mean changes in HbA_{1c} at week 32 were -1.9 and -1.4% with combination therapy compared to pioglitazone, respectively (between-group differences, -0.5%; P<0.001). A greater proportion of patients achieved an HbA_{1c} <7.0% at week 32 with combination therapy compared to pioglitazone (57 vs 43%; P<0.001). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
pioglitazone 30 mg/day, titrated up to 45 mg/day			Change from baseline FPG	Compared to pioglitazone, combination therapy resulted in a greater least squares mean reductions in FPG (-56.0 vs -44.0 mg/dL; P<0.001) and 2-hour PPG (-102.2 vs -82.0 mg/dL; P<0.001) at week 32. A substantially greater reduction in FPG (-40.5 vs -13.0 mg/dL; P<0.001) was observed at week 1 with combination therapy compared to pioglitazone. A greater reduction in the fasting proinsulin:insulin and a greater increased in HOMA-B were observed with combination therapy compared to pioglitazone, while greater decreases in fasting insulin and HOMA-IR, and a greater increase in quantitative insulin sensitivity check index were observed with pioglitazone compared to combination therapy. Combination therapy resulted in a decrease in body weight (-1.4 kg) and pioglitazone resulted in an increase in body weight (3.0 kg; P<0.001). Higher incidences of diarrhea (15.3 vs 4.3%; P<0.001), nausea (4.6 vs 1.2%; P=0.02), and vomiting (1.9 vs 0.0%; P=0.026), and a lower incidence of edema (1.1 vs 7.0%; P<0.001) were observed with combination therapy compared to pioglitazone. There was no difference between the two treatments in the incidence of hypoglycemia (8.4 vs 8.3%; P=0.055).
Scott et al.[69] (2008) Metformin (existing therapy) and sitagliptin 100 mg QD vs metformin (existing therapy) and rosiglitazone 8 mg QD	AC, DB, MC, PG, RCT Type 2 diabetics 18 to 75 years of age receiving stable metformin doses (≥1,500 mg/day for ≥10 weeks) and inadequate glycemic control (HbA_{1c} ≥7.0 and ≤11.0%)	N=273 18 weeks	Primary: Change in baseline HbA_{1c} Secondary: Change in baseline FPG, fasting serum insulin, fasting serum proinsulin, β cell function, insulin resistance, and lipid profile	Primary: Sitagliptin significantly decreased HbA_{1c} compared to placebo (treatment difference, -0.50%; 95% CI, -0.87 to -0.60; P≤0.001). Similar results were observed with rosiglitazone (treatment difference, -0.57%; 95% CI, -0.76 to -0.37; P value not reported). There was no difference between sitagliptin and rosiglitazone (treatment difference, -0.06%; 95% CI, -0.25 to 0.14). The proportion of patients achieving an HbA_{1c}<7.0% was significantly greater with sitagliptin (55%; P=0.006) and rosiglitazone (63%; P value not reported) compared to placebo (38%). There was no difference between sitagliptin and rosiglitazone (treatment difference, 8%; 95% CI, -6 to 22; P value not reported). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs metformin and placebo				Sitagliptin (treatment difference, -17.8 mg/dL; 95% CI, -27.6 to -8.1; P≤0.001) and rosiglitazone (treatment difference, -30.6 mg/dL; 95% CI, -40.6 to -20.7; P value not reported) significantly decreased FPG compared to placebo. Rosiglitazone significantly decreased FPG compared to sitagliptin (treatment difference, -12.8 mg/dL; 95% CI, -22.6 to -3.0; P value not reported). Sitagliptin (treatment difference, 16.3; 95% CI, 2.3 to 30.3; P≤0.05) and rosiglitazone (treatment difference, 15.3; 95% CI, 1.0 to 29.6; P value not reported, respectively) had significant increases in HOMA-B compared to placebo. The increase in HOMA-B was not significantly different between sitagliptin and rosiglitazone (P value not reported). Rosiglitazone significantly decreased HOMA-IR compared to placebo (treatment difference, -2.4; 95% CI, -3.4 to -1.4; P value not reported) and sitagliptin (treatment difference, -1.6; 95% CI, -2.6 to -0.7; P value not reported). There decrease in HOMA-IR was similar between sitagliptin and placebo (treatment difference, -0.7; 95% CI, -1.7 to 0.2; P value not reported). Rosiglitazone significantly decreased fasting serum insulin compared to placebo (treatment difference, -3.4 µIU/mL; 95% CI, -5.5 to -1.4; P value not reported) and sitagliptin (treatment difference, -3.53 µIU/mL; 95% CI, -5.50 to -1.40; P value not reported). The proinsulin:insulin ratio was similar across all treatments. Compared to placebo, LDL-C decreased with sitagliptin (treatment difference, -5.3 mg/dL; 95% CI, -14.5 to 3.9; P value not reported) and increased with rosiglitazone (treatment difference, 9.5 mg/dL; 95% CI, 0.2 to 18.7; P value not reported). Compared to placebo, TC significantly decreased with sitagliptin (treatment difference, -6.3 mg/dL; 95% CI, -11.8 to -0.9; P≤0.05) and increased with rosiglitazone (treatment difference, 5.1 mg/dL; 95% CI, -0.3 to 10.6; P value not reported). Compared to placebo, TG significantly decreased with sitagliptin

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				(treatment difference, -16.7 mg/dL; 95% CI, -27.9 to 5.5; P≤0.05) and increased with rosiglitazone (treatment difference, 1.2 mg/dL; 95% CI, -10.1 to 12.6; P value not reported). Compared to sitagliptin, lipid profiles measurements significantly increased with rosiglitazone (P values not reported).
Hermansen et al.[70] (2007) Sitagliptin 100 mg QD, glimepiride 4 to 8 mg daily, and metformin 1,500 to 3,000 mg daily vs sitagliptin 100 mg QD plus glimepiride 4 to 8 mg daily vs glimepiride 4 to 8 mg daily, metformin 1,500 to 3,000 mg daily, and placebo vs glimepiride 4 to 8 mg daily plus placebo	DB, DD, MC, PC, PG, RCT Type 2 diabetics 18 to 75 years of age, HbA_{1c} 6.7 to 10.6%, and inadequately controlled on glimepiride with or without metformin	N=441 24 weeks	Primary: Change in baseline HbA_{1c} Secondary: Change in baseline FPG, plasma lipids, β cell function, and insulin resistance; safety and tolerability	Primary: Sitagliptin significantly decreased HbA_{1c} (P<0.001) compared to placebo (treatment difference, -0.74%; 95% CI, -0.90 to -0.57). Patients who were receiving triple therapy (-0.89%; 95% CI, -1.10 to -0.68) had a significantly greater decrease in HbA_{1c} compared to patients receiving combination therapy (-0.57%; 95% CI, -0.82 to -0.32). A significantly greater proportion of patients receiving sitagliptin achieved an HbA_{1c} <7.0% compared to patients receiving placebo (17.1 vs 4.8%; P<0.001). A significantly greater proportion of patients receiving triple therapy achieved an HbA_{1c} <7.0% compared to patients receiving combination therapy with glimepiride plus metformin (22.6 vs 1.0%; P<0.001). No difference was observed between combination therapy with glimepiride plus sitagliptin compared to glimepiride (10.8 vs 8.7%; P<0.638). Secondary: Sitagliptin significantly decreased FPG compared to placebo (treatment difference, -20.1 mg/dL; 95% CI, -28.4 to -11.8; P<0.001). Sitagliptin demonstrated neutral effects on plasma lipids compared to placebo (specific figures not reported). A significant increase in HOMA-B was achieved with sitagliptin compared to placebo (11.3 [95% CI, 4.4 to 18.1] vs -0.7% [95% CI, -8.2 to 6.8]; P<0.001). There were no differences in fasting proinsulin, proinsulin:insulin ratio, HOMA-IR, and quantitative insulin sensitivity check index between the treatments. Sitagliptin significantly increased fasting insulin compared to placebo (1.8 vs 0.1 μIU/mL; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Sitagliptin was well tolerated, both in combination with glimepiride and in triple therapy. There was a higher incidence of overall adverse events (difference of 8.0%; 95% CI, 2.2 to 13.9) observed with sitagliptin compared to placebo, with the majority of that difference due to rates of minor to moderate hypoglycemia. A significant increase in body weight of 0.8 kg (95% CI, 0.4 to 1.2) was noted with sitagliptin compared to a slight decrease in weight with placebo (-0.4 kg; 95% CI, -0.8 to 0.1).
Rigby et al.[71] (2010) Rosiglitazone 4 mg daily (QD or BID) and metformin (existing therapy) vs sitagliptin 100 mg QD and metformin (existing therapy) vs colesevelam 3.75 g daily (QD or BID) and metformin (existing therapy)	OL Patients 18 to 80 years of age with type 2 diabetes mellitus who had inadequate glycemic control (HbA_{1c} 6.5% to 10.0% on a stable regimen of metformin (1,500-2,550 mg daily), with LDL-C ≥60 mg/dL and TGs <500 mg/dL	N=169 16 weeks	Primary: Change in HbA_{1c} from baseline to week 16 Secondary: Change in HbA_{1c} from baseline to week 8, change in FPG and fasting insulin from baseline to weeks 8 and 16, change in 2-hour PPG and postprandial insulin after a meal tolerance test, change in lipid parameters, percentage of participants who achieved an HbA_{1c} reduction >0.7% from baseline, percentage of participants who achieved HbA_{1c} <7.0%	Primary: At week 16, HbA_{1c} was reduced from baseline in all treatment groups (LS mean change from baseline): colesevelam -0.3% (95% CI, -0.52 to -0.02; P=0.031); rosiglitazone -0.6% (95% CI, -0.83 to -0.32; P<0.001); sitagliptin -0.4% (95% CI, -0.64 to -0.13; P=0.009). Secondary: At week 8, HbA_{1c} was reduced from baseline with colesevelam and sitagliptin (-0.3%; P=0.006 and -0.5%; P<0.001, respectively), but not with rosiglitazone (-0.2%; P=0.109). FPG was significantly reduced from baseline at week 8 and week 16 in all treatment groups. The 2-hour PPG levels were significantly reduced from baseline at week 16 in all treatment groups. There was no significant change in fasting insulin or 2-hour postprandial insulin from baseline to week 16 in any treatment group. Insulin resistance did not change with colesevelam or sitagliptin; however, there was a significant reduction with rosiglitazone from baseline to week 16 (P=0.008). LDL-C was significantly reduced from baseline with colesevelam (-11.6%; P=0.001), but was significantly increased with both rosiglitazone (7.8%; P=0.040) and sitagliptin (7.7%; P=0.011).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				TC levels were unchanged from baseline with colesevelam and sitagliptin; however, they were significantly increased with rosiglitazone from baseline to week 16 (P=0.006). Non-HDL-C levels were unchanged with colesevelam; however, they were significantly increased with rosiglitazone (P=0.001) and sitagliptin (P=0.029). Median TG levels increased significantly from baseline with colesevelam (P<0.00l) and rosiglitazone (P<0.00l); however, sitagliptin did not significantly affect TG levels. HDL-C levels did not change significantly from baseline with any treatment. At week 16, 23.2% of patients in the colesevelam group, 48.l % of patients in the rosiglitazone group, and 34.5% of patients in the sitagliptin group achieved a reduction in HbA_{1c} of 0.7% or greater from baseline. In addition, 10 patients in the colesevelam group, 19 in the rosiglitazone group, and 15 in the sitagliptin group achieved HbA_{1c} <7.0%. The percentages of patients who had an adverse event were 61.4% in the colesevelam group, 46.4% in the rosiglitazone group, and 48.2% in the sitagliptin group. Most of the adverse events were mild to moderate in severity.
Douek et al.[72] (2005) Metformin titrated to 2 grams daily vs placebo All patients received insulin regimens.	DB, MC, PC, RCT Patients ≤75 years of age with type 2 diabetes for ≥2 years starting insulin due to inadequate glycemic control on oral agents	N=183 1 year	Primary: Change in baseline weight Secondary: Changes in baseline HbA_{1c}, insulin dose, frequency of hypoglycemia, treatment satisfaction, well-being from baseline	Primary: Metformin was associated with less weight gain than placebo (mean, 6.1 vs 7.6 kg; adjusted difference, 1.5 kg; 95% CI, 0.2 to 2.9; P=0.02). Secondary: Metformin was associated with a greater decrease in HbA_{1c} (1.5 vs 1.3%; adjusted difference, 0.5%; 95% CI, 0.1 to 0.9%; P=0.02), and a lower insulin requirement (62 vs 86 units; adjusted difference, 25 units; 95% CI, 15 to 34; P<0.001) compared to placebo. Severe hypoglycemia was reported in 10 patients (13%) taking metformin and in one patient (1%) taking placebo (RR, 9.48; 95% CI, 1.24 to 72.2; P=0.009). Treatment satisfaction improved more in patients on metformin than on placebo (P<0.001) as did the positive-well-being score (P=0.02).
Wulffelé et al.[73]	DB, PC, RCT	N=390	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2002) Metformin 850 to 2,250 mg daily vs placebo All patients received insulin regimens.	Patients 30 to 80 years of age with type 2 diabetes who had received a diagnosis of diabetes after the age of 25, who had experienced no episodes of ketoacidosis, and whose past blood-glucose lowering treatments consisted of oral agents but now consisted of insulin or a combination of insulin and metformin	16 weeks interim analysis	Changes in HbA_{1c}, insulin requirements, body weight, BMI, BP, and plasma lipids Secondary: Not reported	Mean HbA_{1c} was 6.94% for metformin and 7.6% for placebo (P<0.0001). Mean daily glucose level decreased from 8.8±2.1 to 8.5±1.7 mmol/L in the placebo group (mean decrease, -0.16; 95% CI, -0.53 to 0.22 mmol/L) and from 8.8±2.2 to 7.8±1.7 mmol/L in the metformin group (mean decrease, -1.04; 95% CI, -1.5 to 0.52 mmol/L; P=0.006 vs placebo). Mean insulin requirements were significantly different for metformin (63.8 IU) as compared to placebo (71.3 IU; P<0.0001). Mean weight reduction was significant for metformin (-0.4 kg) as compared to placebo (1.2 kg; P<0.01). BMI increased by 0.4±2 kg in the placebo group and decreased by 0.2±0.9 kg in the metformin group (P=0.01 vs placebo). There was a small increase in mean SBP and DBP in both groups, but the difference was not significant between the groups (P=0.87 for SBP and P=0.92 for DBP). In the placebo group, mean plasma TC and LDL-C concentrations decreased by -0.04 mmol/L (95% CI, -0.15 to 0.07) and -0.02 mmol/L (95% CI, -0.16 to 0.06), respectively. In the metformin group, mean plasma TC and LDL-C concentrations decreased by -0.25 mmol/L (95% CI, -0.35 to -0.15) and -0.21 mmol/L (95% CI, -0.33 to -0.15), respectively (P<0.01 vs placebo for both). Changes in plasma HDL-C and TG concentrations were not significant in either group. Mild and transient gastrointestinal complaints were reported more frequently in the metformin group (56%) as compared to the placebo group (13%; P<0.0001). Secondary: Not reported
Yki-Järvinen et al.[74]	MC, OL, PG, RCT	N=110	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2006) Bedtime insulin glargine plus metformin (G+MET) vs bedtime NPH plus metformin (NPH+MET) Initial bedtime doses were 10 units for patients who were previously on metformin alone and 20 units for patients who were previously on both metformin and a sulfonylurea. All sulfonylurea medications were discontinued according to the study protocol. Insulin doses were titrated to achieve an FPG 72 to 100 mg/dL in both groups.	Men and women 35 to 75 years of age with type 2 diabetes previously treated with a stable dose of sulfonylurea and metformin (>1.5 g) or metformin alone for at least 3 months prior to screening, with a BMI 20 to 40 kg/m^2, HbA_{1c} ≥8.0%, FPG ≥7 mmol/L measured during self monitoring of blood glucose between 4 and 2 weeks prior to study start, and fasting C-peptide ≥0.33 nmol/L	36 weeks	Change in HbA_{1c} from baseline Secondary: Diurnal glucose concentrations, symptomatic hypoglycemia	At 36 weeks, HbA_{1c} decreased from 9.13±0.15% to 7.14±0.12% and from 9.26±0.15% to 7.16±0.14% in the G+MET and NPH+MET groups, respectively. The changes in HbA_{1c} were determined to be not significant between groups (P value not reported). Secondary: The diurnal profiles were consistently lower in the G+MET group compared to the NPH+MET group (8.6±0.3 vs 10.1±0.3 mmol/L, respectively; P=0.002). During the first 12 weeks, the G+MET group had significantly lower number of episodes of symptomatic hypoglycemia than the NPH+MET group, but the rates became similar thereafter. The frequency of hypoglycemia averaged 5.4 and 8.0 episodes/patient-year for the G+MET and NPH+MET groups, respectively (P=0.12).
Horton et al.[75] (2000)	DB, PC, PRO, RCT	N=701	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Nateglinide 120 mg TID before each meal plus metformin 500 mg TID immediately after the start of each meal vs nateglinide 120 mg TID before each meal vs metformin 500 mg TID immediately after the start of each meal vs placebo	Patients ≥30 years of age with type 2 diabetes for ≥3 months with a BMI 20 to 35 kg/m^2, and all patients needed to have been treated with diet alone with an HbA_{1c} 6.8 to 11.0% and FPG level ≤15 mmol/L	24 weeks	Change in HbA_{1c}, FPG, glucose AUC after Sustacal challenge from baseline Secondary: Not reported	Adjusted mean change from baseline in HbA_{1c}, FPG, and glucose AUC after Sustacal challenge were significantly reduced from baseline (P≤0.0001) in patients receiving active treatment. HbA_{1c}, FPG, and glucose AUC were all significantly reduced compared to placebo (P≤0.001), except from glucose AUC with metformin monotherapy. The decrease in HbA_{1c} was greater for metformin compared to nateglinide, the between group difference was small (0.3% difference; P≤0.01). The decrease in FPG was greater with the metformin group compared to the nateglinide group, the between group difference was 0.9 mmol/L (P<0.001). The combination of nateglinide plus metformin was additive (HbA_{1c}, -1.4% and FPG, -2.4 mmol/L; P≤0.01 vs either monotherapy). After a Sustacal challenge, there was a greater reduction in mealtime glucose with nateglinide compared to metformin or placebo ($AUC_{0\text{-}130\ min}$, -2.1, -1.1, and 0.6 mmol/hr/L, respectively; P≤0.0001). A greater reduction was seen with nateglinide plus metformin ($AUC_{0\text{-}130\ min}$, -2.5 mmol/hr/L; P≤0.0001 vs metformin and placebo). Secondary: Not reported
Marre et al.[76] (2002) Metformin 1,000 mg BID and nateglinide 60 to 120 mg TID before meals vs	DB, MC, PG, RCT Patients ≥30 years of age with type 2 diabetes for ≥6 months with HbA_{1c} 6.8 to 11.0%, BMI 20 to 35 kg/m^2, and were treated with metformin for a minimum of 3	N=467 24 weeks	Primary: Change in HbA_{1c} from baseline Secondary: Change in FPG, body weight, and lipid profile (TC, fasting TGs, LDL-C, HDL-C)	Primary: Mean HbA_{1c} was reduced significantly from baseline when compared to the placebo group for the nateglinide 60 mg group (-0.36%; 95% CI, -0.59 to -0.13; P=0.003) and for the nateglinide 120 mg group (-0.51%; 95% CI, -0.82 to -0.36; P<0.001) at end point. Dose-dependent reduction in HbA_{1c} was seen with nateglinide irrespective of baseline parameters, with larger mean reductions seen with nateglinide 120 mg. There was little or no change in HbA_{1c} at end point in the placebo group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
metformin 1,000 mg BID and placebo	months and stabilized at a dose of ≥1,500 mg/day for ≥4 weeks prior to study entry			Secondary: There were modest changes from baseline in FPG in the nateglinide groups and an increase was seen in the placebo group, the difference compared to baseline was significant in both the nateglinide 60 and 120 mg groups (P=0.044 and P=0.003, respectively). There were no notable changes in body weight at end point in the patients that received placebo (0.1 kg) or nateglinide 60 mg (0.4 kg). There was a significant increase (P<0.001) in mean weight of 0.9 kg in the nateglinide 120 mg group as compared to baseline. Fasting TGs were significantly reduced in the nateglinide 120 mg group as compared to the placebo group at end point (P=0.042). The mean changes in TC, LDL-C, and HDL-C remained almost unchanged throughout the study.
Raskin et al.[77] (2003) Metformin 1,000 mg BID and nateglinide 120 mg TID before meals vs metformin 1,000 mg BID and repaglinide 1 to 4 mg TID before meals	MC, OL, PG, RCT Patients ≥18 years of age with type 2 diabetes for ≥3 months, BMI 24 to 42 kg/m^2, HbA_{1c} 7.0 to 12.0% on previous monotherapy with a sulfonylurea, metformin, or low dose glyburide plus metformin	N=192 16 weeks	Primary: Final HbA_{1c} values and changes in HbA_{1c} from baseline Secondary: Changes in FPG and assessment of glucose area under the time concentration curves from 0 to 240 minutes ($AUC_{0\text{-}240\ min}$), insulin $AUC_{0\text{-}240\ min}$, and glucagon $AUC_{0\text{-}240\ min}$ after a liquid test meal at baseline and at study end point	Primary: Mean HbA_{1c} changes from baseline were significantly greater in the repaglinide group compared to the nateglinide group (-1.28 vs -0.67%; P<0.001). The final HbA_{1c} at 16 weeks was 7.1±1.1% for the repaglinide group and 7.5±1.4% for the nateglinide group. The percent of patients who achieved final HbA_{1c} values ≤7.0% was 59% for the repaglinide group and 47% for the nateglinide group (P value not reported). Secondary: FPG values were significantly different between the two treatment groups with one week of therapy. Mean changes in FPG values from baseline were significantly greater for the repaglinide group (-39 vs -21 mg/dL for nateglinide group; P=0.002). The final FPG at 16 weeks was 150.0±45.1 mg/dL for the repaglinide group and 170±52 mg/dL for the nateglinide group. At the end of the 16 week maintenance study, 48% of the repaglinide group had reductions of FPG values >40 mg/dL and 26% of the nateglinide group had a response of this magnitude.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Mean end point reductions in PPG levels from baseline were not significantly different between the groups (glucose $AUC_{0\text{-}240\ min}$). The treatments were also similar for changes in insulin $AUC_{0\text{-}240\ min}$ and glucagon $AUC_{0\text{-}240\ min}$ during the study (P values not reported). There were no patients in either group who experienced major hypoglycemic episodes (requiring the assistance of another person). The most frequent adverse event in both groups was upper respiratory infection (12 vs 21%). Adverse events that occurred from 3 to 8% included nausea, viral infection, accidental injury, sinusitis, diarrhea, and headache. The repaglinide group had 5% incidence of chest pain and arthralgia, as compared to 1% for each in the nateglinide groups. Mean changes from baseline in weight were small for both groups, 0.6 kg gain for repaglinide compared to 0.5 kg loss with nateglinide.
Gerich et al.[78] (2003) PRESERVE-β Study Metformin 500 to 2,000 mg daily plus nateglinide 120 mg TID vs metformin 500 to 2,000 mg daily plus glyburide 1.25 to 10 mg daily	DB, MC, RCT Men and women 18 to 77 years of age with type 2 diabetes, drug naïve, HbA_{1c} 7.0 to 11.0%, FPG ≤15 mmol/L, BMI 22 to 45 kg/m^2 and inadequately controlled on diet and exercise	N=428 104 weeks	Primary: Change in HbA_{1c} from baseline (average of weeks -2 and 0) to week 104 Secondary: Change from baseline to week 104 in FPG, body weight, $AUC_{0\text{-}120\ min}$ of glucose during oral glucose tolerance tests	Primary: Both treatments maintained similar reductions in HbA_{1c}. The mean change in HbA_{1c} from baseline to week 104 in the nateglinide plus metformin group (-1.2±0.1%) was similar (P=0.1730) to that in the glyburide plus metformin group (-1.5±0.1%). The changes in HbA_{1c} were significant for both groups as compared to baseline (P<0.0001) after one and two years of treatment and there was no significant difference between the groups. Secondary: Mean change in FPG was -1.6±0.2 mmol/L in patients in the nateglinide plus metformin group (P<0.0001 vs baseline) and -2.4±0.2 mmol/L in patients in the glyburide plus metformin group (P<0.0001 vs baseline; P=0.0078 vs nateglinide plus metformin). Body weight decreased in the nateglinide plus metformin group (-0.4±0.4 kg) and increased in the glyburide plus metformin group (0.8±0.5 kg). The change from baseline was significant for the glyburide plus metformin group (P=0.0011) only (P=0.8413 for the nateglinide plus metformin group). The difference between groups was statistically significant (P=0.0115).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				No data was reported for AUC of glucose during oral glucose tolerance tests.
Schwarz et al.[79] (2008) Metformin 2,000 mg QD and nateglinide 120 mg TID before meals vs metformin 2,000 mg QD and glyburide 10 mg QD	AC, DB, MC, RCT Men and women ≥65 years of age with type 2 diabetes, drug naïve, HbA_{1c} 7.0 to 11.0%, FPG ≤15 mmol/L, BMI of 22 to 45 kg/m^2	N=69 104 weeks	Primary: Change in HbA_{1c} from baseline Secondary: Change from baseline to week 104 in FPG, two-hour PPG using the incremental AUC ($AUC_{0\text{-}120\ min}$) of glucose during oral glucose tolerance tests, the proportion of patients achieving a target HbA_{1c} <7.0 or ≤6.5%, adverse events	Primary: Similar reductions in HbA_{1c} were seen with both treatments. The average change in HbA_{1c} from baseline to week 104 in the nateglinide plus metformin group (-1.2±0.2%) was similar (P=0.310) to that in the glyburide plus metformin group (-1.2±0.1%). The changes in HbA_{1c} were significant for both groups as compared to baseline (P<0.001) after two years of treatment and there was no significant difference between the groups. Secondary: Mean change in FPG was -26±6 mg/dL in patients receiving nateglinide plus metformin (P<0.001 vs baseline) and -36±6 mg/dL in patients receiving glyburide plus metformin (P<0.001 vs baseline) (P=0.234 between the groups). There was no significant changes in two-hour PPG from baseline for nateglinide plus metformin glyburide plus metformin groups (-15±7 mg/dL; P=0.071 and -8±8 mg/dL; P=0.385, respectively). The proportion of patients who achieved a target HbA_{1c} <7.0% in the nateglinide plus metformin group was not significantly different compared to the glyburide plus metformin group (70 vs 65%, respectively; P=0.736). Similar proportions of patients in the nateglinide plus metformin group and the glyburide plus metformin group maintained a target HbA_{1c} of ≤6.5% (40 and 60%, respectively; P=0.206). Approximately 94% of patients in the nateglinide plus metformin group and 88% of patients in the glyburide plus metformin group reported one or more adverse events. One mild hypoglycemic event occurred with nateglinide plus metformin treatment vs 8 mild-to-severe hypoglycemic events with glyburide plus metformin treatment (P<0.023).
Derosa et al.[80] (2009)	DB, MC, PG, RCT	N=248 12 months	Primary: Changes in BMI, FPG and PPG,	Primary: BMI did not show any significant change during the study.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Metformin 1,500 to 3,000 mg daily plus nateglinide 60 mg TID vs metformin 1,500 to 3,000 mg daily plus glyburide 7.5 to 12.5 mg daily	Patients ≥18 years of age with type 2 diabetes, HbA_{1c} >7.0%, BMI 25 to 28 kg/m^2, and hypertensive (SBP/DBP, >130/≥85 mmHg)		HbA_{1c}, fasting and postprandial plasma insulin, HOMA index, and lipid profile, BP	A significant reduction in HbA_{1c} was shown after 9 months (P<0.05) and 12 months (P<0.01) in the nateglinide group compared to the baseline value. A significant reduction in HbA_{1c} was seen with glyburide after 12 months (P<0.05) compared to baseline. The HbA_{1c} at 12 months was 6.4% in the nateglinide group compared to 7.3% in the glyburide group (P<0.05). After nine and 12 months, mean FPG levels were significantly decreased in the nateglinide and glyburide groups (P<0.05 and P<0.01, respectively) compared to baseline. Significant changes in PPG were found at nine months (P<0.05) in the nateglinide group and after 12 months in glyburide and nateglinide groups (P<0.05 and P<0.01, respectively) compared to baseline. Fasting plasma insulin and postprandial plasma insulin did not show any significant change after three, six, nine and 12 months in both groups compared to the baseline. HOMA index decrease was obtained only at 12 months (P<0.05) compared to the baseline value in both groups, No significant change was observed in TC, LDL-C, HDL-C, TG, Apo A-I, Apo B, SBP, DBP and heart rate in either group after three, six, nine and 12 months.
Wang et al.[81] (abstract) (2011) Repaglinide 1 mg TID, titrated up to 4 mg TID vs repaglinide 1 mg TID plus metformin	AC, OL, PG, RCT Patients 18 to 75 years of age with type 2 diabetes, HbA_{1c} >8.5%, BMI ≤35 kg/m^2, and who were naïve to oral antidiabetic agents,	N=432 16 weeks	Primary: Change in baseline HbA_{1c} Secondary: FPG, two-hour PPG, seven-point plasma glucose, safety	Primary: Mean HbA_{1c} reduction was 4.51±1.64% with combination therapy and 4.05±1.59% with repaglinide. Estimated mean treatment difference for combination therapy vs repaglinide was -0.30% (95% CI, -0.49 to -0.11; P< 0.01). Secondary: Combination therapy demonstrated significant improvements compared to repaglinide in FPG, seven-point plasma glucose, and lunchtime and dinnertime two-hour PPG (P<0.05 for all).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
500 mg TID, titrated up to 4 mg TID and 500 mg TID				Hypoglycemia rates were 2.04 events/patient-year with combination therapy compared to 1.35 events/patient-year with repaglinide (P=0.058). Adverse events were comparable between the two treatments.
Moses et al.[82] (1999) Repaglinide 0.5 to 4 mg TID before each meal plus metformin 1,000 to 3,000 mg/day vs repaglinide 0.5 to 4 mg TID before each meal vs metformin 1,000 to 3,000 mg/day	DB, MC, PG, RCT Patients 40 to 75 years of age with type 2 diabetes treated with metformin alone (1 to 3 g/day) for >6 months and had not achieved optimal glycemic control (HbA_{1c} >7.0%) and BMI ≥21 kg/m^2	N=83 3 months	Primary: Change in baseline HbA_{1c} and FPG Secondary: Change in fasting insulin, C-peptide levels, fasting TG, TC, HDL-C, LDL-C, FFA, body weight	Primary: Patients in the metformin plus repaglinide group had a significant decrease in HbA_{1c} from 8.3 to 6.9% (P=0.0016) and FPG from 10.2 to 8.0 mmol/L (P=0.0003) compared to baseline. There were no significant changes in HbA_{1c} or FPG for patients receiving metformin alone and repaglinide alone. The HbA_{1c} and FPG changes from baseline for metformin plus repaglinide vs metformin alone and metformin plus repaglinide vs repaglinide were significant (P<0.05 for all). Secondary: Fasting insulin and C-peptide levels increased significantly from baseline in both groups receiving repaglinide (P<0.05 for both). Lipid levels (TC, HDL-C, LDL-C, TG, FFA) did not change significantly from baseline in the metformin plus repaglinide group. No significant differences were found between the metformin plus repaglinide group and the monotherapy groups. In both groups receiving repaglinide there was an increase in body weight which was significant compared to baseline (P<0.05 for both).
Civera et al.[83] (2008) Metformin 850 mg BID, repaglinide 2 mg TID before meals, and NPH insulin before dinner vs metformin 850 mg BID and NPH insulin before dinner	OL, PG Patients with poorly controlled type 2 diabetes despite being on two or more oral antidiabetic drugs	N=37 24 weeks	Primary: HbA_{1c}, hypoglycemia, body weight Secondary: Not reported	Primary: The HbA_{1c} was lower in the repaglinide triple therapy group (7.2%) compared to the metformin plus NPH insulin group (8.8%; P=0.02) and the NPH insulin group (8.4%; P=0.02). The absolute reduction in HbA_{1c} was -2.4% in the repaglinide triple therapy group compared to -0.7% (P=0.01) in the metformin plus NPH insulin group and -1.4% in the insulin NPH group. Lower PPG values were seen with the repaglinide triple therapy group compared to the other two treatment groups (P<0.01). Significant differences in weight gain and hypoglycemia were not seen.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs NPH insulin BID				Secondary: Not reported
Black et al.[84] (2007) Meglitinide vs meglitinide plus metformin vs meglitinide plus insulin vs metformin vs placebo	MA (15 trials) Patients with type 2 diabetes	N=3,781 Duration varied	Primary: Mortality and morbidity Secondary: Change in HbA_{1c}, weight or BMI, hypoglycemia, adverse effects, quality of life	Primary: No trials reported the effect of meglitinides on mortality and morbidity. Secondary: In the 11 trials comparing meglitinides to placebo, both repaglinide and nateglinide resulted in reductions in HbA_{1c} (0.1 to 2.1% and 0.2 to 0.6%, respectively). In two trials comparing repaglinide to nateglinide, reduction in HbA_{1c} was similar. When compared to metformin, both repaglinide and nateglinide showed similar or slightly smaller reduction in HbA_{1c} compared to metformin. The combination therapy of metformin plus a meglitinide showed a clinically significant reduction in HbA_{1c} compared to metformin. Weight gain was generally greater in patients receiving meglitinides compared to patients receiving metformin. Evidence from the meglitinide trials with metformin suggests that both repaglinide and nateglinide had fewer gastrointestinal adverse events including diarrhea. There was no evidence of serious adverse events associated with meglitinides. There were more reports of hypoglycemia episodes in patients receiving meglitinides compared to patients receiving placebo. In the two head-to-head trials of repaglinide and nateglinide, fewer patients receiving nateglinide reported hypoglycemia symptoms (2 vs 7%). When compared to metformin, patients receiving meglitinides reported more hypoglycemia episodes. There were two trials that assessed quality of life in patients receiving repaglinide vs placebo and in patients receiving repaglinide plus insulin vs metformin plus insulin. There were no substantial changes in quality of life using a variety of validated diseases specific and nonspecific tools. Treatment satisfaction using the World Health Organization Diabetes

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Treatment Satisfaction Questionnaire improved significantly in patients receiving repaglinide compared to patients receiving placebo.
Bayraktar et al.[85] (1996) Metformin 500 mg TID and sulfonylurea vs acarbose 50 to 100 mg TID and sulfonylurea	RCT, XO Patients from 30 to 63 years of age with type 2 diabetes for 2 to 20 years, HbA_{1c} >8.5%, FPG >7.7 mmol/L, or a PPG>10 mmol/L on maximum doses of gliclazide† (240 mg daily)	N=18 20 weeks	Primary: Changes in FPG, PPG, HbA_{1c}, TG, cholesterol, fibrinogen, insulin levels, and C-peptide levels from baseline Secondary: Not reported	Primary: Mean FPG, PPG, and HbA_{1c} decreased at the end of each combination treatment period as compared with baseline levels (P<0.05). PPG level in the acarbose group was lower than the level achieved by the group using metformin (P<0.05). There was a significant decrease between pre- and posttreatment two-hour PPG levels in each group (-5.3±0.4 for acarbose vs -2.9±0.3 for metformin, P<0.05). There were small reductions in fibrinogen, insulin, and C-peptide levels in each group, but the differences were not statistically significant. Secondary: Not reported
Abbasi et al.[86] (2004) Metformin 500 to 1,000 mg BID added to existing sulfonylurea monotherapy vs metformin 500 to 1,000 mg BID added to existing dietary therapy	RCT Patients with type 2 diabetes with relatively poor glycemic control with FPG >9.5 mmol/L on dietary therapy alone or sulfonylurea monotherapy, BMI <40 kg/m^2, and no apparent cardiovascular disease	N=31 12 weeks	Primary: Changes in fasting glucose, HbA_{1c}, lipid concentrations Secondary: Not reported	Primary: FPG decreased to a similar degree with diet therapy (metformin) (12.45±0.48 vs 9.46±0.47 mmol/L; P<0.001) and combined sulfonylurea plus metformin (14.09±0.51 vs 10.57±0.85 mmol/L; P=0.001). The changes in the diet therapy (metformin) group compared to the combined sulfonylurea plus metformin group was not significant (P=0.58). Changes in fasting HbA_{1c} from baseline were significant for diet therapy (metformin) (P<0.001) and combined sulfonylurea plus metformin (P<0.002). The changes were not significant when compared to each other (P=0.30). Fasting TC, TG, HDL-C, and LDL-C did not change significantly in either treatment group (P=0.64, P=0.34, P=0.48, and P=0.85, respectively) for diet therapy (metformin) compared to combined sulfonylurea plus metformin. Fasting remnant lipoprotein cholesterol concentrations were significantly lower in the diet therapy (metformin) group as compared to baseline

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				(0.43±0.09 vs 0.34±0.07 mmol/L; P=0.02). The changes were not significant for diet therapy (metformin) compared to combined sulfonylurea plus metformin (P=0.06). Concentrations of FFA and remnant lipoprotein cholesterol concentrations were lower to a similar degree in both groups, whereas day long plasma insulin concentrations were unchanged. Changes in LDL particle diameter and percent of small dense LDL particles between the groups were not significant at end point (P=0.28 and P=0.73, respectively). Secondary: Not reported
DeFronzo et al.[87] (1995) <u>Protocol 1:</u> Metformin 850 to 2,550 mg daily vs placebo <u>Protocol 2:</u> Metformin plus glyburide vs metformin 500 to 2,500 mg daily vs glyburide 5 to 10 mg BID	2 DB, PG, RCT Moderately obese patients with type 2 diabetes inadequately controlled by diet (Protocol 1) or diet plus glyburide (Protocol 2)	<u>Protocol 1</u> N=289 29 weeks <u>Protocol 2</u> N=632 29 weeks	Primary: Changes in plasma glucose, HbA_{1c}, plasma insulin, lipids, plasma lactate Secondary: Not reported	Primary: <u>Protocol 1:</u> As compared to the placebo group, the metformin group had lower mean FPG concentrations (189±5 vs 244±6 mg/dL; P<0.001). HbA_{1c} levels were also lower in the metformin group (7.1±0.1 vs 8.6±0.2%; P<0.001). The changes from baseline for TC and LDL-C for metformin were significant compared to placebo (P=0.001 and P=0.019, respectively). Fasting plasma lactate levels were similar at all times during the active-treatment in both groups. <u>Protocol 2:</u> Patients in the metformin plus glyburide combination group, compared to the glyburide alone group, had lower mean FPG concentrations (187±4 vs 261±4 mg/dL; P<0.001), and HbA_{1c} values (7.1±0.1 vs 8.7±0.1%; P<0.001). The effect of metformin alone was similar to that of glyburide alone. The changes from baseline were significant compared to glyburide for the following: TC, metformin (P=0.011) and metformin plus glyburide (P=0.001); LDL-C, metformin (P=0.009) and metformin plus glyburide (P=0.001); and TG, each glyburide and metformin plus glyburide (P=0.001)

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Fasting plasma lactate did not change in any of the groups in the course of treatment. Secondary: Not reported
Goldstein et al.[88] (2003) Metformin 500 to 2,000 mg daily vs glipizide 15 mg BID vs glipizide/ metformin 5/500 mg daily (dose titrated up to 4 tablets per day)	DB, MC, PG, RCT Patients with type 2 diabetes and inadequate glucose control (HbA_{1c} 7.5 to 12.0%) despite monotherapy with at least half the maximum labeled daily dose of a sulfonylurea, FPG <300 mg/dL, and BMI ≥25 to ≤40 kg/m^2	N=247 18 weeks	Primary: Change in HbA_{1c} Secondary: Changes in FPG, three-hour PPG, area under the concentration-time curve (AUC), three-hour postprandial insulin incremental AUC during three hours after a standard test meal, fasting insulin level, serum lipid profiles, body weight	Primary: The decreases in HbA_{1c} were significantly greater in the glipizide/metformin group compared to either of the monotherapy groups (P<0.001). A total of 36.6% of patients receiving glipizide/metformin, 8.9% of patients receiving glipizide, and 9.9% of patients receiving metformin had an HbA_{1c} <7.0% at the final visit. Secondary: Combination therapy reduced the FPG from baseline significantly more compared to glipizide and metformin monotherapies (P<0.001). Combination therapy controlled PPG more than metformin monotherapy or glipizide monotherapy, as measured using a three-hour incremental AUC (P=0.002, and P<0.001, respectively). The postprandial insulin three-hour incremental AUC increased from baseline with combination therapy, and decreased with glipizide monotherapy; the differences between these groups were not significant. There was a decrease in the postprandial insulin AUC in the metformin monotherapy group, which was significant (P<0.001 vs combination group). Fasting insulin decreased in the combination therapy group and in the metformin monotherapy group. Fasting insulin increased in the glipizide monotherapy group. The changes in the combination therapy group did not differ significantly from either monotherapy group. There were decreases in body weight in all groups, -0.3 kg with the combination therapy group, -0.4 kg with the glipizide monotherapy group, and -2.7 kg in the metformin monotherapy group. The changes in the metformin monotherapy group were significant compared to the combination therapy group (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				There were no significant changes in the fasting lipid profile in the combination group or metformin monotherapy group. There were significant increases from baseline in TC and TG in the glipizide monotherapy group.
Garber et al.[89] (2002) Metformin 500 mg daily vs glyburide 2.5 mg daily vs glyburide/ metformin 1.25/250 mg daily vs glyburide/ metformin 2.5/500 mg daily vs placebo Doses were titrated to a maximum of 4 tablets per day.	DB, MC, PC, PG, RCT Patients with type 2 diabetes with inadequate glycemic control with diet and exercise, HbA_{1c} >7.0%, normal renal and liver function, and a BMI ≤38 kg/m^2	N=806 20 weeks	Primary: Change in HbA_{1c} Secondary: Changes in FPG, two-hour PPG, fasting and two-hour insulin levels, serum lipid concentrations, body weight	Primary: Patients in both glyburide/metformin groups had significantly greater mean reduction from baseline HbA_{1c} (level of 8.2%) compared to the placebo group (P<0.001). The reductions in HbA_{1c} from baseline for each glyburide/metformin group were significantly greater than the placebo or metformin groups (P<0.001). The reduction in HbA_{1c} in the glyburide/metformin 1.25/250 mg group was significantly greater compared to the glyburide group (P<0.016), and for the glyburide/metformin 2.5/500 mg group compared to the glyburide group (P<0.004). Sixty-six percent of the patients in the glyburide/metformin 1.25/250 mg group (P=0.006 vs metformin) and 72% of the patients in the glyburide/metformin 2.5/500 mg group (P<0.001 vs metformin, P=0.037 vs glyburide) had achieved an HbA_{1c} <7.0% compared to 60% of the patients in the glyburide group, 50%of patients in the metformin group, and 20% of patients in the placebo group. Secondary: Mean decreases in FPG concentrations were significantly greater for both combination groups compared to the placebo (P<0.001) and metformin groups (P<0.001). Mean decreases in FPG were numerically greater in both combination groups compared to the glyburide group, but the differences were not significant. Glyburide/metformin 1.25/250 mg group, glyburide/metformin 2.5/500 mg group, and the glyburide group had modest changes in body weight of 1.4, 1.9, and 1.7 kg, respectively, compared to 0.7 and 0.6 kg mean decrease in patients receiving placebo and metformin, respectively. The mean changes in body weight for the glyburide/metformin groups and the glyburide group were significantly different from placebo.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				There were no significant changes seen in TC, LDL-C, or HDL-C, and TGs with any treatment.
Marre et al.[90] (2002) Metformin 500 mg daily vs glyburide 5 mg daily vs glyburide/ metformin 2.5/500 mg daily vs glyburide/ metformin 5/500 mg daily Doses were titrated to a maximum of 4 tablets per day.	DB, MC, PG, RCT Patients >18 years of age with type 2 diabetes with a FPG ≥126 mg/dL despite treatment with monotherapy metformin ≥850 mg BID or ≥500 mg TID, diet, and exercise for 2 months prior to enrollment, and BMI <40 kg/m^2	N=411 16 weeks	Primary: Change in HbA_{1c} Secondary: Changes in FPG, fructosamine levels	Primary: Mean HbA_{1c} levels improved in all groups. There were significantly greater reductions in the patients receiving combination therapy as compared to either monotherapy (P<0.05). There were no significant differences in the amount of the reductions in the HbA_{1c} between the two combination therapies or the two monotherapies. Seventy-five percent of the glyburide/metformin 2.5/500 mg group and 63.8% of the glyburide/metformin 5/500 mg group achieved an HbA_{1c} <7.0% as compared to the metformin (37.6%) or glyburide (41.9%) groups (P=0.001 for both). Secondary: FPG decreased in all groups. There were significant improvements in both the combination groups compared to either monotherapy (P<0.05). There were no significant differences in effects on FPG between either of the combination therapies or the monotherapies. Mean decreases in fructosamine in both combination groups were significantly greater (P<0.05) compared to the changes seen in the monotherapy groups.
Johnson et al.[91] (2005) Metformin and sulfonylurea vs metformin monotherapy	RETRO Patients ≥30 years of age who were new users of oral antidiabetic drugs (sulfonylurea monotherapy, metformin monotherapy, or	N=4,124 N=2,138 sulfonylurea monotherapy N=923 metformin monotherapy	Primary: Composite end point of fatal or nonfatal cardiovascular related events Secondary: Not reported	Primary: A total of 381 patients died from cardiovascular causes and 715 were hospitalized at least once for cardiovascular reasons. Patients in the metformin monotherapy group had the lowest nonfatal hospitalization rate for cardiovascular causes (53.7 hospitalizations per 1,000 person years) compared to sulfonylurea monotherapy patients (75.3 per 1,000 person years; P<0.05) and compared to combination therapy patients (90.2 per 1,000 person years; P<0.05). Nonfatal cardiovascular related hospitalization rates were similar for sulfonylurea monotherapy patients and combination therapy patients (P=0.08).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs sulfonylurea monotherapy	combination therapy of sulfonylureas and metformin)	N=1,081 combination therapy Duration not reported		Metformin monotherapy was associated with a lower risk of the composite end point (adjusted HR, 0.81; 95% CI, 0.68 to 0.97) as compared to sulfonylurea monotherapy. Cardiovascular hospitalizations were similar for sulfonylurea monotherapy and combination therapy (P=0.32). Secondary: Not reported
Hollander et al.[92] (2015) Insulin glargine+ one oral antidiabetes drug (metformin or sulfonylurea) wherein previous TZD therapy was dropped and replaced with insulin glargine (GLAR +1 OAD) vs three oral antidiabetes drugs (3OAD) wherein patients receiving TZD and metformin received add-on sulfonylurea (glyburide) and patients receiving TZD and sulfonylurea	MC, OL, RCT Type 2 diabetes patients 18 to 79 years of age with a HbA_{1c} of 7.5 to 12.0% despite ≥3 months of treatment with a TZD plus metformin or a sulfonylurea	N=337 48 weeks	Primary: Change in HbA_{1c} Secondary: Changes in FPG, weight, BMI, and serum lipid profile	Primary: Substitution of insulin glargine for a TZD and addition of a third OAD resulted in an adjusted mean change in HbA_{1c} from baseline of −1.66% and −1.86%, respectively (adjusted mean difference 0.20; 95% CI, −0.11 to 0.51). The upper limit of the 95% CI for the difference in the adjusted mean changes from baseline to endpoint for HbA_{1c} was 0.51%; therefore, the primary efficacy analysis did not demonstrate equivalent glycemic control during treatment with GLAR + 1 OAD and 3OAD as measured by HbA_{1c} levels. In patients originally taking sulfonylurea, there was a significantly greater reduction in HbA_{1c} in those adding metformin to TZD and sulfonylurea versus those switching the TZD for GLAR + SU at weeks 12, 24, and 48. Secondary: Adjusted mean FPG at baseline was similar between the two treatment arms (GLAR + 1 OAD 193.0 mg/dL vs 3OAD 199.5 mg/dL; P=0.4299). FPG reduced significantly from baseline to endpoint (P<0.0001 for both arms). Weight gain was observed in both treatment arms at each study visit and at endpoint. At each visit, patients in the GLAR + 1 OAD arm gained less weight than those in the 3OAD arm; this difference was significant at week 12 (P=0.0035). A similar pattern was observed for BMI. Overall, insulin glargine + metformin was as effective as 3OAD in achieving glycemic control but with greater improvements in lipid parameters, less weight gain, and lower hypoglycemia rates.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
received add-on metformin (3OAD)				
Duckworth et al.[93] (2003) Glyburide/ metformin	RETRO Patients 18 to 80 years of age with type 2 diabetes were eligible if they had received a combination product with glyburide and metformin for ≥90 days and had been treated with glipizide or glyburide plus metformin for ≥6 months prior to switching to the combination product of glyburide/ metformin	N=72 196 days (mean follow-up)	Primary: Changes in HbA_{1c}, lipid parameters, weight Secondary: Not reported	Primary: The mean baseline HbA_{1c} in the total population was 8.3±1.7%. The mean reduction in HbA_{1c} was 0.6% (P=0.002) with a mean follow-up of 196 days after the initiation of glyburide/metformin. The mean daily doses of glyburide and metformin at baseline and at final follow-up were 17.2 and 1,607 mg and 14.7 and 1,750 mg, respectively. The greatest decrease in HbA_{1c} was observed in patients with a baseline HbA_{1c} ≥8.0% (n=37). This group had a mean reduction of HbA_{1c} of 1.3% (P=0.0002) with similar doses of glyburide (14.7 vs 16.9 mg; P=0.077) and metformin (1,743 vs 1,624 mg; P=0.11) in both treatment periods. There were no significant changes in TC, HDL-C, LDL-C, or TG from baseline. There were no significant changes in body weight from a baseline level of 104.3 kg to the last follow-up weight of 104.0 kg (P=0.0645). There were no significant differences in patient adherence to the regimen (92.4% before vs 90.9% after). Secondary: Not reported
Blonde et al.[94] (2003) Glyburide coadministered with metformin vs glyburide/ metformin	RETRO Patients with type 2 diabetes new to the combination product glyburide/ metformin or glyburide coadministered with metformin between August 2000 and	N=1,421 ~ 6 month (follow-up period)	Primary: Change in HbA_{1c} Secondary: Not reported	Primary: The mean HbA_{1c} for the two groups at baseline were similar, 9.1% for the combination product and 9.2% for the individual agents coadministered. During the follow-up period, patients taking the combination product had a lower mean daily dose of glyburide and metformin than patients receiving the individual agents coadministered regardless of baseline HbA_{1c}. Fifty-six percent of patients in the combination group achieved an HbA_{1c} <7.0% compared to 31.2% of patients receiving the individual agents coadministered. The mean HbA_{1c} decrease from baseline in the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	July 2001 and had HbA_{1c} levels at baseline within 79 to 194 days of initiating combination therapy			combination group was -2.02% and -1.49% when the individual agents were coadministered. The regression results indicated that patients taking the combination product had a significantly greater (P<0.0001) reduction in HbA_{1c} than patients receiving the individual agents coadministered. Patients receiving the combination product with baseline HbA_{1c} ≥8.0% experienced a significantly (P<0.0001) greater decrease in HbA_{1c} of 2.93% compared to 1.92% for the individual agents coadministered. For patients with baseline HbA_{1c} <8.0%, the difference between the HbA_{1c} responses remained significant. The reductions in HbA_{1c} were smaller for both the combination product and the individual agents coadministered (-0.54 and -0.23%; P=0.0017). Patients were more adherent with the combination product than the individual agents coadministered (84% days with drug supply vs 76% days with drug supply, respectively; P<0.0001). The mean decreases in HbA_{1c} were similar for those patients ≥80% adherent and <80% adherent for the combination product (2.12 vs 2.19%; P value not significant) and the individual agents coadministered (1.47 vs 1.24%; P value not significant). Secondary: Not reported
Lewin et al.[95] (2007) Metformin XR (Glumetza®) 1,500 mg QD, 2,000 mg QD, or 1,000 mg BID and glyburide 15 mg QD vs glyburide 15 mg QD	DB, MC, RCT Type 2 diabetic patients 18 to 79 years of age, drug naïve or previously treated with oral antidiabetic medications (monotherapy with any oral antidiabetic medications up to half the maximum	N=607 30 weeks	Primary: Change baseline HbA_{1c} Secondary: Changes in HbA_{1c} and FPG at week eight, fructosamine, TC, HDL-C, LDL-C, TG, weight, BMI, discontinuation	Primary: There were significant reductions in HbA_{1c} from baseline to week 30 in all combined metformin and sulfonylurea groups compared to the sulfonylurea monotherapy group (-0.74 vs 0.08%, respectively; P<0.001). Secondary: There were significant reductions from baseline in mean FPG and in mean HbA_{1c} at week eight in all combined metformin and sulfonylurea groups compared to the sulfonylurea monotherapy group (P<0.001). There were significant differences between the combined metformin and sulfonylurea groups and the monotherapy group for mean changes in fructosamine, TC, HDL-C, and LDL-C (P<0.001 for all).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	therapeutic dose), HbA_{1c} 7.5 to 12.0% in drug-naïve patients or 6.5 to 12.0% in prior drug treatment patients, FPG 200 to 400 mg/dL (drug naïve patients) or 120 to 250 mg/dL (prior drug treatment patients) and C-peptide levels >0.8 ng/mL		rates, adverse events	There were significant increases from baseline in mean weight and BMI in the monotherapy sulfonylurea group (P<0.001). In comparison, there was no significant change in weight and a smaller increase in mean BMI in the combined metformin and sulfonylurea groups (P=0.028). There was a significant difference in the rates of hypoglycemia between groups, which were 11.6% in the combined metformin and sulfonylurea groups and 4.2% in the monotherapy sulfonylurea group (P=0.007). However, no significant difference between these two groups was observed for gastrointestinal events. Forty patients (9.3%) in the combined metformin and sulfonylurea groups and three patients (2.1%) in the monotherapy sulfonylurea group discontinued treatment due to an adverse event, mainly hypoglycemia (P=0.001).
Chien et al.[96] (2007) Metformin 500 mg BID vs glyburide 5 mg BID vs glyburide/ metformin 2.5/500mg BID vs glyburide/ metformin 5/500 mg BID	DB, MC, PG, RCT Patients 30 to 75 years of age with type 2 diabetes, BMI 18.5 to 35.0 kg/m^2, FPG 140 to 250 mg/dL, and HbA_{1c} 7.0 to 12.0% at the screening visit and FPG ≥140 mg/dL at the second visit, maintained stable sulfonylurea regimen, with or without metformin use	N=100 16 weeks	Primary: Change in baseline HbA_{1c} Secondary: Change in baseline FPG, adverse events	Primary: After 16 weeks, the HbA_{1c} increased in patients receiving glyburide (0.52%; P=0.0018) and there was no change in patients receiving metformin (0.09%; P value not significant). After 16 weeks, treatment with glyburide/metformin 2.5/500 mg resulted in a greater reduction in HbA_{1c} compared to glyburide or metformin (-1.77%; P<0.001 and -1.34%; P=0.002). Treatment with glyburide/metformin 5/500 mg resulted in a greater reduction in HbA_{1c} compared to glyburide or metformin alone (-1.73%; P<0.001 and -1.30%; P=0.005). After 16 weeks, 19 and 24% of patients in the glyburide/metformin groups (2.5/500 mg and 5/500 mg, respectively) had an HbA_{1c} <7.0% compared to 12.0% in the metformin monotherapy group and 6% in the glyburide monotherapy group. Secondary: Mean changes in FPG from baseline were -43 mg/dL in the glyburide group, -41 mg/dL in the metformin group, -98 mg/dL in the glyburide/metformin 2.5/500mg group, and -101 mg/dL in the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
The doses were titrated every 2 weeks to a maximum of 4 tablets per day if the exceeded 140 mg/dL.				glyburide/metformin 5/500 mg group. The two glyburide/metformin groups had significant reductions from baseline compared to the monotherapy groups (P<0.0125 compared to glyburide and metformin). Treatment with glyburide/metformin 2.5/500 mg resulted in a 55 mg/dL reduction in FPG compared to glyburide (P=0.001) and a 57 mg/dL reduction in FPG compared to metformin (P=0.001). Treatment with glyburide/metformin 5/500 mg resulted in a in a 58 mg/dL reduction in FPG compared to glyburide (P<0.001) and a 60 mg/dL reduction in FPG compared to metformin (P=0.001). Ninety-eight episodes of adverse events were reported from the screening visit to the end of the study. Four (14.3%) patients reported adverse events associated with hypoglycemia in the glyburide/metformin 2.5/500 mg group, and two (8.3%) patients reported adverse events associated with gastrointestinal disease among all patients who took metformin during the entire course of the study. The highest incidence of gastrointestinal adverse effects was 32.0% in metformin group, and the lowest was 7.7% in the glyburide/metformin 2.5/500 mg group (P=0.021).
Einhorn et al.[97] (2000) Metformin (existing therapy) vs metformin (existing therapy) and pioglitazone 30 to 45 mg	DB, PC, RCT Patients with poorly controlled type 2 diabetes (HbA_{1c} ≥8.0%) with metformin monotherapy	N=328 16 weeks	Primary: Change in HbA_{1c}, FPG, insulin, lipoproteins, and C-peptide Secondary: Not reported	Primary: Reductions in HbA_{1c} with pioglitazone add-on therapy were significantly lower compared to placebo (-0.83% difference between treatment groups; P≤0.05). Reductions in FPG with pioglitazone add-on therapy were significantly lower compared to placebo (-37.7 mg/dL difference between treatment groups; P≤0.05). Pioglitazone reduced fasting C-peptide levels (-0.1 ng/mL) while placebo increased levels (0.1 ng/mL; P≤0.05). Pioglitazone reduced fasting C-insulin levels (-2.1 ng/mL) while placebo increased levels (0.4 ng/mL; P<0.05). Pioglitazone add-on therapy significantly reduced TG (-9.7 vs 8.5 mg/dL; P≤0.05) and increased HDL-C (10.2 vs 1.5 mg/dL; P≤0.05) compared to placebo.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Both treatment groups increased LDL-C (7.7 vs 11.9 mg/dL; P value not significant). No significant difference between treatment groups in number of adverse events was observed. Higher rate of edema was reported with pioglitazone (5.9 vs 2.5%). Weight loss was observed with placebo (-1.36 kg) while patients receiving pioglitazone had weight gain (0.95 kg; P value not reported). Secondary: Not reported
Kaku et al.[98] (2009) Metformin 500 to 750 mg daily vs pioglitazone 15 to 30 mg QD and metformin 500 to 750 mg daily	DB, PC, PG, RCT Patients 20 to 65 years of age with type 2 diabetes, HbA_{1c} 6.5 to 10.0%, who were drug naïve or on metformin monotherapy	N=169 28 weeks	Primary: HbA_{1c}, FPG, fasting insulin, insulin resistance, lipid parameters Secondary: Not reported	Primary: At week 28, mean change in HbA_{1c} from baseline was -0.67% with pioglitazone compared to 0.25% with placebo (P<0.0001). More patients receiving pioglitazone achieved an HbA_{1c} <6.5% compared to placebo (38.6 vs 8.1%, respectively; P<0.0001). At week 28, mean change in FPG from baseline was -20.5 mg/dL with pioglitazone compared to 1.9 mg/dL with placebo (P<0.0001). Mean fasting insulin concentrations were reduced to a greater extent with pioglitazone (-2.15 mU/mL) compared to placebo (-0.38 mU/mL; P=0.021). Insulin resistance was reduced more by pioglitazone compared to placebo (-1.34 vs -0.15; P=0.0025). The main differences in lipids between pioglitazone compared to placebo were significant increases in TC (P=0.0057) and HDL-C (P<0.0001). Adiponectin levels were significantly increased by pioglitazone compared to placebo (P=0.0001). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Perez et al.[99] (2009) Pioglitazone/ metformin 15/850 mg BID vs pioglitazone 15 mg BID vs metformin 850 mg BID	DB, PG, RCT Patients ≥18 years of age with type 2 diabetes, HbA_{1c} 7.5 to 10.0%, BMI ≤45 kg/m^2, who were drug naïve	N=600 24 weeks	Primary: Change in baseline HbA_{1c} Secondary: HbA_{1c} responder rate, changes in baseline FPG, fasting insulin, insulin resistance	Primary: At week 24, mean change in HbA_{1c} from baseline was -1.83% with pioglitazone/metformin compared to -0.96% pioglitazone and -0.99% with metformin (P<0.0001 for combination therapy vs either monotherapy). Secondary: In the pioglitazone/metformin group, 63.8% achieved HbA_{1c} <7.0% compared to 46.9% with pioglitazone and 38.9% with metformin (P value not reported). Pioglitazone/metformin led to the greatest reduction in FPG from baseline to final visit (-39.9 mg/dL) compared to -22.2 mg/dL with pioglitazone and -24.8 mg/dL with metformin (P<0.01 for combination therapy vs either monotherapy). Pioglitazone/metformin led to the greatest reduction in fasting insulin from baseline to final visit (-3.91 µIU/mL), followed by pioglitazone (-3.18 µIU/mL). Both reductions were significantly greater compared to metformin (-0.98 µIU/mL; P<0.05). At week 24, the greatest decrease in insulin resistance was seen with pioglitazone/metformin and pioglitazone compared to metformin; however, the difference was significant only with pioglitazone/metformin (P<0.01).
Seufert et al.[100] (2008) <u>Study 1</u> Metformin (existing therapy) and pioglitazone 15 to 45 mg QD vs metformin (existing therapy) and	2 MC, RCT Patients 35 to 75 years of age with type 2 diabetes who were inadequately controlled on either metformin or sulfonylurea monotherapy (HbA_{1c} 7.5 to 11.0%), and fasting	N=1,269 104 weeks	Primary: Change in HbA_{1c} from baseline, FPG, glucose excursions using Three hour oral glucose tolerance test, insulin sensitivity Secondary: Not reported	Primary: *Study 1* The mean change in HbA_{1c} from baseline to week 104 was -0.89% with pioglitazone and metformin compared to -0.77% with gliclazide and metformin (P=0.20). The mean change in FPG from baseline to week 104 was -1.8 mmol/L with pioglitazone and metformin compared to -1.1 mmol/L with gliclazide and metformin (P<0.001). Pioglitazone therapy in patients failing metformin therapy achieved decreases in glucose excursions at the end of the two-year treatment

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
gliclazide† 80 to 320 mg daily Study 2 Metformin 850 to 2,550 mg daily and sulfonylurea vs pioglitazone 15 to 45 mg QD and sulfonylurea therapy (existing therapy)	C-peptide >1.5 ng/mL)			period. This effect was not seen in the patients receiving gliclazide for two years as add-on therapy to failing metformin. Insulin sensitivity increased when pioglitazone was added to metformin therapy (+13.8%) compared with a decrease when gliclazide was added to metformin (-7.2%; P<0.0001). *Study 2* The mean change in HbA_{1c} from baseline to week 104 was -1.03% for patients receiving pioglitazone and sulfonylurea compared to -1.16% for patients receiving metformin and sulfonylurea (P=0.173). The mean change in FPG from baseline to week 104 was -2.0 mmol/l with pioglitazone and sulfonylurea compared to -1.9 mmol/l with metformin and sulfonylurea (P=0.506). The addition of pioglitazone to failing sulfonylurea therapy for two years resulted in a decrease of post-load glucose excursions which was not seen when metformin was added to sulfonylurea treatment. Insulin sensitivity increased when pioglitazone was added to sulfonylurea, (+5.8%) compared to an increase of +3.9% when metformin was added to sulfonylurea (P=0.581 between treatments). Secondary: Not reported
Matthews et al.[101] (2005) Metformin (existing therapy) and pioglitazone 15 to 45 mg QD vs	DB, RCT Patients with type 2 diabetes that was poorly controlled (HbA_{1c} 7.5 to 11.0%) with metformin monotherapy	N=630 12 months	Primary: Effect on HbA_{1c} Secondary: Effect on FPG, insulin, lipoproteins, and C-peptide	Primary: Similar reductions in HbA_{1c} were observed in pioglitazone- (-0.99%) and gliclazide-treated groups (-1.01%; P=0.837). Secondary: Similar reductions in FPG were observed in pioglitazone- (-2.1 mmol/L) and gliclazide- (-1.6 mmol/L) treated groups (P=0.506). Gliclazide significantly reduced LDL-C compared to pioglitazone (-4.2 mg/dL vs +10.4 mg/dL; P=0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
metformin (existing therapy) and gliclazide† 80 to 320 mg QD				Pioglitazone significantly reduced TG (-53.1 vs -19.5 mg/dL; P<0.001) and increased HDL-C (6.9 mg/dL vs no change; P<0.001) compared to gliclazide.
Charbonnel et al.[102] (2005) Metformin (existing therapy) and pioglitazone 15 to 45 mg QD vs metformin (existing therapy) and gliclazide† 80 to 320 mg QD	DB, RCT Patients with type 2 diabetes that was poorly controlled (HbA_{1c} 7.5 to 11.0%) with metformin monotherapy	N=630 24 months	Primary: Effect on HbA_{1c} Secondary: Effect on FPG, insulin, lipoproteins, and C-peptide	Primary: Similar reductions in HbA_{1c} were observed with pioglitazone add-on therapy (-0.89%) and with gliclazide add-on therapy (-0.77%; P=0.200) after two years. Secondary: Significant reductions in FPG were observed with pioglitazone add-on therapy (-1.8 mmol/L) compared to gliclazide add-on therapy (-1.1 mmol/L; P<0.001) after two years. Gliclazide add-on therapy had significantly reduced LDL-C compared to pioglitazone add-on therapy (-6 vs +2 mg/dL; P<0.001). Pioglitazone add-on therapy significantly reduced TG (-23 vs -7 mg/dL; P<0.001) and increased HDL-C (22 vs 7 mg/dL; P<0.001) compared to gliclazide add-on therapy. No significant difference between treatment groups in number of adverse events or discontinuation due to adverse events was reported. Less weight gain was observed with gliclazide add-on therapy to metformin (1.2 kg) compared to pioglitazone add-on therapy (2.5 kg).
Hanefeld et al.[103] (2004) Metformin 850 to 2,250 mg daily and sulfonylurea (existing therapy) vs	DB, MC, PG, RCT Patients with type 2 diabetes inadequately controlled on sulfonylurea monotherapy	N=639 12 months	Primary: Change in HbA_{1c} Secondary: FPG, fasting plasma insulin, lipids, urinary albumin and creatinine (to determine	Primary: HbA_{1c} was reduced by 1.20 and 1.36% in the pioglitazone and metformin groups, respectively (P=0.065 for differences between treatments). Secondary: FPG (P=0.528) and fasting plasma insulin (P=0.199) were also reduced but the between-treatment differences were not statistically significant. Pioglitazone addition to sulfonylurea significantly reduced TG (-16 vs -9%; P=0.008) and increased HDL-C (14 vs 8%; P<0.001) compared with metformin addition.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
pioglitazone 15 to 45 mg QD and sulfonylurea (existing therapy)			albumin-to-creatinine ratio)	LDL-C was increased 2% by the addition of pioglitazone and decreased 5% by the addition of metformin to sulfonylurea monotherapy (P<0.001). Urinary albumin-to-creatinine ratio was reduced by 15% in the pioglitazone group and increased 2% in the metformin group (P=0.017). Both combinations were well tolerated with no evidence of hepatic or cardiac toxicity in either group.
Comaschi et al.[104] (2008) Metformin/ glibenclamide* 400/2.5 mg 1 to 3 tablets daily vs pioglitazone 15 to 30 mg QD as add-on to existing oral hypoglycemic therapy (either metformin or sulfonylurea)	MC, OL, PG, RCT Patients ≥35 years of age with type 2 diabetes who had received treatment with a stable dose of either metformin or a sulfonylurea as monotherapy for at least 3 months before study entry, HbA_{1c} 7.5 to 11.0%, and fasting C-peptide >0.33 nmol/L	N=250 6 months	Primary: Change in HbA_{1c} from baseline to six months Secondary: Change in lipid profiles after six months of treatment	Primary: Pioglitazone-based combination therapy and fixed-dose metformin/glibenclamide resulted in similar reductions in HbA_{1c} (-1.11 vs -1.29%, respectively; P=0.192) and FPG (-2.13 vs -1.81 mmol/L, respectively; P=0.370). Secondary: No changes in TC were observed with pioglitazone-based therapy (-0.017 mmol/L) compared to the fixed-dose combination of metformin/glibenclamide (-0.099 mmol/L; P=0.479). The addition of pioglitazone to metformin or a sulfonylurea led to a slight increase in HDL-C (+0.04 mmol/L) compared to a reduction in HDL-C with metformin/glibenclamide (-0.09 mmol/L; P<0.001). There was no significant change in non-HDL-C in patients treated with pioglitazone-based therapy (-0.06 mmol/L) or the fixed-dose combination of metformin/glibenclamide (-0.01 mmol/L; P=0.677). There was no significant change in LDL-C in patients treated with pioglitazone-based therapy (+0.06 mmol/L) or the fixed-dose combination of metformin/glibenclamide (-0.03 mmol/L; P=0.425) There was a significant reduction in TGs with pioglitazone-based therapy (-0.25 mmol/L) compared to no change with the fixed-dose combination of metformin/glibenclamide (0.03 mmol/L; P=0.045).
Abdul-Ghani et al.[105] (2015)	OL, RCT	N=221	Primary: HbA_{1c}	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
EDICT Metformin (escalating dose) vs triple therapy (metformin/ pioglitazone/ exenatide)	Drug-naïve, recently diagnosed (<2 years) subjects 30 to 75 years of age with type 2 diabetes mellitus	2 years	Secondary: Percentage of participants achieving HbA_{1c} <6.5 and <7.0%; decrease in fasting and postprandial plasma glucose; change in body weight; and rate of hypoglycemic events	Baseline HbA_{1c} was identical in both groups (8.6%) and during the first six months decreased in both treatment arms. At six months, there was a small but significant HbA_{1c} difference (0.2%, P=0.03) between groups (triple therapy 6.0% vs metformin therapy 6.2%). After six months, HbA_{1c} gradually increased with metformin therapy to 6.5% at 24 months and remained stable at 5.95% with triple therapy; thus, the difference in HbA_{1c} between the two treatments progressively increased with time and was significantly different at two years (change in HbA_{1c} 0.55%; P<0.0001). Secondary: More participants receiving metformin therapy failed to maintain the treatment goal (HbA_{1c} <6.5%) than did those receiving triple therapy (44 vs 17%; P=0.003). A total of 40 participants receiving metformin therapy failed to maintain HbA_{1c} at <6.5% at/after six months compared with only 13 participants receiving triple therapy (P<0.0001). More participants receiving triple therapy (61%) had HbA_{1c} reduced to the normal range (<6.0%) than those receiving metformin therapy (27%; P<0.0001). The median HbA_{1c} of participants receiving triple therapy was 5.9% compared with 6.4% for those receiving metformin therapy. More than 90% of participants receiving triple therapy maintained HbA_{1c} at <7.0% versus <75% of participants receiving metformin therapy. The most common adverse event was hypoglycemia, reported by 46 and 14% of participants receiving metformin and triple therapy, respectively. The overall frequency of hypoglycemic events was greater in participants receiving metformin therapy (2.2 vs 0.31 events/participant per year; P<0.0001).
Borges et al.[106] (2011) Rosiglitazone/ metformin vs metformin	DB, MC, RCT Drug naïve patients with type 2 diabetes	N=688 18 months	Primary: Change in baseline HbA_{1c}, FPG Secondary: Bone mineral density	Primary: Combination therapy was more efficacious in achieving significant reductions in HbA_{1c} (P<0.0001) and FPG (P<0.001) compared to metformin. In addition, more patients achieved HbA_1c and FPG goals with combination therapy compared to metformin. Secondary: In a bone substudy, at week 80 combination therapy was associated with significantly lower bone mineral density compared to metformin in the lumbar spine (P<0.0012) and total hip (P=0.0005, respectively). There was

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				no difference between treatments for distal one-third of radius, femoral neck, and total bone mineral densities (P values not reported).
Fonseca et al.[107] (2000) Metformin 2,500 mg daily vs metformin 2,500 mg and rosiglitazone 4 mg daily vs metformin 2,500 mg and rosiglitazone 8 mg daily	DB, PC, RCT Patients with poorly controlled type 2 diabetes (mean FPG 140 to 300 mg/dL) with metformin; baseline HbA_{1c} 8.6% in the metformin treatment group, 8.9% in the rosiglitazone/ metformin 4/2,500 mg treatment group and 8.9% in the rosiglitazone/ metformin 8/2,500 mg treatment group; patients were excluded if they had NYHA class III-IV heart failure, angina, renal or liver disease, symptomatic neuropathy, or prior use of rosiglitazone or insulin	N=348 26 weeks	Primary: Change in baseline HbA_{1c}, FPG, fructosamine, C-peptide, FFA, lipids, lactate, and estimates of insulin sensitivity (HOMA-S) and β-cell function (HOMA-B) Secondary: Not reported	Primary: Addition of rosiglitazone significantly reduced HbA_{1c} in a dose-related fashion from baseline compared to metformin monotherapy. Mean difference from the metformin control group was -1.0% (P<0.001) with rosiglitazone/metformin 4/2,500 mg and -1.2% with rosiglitazone/metformin 8/2,500 mg (P<0.001). Mean FPG concentrations were reduced significantly with rosiglitazone/metformin 4/2,500 mg (-33 mg/dL; P<0.0001) and with rosiglitazone/metformin 8/2,500 mg (-48.4 mg/dL; P<0.0001). No significant change in FPG was observed with metformin monotherapy. Fructosamine levels were reduced with both rosiglitazone/metformin 4/2,500 mg (-27.9 µmol/L; P value not reported) and rosiglitazone/metformin 8/2,500 mg (-36.8 µmol/L; P value not reported). Fructosamine levels increased with metformin monotherapy (12.3 µmol/L; P value not reported). C-peptide values were reduced significantly in all treatment groups compared to baseline (P<0.05). FFA levels were significantly less in both rosiglitazone/metformin groups compared to metformin monotherapy group (P<0.05). Significant increases in TC, HDL-C and LDL-C were observed with both rosiglitazone groups when compared to metformin monotherapy group (P<0.05). Mean fasting lactate levels were significantly less in both rosiglitazone/metformin groups compared to metformin monotherapy group (P<0.05). Both insulin sensitivity (as measured by HOMA-S) and β-cell function (as measured by HOMA-B) were increased in a dose-dependent fashion with

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				rosiglitazone/metformin compared to metformin monotherapy (P value not reported). Secondary: Not reported
Weissman et al.[108] (2005) Metformin 1,500 mg QD (MET) vs rosiglitazone 8 mg QD and metformin 1,000 mg QD (RSG + MET)	DB, MC, PG, RCT Patients 18 to 75 years of age diagnosed with type 2 diabetes (defined as HbA_{1c} 6.5 to 8.5% for patients receiving combination therapy with metformin and sulfonylurea or HbA_{1c} 7.0 to 10.0% for drug-naïve or patients receiving monotherapy), FPG of 126 to 270 mg/dL and BMI ≥27kg/m^2; any subjects previously receiving metformin or metformin and sulfonylurea must have received ≤metformin 1,000 mg/day for at least 3 months prior to study entry and patients must have stopped previous treatment with TZD	N=766 2-week wash out period followed by 4 to 7 weeks of run-in period and 24 weeks of treatment	Primary: Change in baseline HbA_{1c} Secondary: Change in baseline FPG at week 24, proportion of patients responding to treatment (reduction ≥0.7% for HbA_{1c} and ≥30 mg/dL for FPG at week 24), clinical safety, adverse events, tolerability, clinical laboratory tests	Primary: After 24 weeks, RSG+MET and MET were both effective in improving HbA_{1c} with mean reductions of -0.93% (95% CI, -1.06 to -0.80) and -0.71% (95% CI, -0.83 to -0.60), respectively, with a mean treatment difference of -0.20% (95% CI, -0.36 to -0.04). Secondary: Significant reductions in FPG from baseline were seen in patients receiving RSG+MET (-2.29 mmol/L; 95% CI, -2.59 to -1.99) compared to patients receiving MET (-1.12 mmol/L; 95% CI, -1.43 to -0.82), with a treatment difference of -0.85 mmol/L (95% CI, -1.23 to -0.47). The proportion of patients who responded to treatment (reduction in HbA_{1c} ≥0.7%) was greater in the RSG+MET group than the MET group (59.5 and 49.5%, respectively) with the treatment difference of 10% (95% CI, 1.9 to 18.1). The proportion of FPG responders (reduction in FPG ≥30 mg/dL) was also greater in the RSG+MET group than in the MET group (55.0 vs 32.5%, respectively). The percentage of patients experiencing a gastrointestinal effect was greater in the MET group compared to the RSG+MET group (38.7 and 27.9%). The odds of experiencing a gastrointestinal side effect were 63% greater for patients receiving MET compared to patients receiving RSG+MET (OR, 1.63; 95% CI, 1.19 to 2.24). RSG+MET resulted in a mean weight gain of 1.79 kg (P<0.0001) compared to a mean weight loss of -1.78 kg (P<0.001) with MET.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	at least 3 months prior to screening			There were three deaths during the course of the study with two prior to DB study medication, and one while on RSG+MET; the cause of which was unknown, although it was not considered to be treatment related.
Stewart et al.[109] (2006) Metformin 3,000 mg/day (MET) vs metformin 2,000 mg daily and rosiglitazone 8 mg daily (MET + RSG)	DB, MC, PG, RCT Type 2 diabetic patients 18 to 70 years of age, who were either antidiabetic-drug-naïve with FPG of 7.0 to 9.0 mmol/L and HbA_{1c} 7.0 to 9.0%, or previously treated with oral antidiabetic monotherapy with FPG 6.0 to 8.0 mmol/L and HbA_{1c} 6.5 to 8.0%	N=526 32 weeks	Primary: Proportion of patients achieving HbA_{1c} ≤6.5% at week 32, change in baseline HbA_{1c} Secondary: Proportion of patients achieving target HbA_{1c} and FPG levels, change in baseline FPG and fasting plasma insulin, change in insulin resistance, pancreatic β-cell function, CRP, lipid parameters and 24-hour ambulatory BP, safety	Primary: At week 32, there was a reduction from baseline in mean HbA_{1c} in the MET+RSG group from 7.2 to 6.7% compared to 7.2 to 6.8% in the MET group (P=0.0357). Secondary: The proportion of patients achieving HbA_{1c} ≤6.5% at week 32 was similar in the two groups (P=0.095). The proportion of patients achieving FPG <7.0 mmol/L at week 32 was 56% in the MET+RSG group compared to 38% in the MET group (OR, 2.33; P<0.0001). The reduction in fasting plasma insulin from baseline was greater in the MET+RSG group compared to the MET group (treatment difference, -12.2 pmol/L; P=0.00029). Homeostasis model assessment estimated that insulin sensitivity, β-cell function, CRP, and SBP were greater in the MET+RSG group at week 32 compared to the MET group (P<0.05 for all). TC, HDL-C, and LDL-C increased, free fatty acids decreased, and TG did not change in the MET+RSG group, whereas in the MET group there were decreases in TC, LDL-C, and TG, and increases in HDL-C and FFA. The difference between the treatments was significant for the above parameters (P<0.05). The proportion of patients with reductions in 24-hour mean SBP was greater in the MET+RSG group compared to the MET group (treatment difference, -3.6 mm Hg; P=0.0315). The overall incidences of gastrointestinal adverse events were comparable between groups, but there was a lower incidence of diarrhea in the MET+RSG group (8 vs 18%). Hypoglycemia was reported in 17 patients

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				(7%) in the MET+RSG group compared to 10 patients (4%) in the MET group. There were greater reductions in mean hemoglobin and hematocrit over 32 weeks in the MET+RSG group compared to the MET group (P<0.0001).
Rosak et al.[110] (2005) Metformin (existing therapy) and rosiglitazone 4 to 8 mg	OS, PM Two studies in which type 2 diabetics on metformin therapy received rosiglitazone add-on therapy; baseline HbA_{1c} was 8.1% in both trials	N=11,014 6 months	Primary: Change in baseline HbA_{1c}, FPG, body weight, and BP Secondary: Not reported	Primary: Addition of rosiglitazone significantly reduced HbA_{1c} from baseline (-1.3%; P<0.0001). Addition of rosiglitazone significantly reduced FPG from baseline (-47.0 mg/dL; P<0.0001). Significant reduction in BP from baseline (-7/-3 mm Hg; P<0.0001) was observed with rosiglitazone add-on therapy. Significant reduction in weight (-1.7 kg; P<0.0001) was observed with rosiglitazone add-on therapy. Most commonly reported adverse events were weight gain (0.16%) and edema (0.15%). Secondary: Not reported
Bailey et al.[111] (2005) Metformin 2,500 to 3,000 mg daily vs rosiglitazone/ metformin 4/1,000 to 8/2,000 mg daily	DB, MC, PG, RCT Patients with type 2 diabetes poorly controlled (FPG ≥126 to 216 mg/dL) with metformin alone or in combination with an insulin secretagogue or acarbose; baseline HbA_{1c} 7.4% for rosiglitazone add-on	N=568 24 weeks	Primary: Change in baseline HbA_{1c} Secondary: Change in baseline FPG and insulin, proportion of patients who achieved HbA_{1c} and FPG targets	Primary: Reductions in HbA_{1c} observed with rosiglitazone add-on therapy were significantly lower compared to metformin monotherapy (-0.22% difference between treatment groups; P=0.001). Secondary: Reductions in FPG observed with rosiglitazone add-on therapy were significantly lower compared to metformin monotherapy (-18.3 mg/dL difference between treatment groups; P<0.001). Significant reduction in fasting insulin was observed with rosiglitazone add-on therapy compared to metformin monotherapy (-12.4 pmol/L difference between treatment groups; P=0.001).

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	therapy and 7.5% for metformin; patients were excluded if they had been treated with a TZD or insulin, had unstable cardiovascular or cerebrovascular conditions, or had uncontrolled hypertension			Greater proportion of patients on rosiglitazone add-on therapy (54%) reached HbA_{1c} targets (<7.0%) compared to those treated with metformin monotherapy (36%; OR, 2.42; P<0.001). Greater proportion of patients on rosiglitazone add-on therapy (32%) reached FPG targets (<126 mg/dL) compared to those treated with metformin monotherapy (8%; OR, 5.71; P<0.001). Higher rate of withdrawal due to adverse events with metformin monotherapy (8 vs 4%; no P value reported) was noted. Gastrointestinal disorders were the most commonly reported event that caused withdrawal in the metformin monotherapy group.
Rosenstock et al.[112] (2006) Metformin 500 to 2,000 mg daily vs rosiglitazone 4 to 8 mg daily vs rosiglitazone/ metformin 4/1,000 to 8/2,000 mg daily	DB, MC, RCT Type 2 diabetics with HbA_{1c} >7.5 to 11.0%, with FPG ≤270 mg/dL who were previously treated with diet and exercise or had not been treated with a glucose-lowering agent for more than 15 days within 12 weeks prior to screening	N=468 32 weeks	Primary: Change in baseline HbA_{1c} Secondary: Proportion of patients achieving HbA_{1c} and FPG targets, change in baseline FPG, safety	Primary: Patients receiving rosiglitazone/metformin showed significant improvements in HbA_{1c} with a reduction of -2.3% compared to baseline vs -1.8% with patients receiving metformin (P<0.0008) and -1.6% with patients receiving rosiglitazone (P<0.0001). Secondary: Target HbA_{1c} ≤6.5 and <7.0% were achieved in more patients in the rosiglitazone/metformin group (60 and 77%) than in the metformin (39 and 57%) or rosiglitazone (35 and 58%) groups, respectively (P values not reported). The greatest mean decrease in FPG was seen with rosiglitazone/metformin (-74 mg/dL) and was significant compared to metformin (-50 mg/dL; P<0.0001) and rosiglitazone (-47 mg/dL; P<0.0001). Treatment was well tolerated with nausea, vomiting and diarrhea as the most commonly reported adverse events. Edema was comparable between rosiglitazone/metformin (6%) and rosiglitazone (7%) and lower with metformin.
TODAY Study Group.[113] (2012) TODAY	MC, RCT Patients 10 to 17 years of age, with type 2 diabetes	N=699 3.86 years (average follow-up)	Primary: Loss of glycemic control (HbA_{1c} ≥8.0% for six months or	Primary: Overall, a total of 319 (45.6%) patients reached the primary outcome, with a median time to treatment failure of 11.5 months (range, <1 to 66). Rates of failure were 51.7 (95% CI, 45.3 to 58.2), 38.6 (95% CI, 32.4 to 44.9),

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Metformin vs rosiglitazone 4 mg BID plus metformin vs metformin plus lifestyle intervention (focusing on weight loss through eating and activity behaviors) Patients were treated during a run-in period of 2 to 6 months with metformin 1,000 mg BID to attain an HbA_{1c} <8.0% prior to randomization.			sustained metabolic decompensation requiring insulin) Secondary: Body weight, metabolic outcomes, safety	and 46.6% (95% CI, 40.2 to 53.0) of patients on metformin, rosiglitazone plus metformin, and metformin plus lifestyle intervention, respectively. Rosiglitazone plus metformin was more efficacious to metformin; combination therapy was associated with a 25.3% decrease in the occurrence of the primary outcome compared to metformin (P=0.006). The outcome with metformin plus lifestyle intervention was intermediate, but not significantly different from metformin or rosiglitazone plus metformin (P value not reported). The reasons for treatment failure did not differ significantly across treatments. Prespecified analyses according to sex and race or ethnic group showed differences in sustained effectiveness, with metformin least effective in non-Hispanic black patients and rosiglitazone plus metformin most effective in female patients. Secondary: BMI over time (up to 60 months) differed significantly according to the study treatment (P<0.001 for the overall comparison), and the results of all three pairwise comparisons between treatment groups were also significant. Patients treated with rosiglitazone plus metformin had the greatest increase in BMI and patients receiving metformin plus lifestyle intervention had the least. The change in fat mass from baseline differed significantly across the treatment groups (P<0.05) because of a significant difference between rosiglitazone plus metformin and metformin plus lifestyle interventions. There were no significant between-group differences in the change from baseline for any other outcome. Serious adverse events were reported in 19.2% of all patients, including 18.1, 14.6, and 24.8% with metformin, rosiglitazone plus metformin, and metformin plus lifestyle intervention (P=0.02). Hospitalizations accounted for more than 90% of serious adverse events. Severe hypoglycemia occurred in one, one, and two patients receiving metformin, rosiglitazone plus metformin, and metformin plus lifestyle intervention. No effects of rosiglitazone on bone mineral content or rate of fracture were noted.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Home et al.[114] (2007) RECORD Interim Analysis Metformin plus a sulfonylurea vs rosiglitazone plus either metformin or a sulfonylurea	MC, OL, RCT Patients with type 2 diabetes between the ages of 40 and 75 years, BMI >25.0 kg/m^2, HbA_{1c} 7.1 to 9.0% while receiving maximum permitted or tolerated doses of metformin or a sulfonylurea; exclusion criteria were the current use of other glucose-lowering agents, hospitalization for a major cardiovascular event in the previous 3 months, a planned cardiovascular intervention, heart failure, clinically significant hepatic disease, renal impairment, and uncontrolled hypertension	N=4,447 (n=1,117 rosiglitazone plus metformin; n=1,103 rosiglitazone plus sulfonylurea; n=2,227 metformin plus sulfonylurea) Mean follow-up 3.75 years for the unplanned interim analyses (study was designed to be 6 years)	Primary: Hospitalization or death from cardiovascular causes Secondary: Death from cardiovascular causes and from any cause, MI, congestive heart failure, and composite of death from cardiovascular causes, MI and stroke	Primary: For adjudicated primary end points (hospitalization or death from cardiovascular causes), the HR was 1.08 (95% CI, 0.89 to 1.31; P=0.43) with 217 events in the rosiglitazone group and 202 events in the control group. An additional 91 patients (50 in the rosiglitazone group and 41 in the control group) had potential primary events reported by investigators, but these events were pending adjudication. Secondary: There was no statistically significant difference between the rosiglitazone group and the control group for the following secondary end points: death from cardiovascular causes (HR, 0.83; 95% CI, 0.51 to 1.36; P=0.46) or any cause (HR, 0.93; 95% CI, 0.67 to 1.27; P=0.63), MI (HR, 1.16; 95% CI, 0.75 to 1.81; P=0.50), or the composite of cardiovascular death, MI and stroke (HR, 0.97; 95% CI, 0.73 to 1.29; P=0.83). However, the power to detect significant differences was low, as reflected by the wide 95% CI. Patients in the rosiglitazone group had a significantly higher risk of congestive heart failure than did patients in the control group, with 38 vs 17 adjudicated events (HR, 2.24; 95% CI, 1.27 to 3.97; P=0.006).
Home et al.[115] (2009) RECORD Metformin plus	MC, OL, RCT Patients 40 to 75 years of age with type 2 diabetes and BMI ≥25 kg/m^2, on	N=4,458 5.5 years (mean follow-up)	Primary: Time to first cardiovascular hospitalization or cardiovascular death	Primary: The primary end point (cardiovascular hospitalization or cardiovascular death) occurred in 321 and 323 patients receiving rosiglitazone and active control, respectively (HR, 0.99; 95% CI, 0.85 to 1.16; P=0.93). Secondary:

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a sulfonylurea vs rosiglitazone plus either metformin or a sulfonylurea	maximum tolerated doses of metformin or a sulfonylurea monotherapy, and inadequate glycemic control (HbA_{1c} 7.0 to 9.0%)		Secondary: Cardiovascular death, all-cause mortality, MI, stroke, composite of cardiovascular death, MI, and stroke	There was no significant difference between rosiglitazone and active controls for the following end points: cardiovascular death (HR, 0.84; 95%, CI 0.59 to 1.18; P=0.32), all-cause mortality (HR, 0.86; 95% CI, 0.68 to 1.08; P=0.19), MI (HR, 1.14; 95% CI, 0.80 to 1.63; P=0.47), stroke (HR, 0.72; 95% CI, 0.49 to 1.06; P=0.10), and the composite of cardiovascular death, MI, or stroke (HR, 0.93; 95% CI, 0.74 to 1.15; P=0.50). Heart failure occurred in 61 patients receiving rosiglitazone compared to 29 patients receiving active control (HR, 2.10; 95% CI, 1.35 to 3.27; P=0.0010). There were no serious adverse event reports of macular edema. The incidence of bone fractures was higher with rosiglitazone compared to active control (RR, 1.57; 95% CI, 1.26 to 1.97; P<0.0001). The risk was higher in women than in men (RR, 1.82; 95% CI, 1.37 to 2.41 vs RR, 1.23; 95% CI, 0.85 to 1.77; P=0.10). The excess of fractures in patients on rosiglitazone was primarily in the upper limb (RR, 1.57; 95% CI, 1.12 to 2.19; P=0.0095) and distal lower limb (RR, 2.60; 95% CI, 1.67 to 4.04; P<0.0001). Hip and femur fracture did not increase with rosiglitazone treatment. There was a nonsignificant increase in spinal fractures.
Mahaffey et al.[116] (2013) RECORD re-evaluation Rosiglitazone plus either metformin or a sulfonylurea vs metformin plus a sulfonylurea	RETRO Patients 40 to 75 years of age with type 2 diabetes and BMI ≥25 kg/m^2, on maximum tolerated doses of metformin or a sulfonylurea monotherapy, and inadequate glycemic control (HbA_{1c} 7.0 to 9.0%)	N=4,458 5.5 years (mean follow-up)	Primary: Time to first cardiovascular hospitalization or cardiovascular death Secondary: Cardiovascular death, all-cause mortality, MI, stroke, composite of cardiovascular death, MI, and stroke	Primary: For the primary end point (time to first occurrence of CV (or unknown cause) death, MI, or stroke) no statistically significant difference was observed between rosiglitazone and metformin/sulfonylurea using the original RECORD end point definitions (HR, 0.95; 95% CI, 0.78 to 1.17). For the primary end point, no meaningful difference between rosiglitazone and metformin/sulfonylurea was observed using the original RECORD end point definitions (HR, 0.95; 95% CI 0.78 to 1.17) or new FDA end point definitions (HR, 0.97; 95% CI, 0.79 to 1.18). Furthermore, these results are similar to results from the original RECORD study (HR, 0.93; 95% CI, 0.74 to 1.15). Secondary: The original RECORD study results and the Duke Clinical Research Institute clinical events classification results were also similar for the

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				individual components of the composite end point. These findings and the additional sensitivity analyses performed support the original RECORD results and suggest that when using essentially the same data, the observations were not affected by different clinical events classification processes, physician adjudicators, or end point definitions.
Home et al.[117] (2007) Metformin plus a sulfonylurea vs rosiglitazone plus either metformin or a sulfonylurea	MC, OL, PG, RCT Patients 40 to 75 years of age with type 2 diabetes and BMI ≥25 kg/m^2, on maximum tolerated doses of metformin or a sulfonylurea monotherapy, and inadequate glycemic control (HbA_{1c} 7.0 to 9.0%)	N=1,122 18 months	Primary: Change in baseline HbA_{1c} Secondary: FPG, serum lipids, HOMA basal insulin sensitivity and islet β-cell function (HOMA %β), body weight, inflammatory/ thrombotic markers, CRP	Primary: At 18 months, HbA_{1c} reduction on background metformin was similar with rosiglitazone and sulfonylurea (difference, 0.07%; 95% CI, -0.09 to 0.23; P value not significant), as was the change when rosiglitazone or metformin was added to sulfonylurea (difference, 0.06%; 95% CI, -0.09 to 0.20; P value not significant). Secondary: Differences in FPG were not significant at 18 months (rosiglitazone vs sulfonylurea, -0.36 mmol/L; P=0.062 and rosiglitazone vs metformin, -0.34 mmol/L; P=0.089). Rosiglitazone increased TC (P≤0.001) and LDL-C (P=0.000) and reduced nonesterified fatty acids (P=0.000) at 18 months compared to the control. An increase in HDL-C and TG was observed with rosiglitazone compared to sulfonylurea (0.08 vs 0.02 mmol/L; P=0.001, 0.40 vs 0.15 mmol/L; P=0.016, respectively), but not with metformin (P value not significant for both). HOMA-estimated basal insulin sensitivity was substantially increased with rosiglitazone compared to the respective controls (P<0.001 for both). Both rosiglitazone and sulfonylurea when added to metformin increased HOMA %β, but this increase was greater with the sulfonylurea (P<0.001). Rosiglitazone or metformin added to background sulfonylurea also increased HOMA %β, to a similar extent (P value not significant). Rosiglitazone was associated with a significant increase in body weight compared to metformin (P<0.001) and a sulfonylurea (P=0.003). At 18 months, plasminogen activator inhibitor-1 antigen decreased from baseline with rosiglitazone, with a significant difference compared to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				sulfonylureas (-5.7 vs 7.0%; P=0.047); rosiglitazone and metformin did not differ (P value not significant). There was a significant reduction in CRP with rosiglitazone compared to a sulfonylurea (P<0.001) and metformin (P=0.001).
Komajda et al.[118] (2008) RECORD Metformin plus a sulfonylurea vs rosiglitazone plus either metformin or a sulfonylurea	MC, OL, RCT Patients 40 to 75 years of age with type 2 diabetes and BMI ≥25 kg/m^2, on maximum tolerated doses of metformin or a sulfonylurea monotherapy, and inadequate glycemic control (HbA_{1c} 7.0 to 9.0%)	N=668 12 months	Primary: Change from baseline in 24-hour ambulatory BP at six months and 12 months Secondary: Not reported	Primary: For patients receiving rosiglitazone and a sulfonylurea, the reduction in 24-hour SBP was greater at six months (-3.8 mm Hg) and 12 months (-3.8 mm Hg) than with metformin and sulfonylurea therapy (-1.2 mm Hg and -1.3 mm Hg, respectively; six months, P=0.015; 12 months, P=0.031). Reductions in 24-hour DBP were greater at 6 months and 12 months for patients receiving rosiglitazone and a sulfonylurea (-3.1 mm Hg and -3.7 mm Hg) compared to metformin and sulfonylurea (-0.4 mm Hg and -0.6 mm Hg; both P<0.001). At 12 months, the reduction in 24-hour SBP was greater for rosiglitazone and metformin (-4.9 mm Hg) than for metformin and sulfonylurea (-2.2 mm Hg; P=0.016). At 12 months, the reduction in DBP was greater for rosiglitazone and metformin (-3.8 mmHg) than for metformin and sulfonylurea (-1.7 mm Hg; P=0.003). At six months, the reductions in SBP and DBP were not significantly different for rosiglitazone and metformin compared to metformin and sulfonylurea (SBP; P value not significant, DBP; P=0.049). Secondary: Not reported
Hamann et al.[119] (2008) Metformin 2,000 mg daily and glibenclamide*	DB, PG, RCT Overweight patients (BMI ≥25 kg/m^2) with type 2 diabetes, HbA_{1c} 7.0 to 10.0%, who	N=596 52 weeks	Primary: Change in HbA_{1c} from baseline to week 52 Secondary: Change in FPG,	Primary: At week 52, mean change in HbA_{1c} from baseline was -0.78% for RSG+MET compared to -0.86% with SU+MET (95% CI, -0.08 to 0.25). Secondary: Reductions in FPG from baseline to week 52 was -2.29 mmol/L with RSG+MET compared to -2.25 mmol/L with SU+MET (P=0.8095).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
5 mg or gliclazide† 80 mg (SU+MET) vs rosiglitazone/ metformin fixed dose combination 4/2,000 mg daily (RSG+MET)	received metformin ≥850 mg/day for at least 8 weeks		β-cell function, insulin resistance, hypoglycemia, BP	The degree of β-cell failure was significantly greater with SU+MET compared to RSG+MET as measured by the coefficient of failure (0.543 vs 0.055 HbA_{1c}%/year, respectively; P=0.0002). Insulin sensitivity increased 55% with RSG+MET compared to 12.3% with SU+MET (P<0.0001). Hypoglycemia occurred in 30% of patients receiving SU+MET compared to 6% of patients receiving RSG+MET (P<0.0001). After 52 weeks, 24-hour diastolic and systolic ambulatory BPs were reduced with RSG+MET, but not with SU+MET. The difference between treatments was significant for diastolic ambulatory BPs (-2.9 mm Hg; P=0.0013), but not for systolic ambulatory BP (-2.6 mm Hg; P=0.0549).
Diabetes Prevention Studies				
Knowler et al.[120] (2002) Metformin 850 mg BID vs placebo with standard lifestyle recommendations vs intensive lifestyle modifications designed to achieve and maintain both a 7% weight loss and 150 minutes of exercise a week	DB, MC, PC, RCT Nondiabetic patients ≥25 years of age at high risk with elevated fasting and post-load plasma glucose concentrations, BMI ≥24 kg/m^2 or ≥22 kg/m^2 for Asian patients, a plasma glucose concentration 95 to 125 mg/dL, and 140 to 199 mg/dL 2 hours after a 75 g oral glucose load	N=3,234 2.8 years (mean)	Primary: Diabetes, diagnosed on the basis of an annual oral glucose-tolerance test or a semiannual FPG test, according to the 1997 criteria of the American Diabetes Association: a value for plasma glucose of 126 mg/dL or higher in the fasting state or 200 mg/dL or higher two hours after a 75 g oral glucose load	Primary: Incidence of diabetes was 11.0, 7.8, and 4.8 cases per 100 person-years in the placebo, metformin, and intensive lifestyle-intervention groups, respectively. Incidence of diabetes was 58% lower (95% CI, 48 to 66) in the intensive lifestyle-intervention group and 31% lower (95% CI, 17 to 43) in the metformin group than in the placebo group. Incidence of diabetes was 39% lower (95% CI, 24 to 51) in the intensive lifestyle-intervention group than in the metformin group. Incidence of diabetes differed significantly among the three groups (P<0.001 for each comparison). The estimated cumulative incidence of diabetes at three years was 28.9, 21.7, and 14.4% in the placebo, metformin, and intensive lifestyle groups, respectively. Using these results, to prevent one case of diabetes during a three-year period, 6.9 persons would have to participate in the intensive lifestyle-intervention group and 13.9 persons would have to receive metformin.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Secondary: Not reported	Secondary: Not reported
Orchard et al.[121] (2005) Metformin 850 mg BID vs placebo with standard lifestyle recommendations vs intensive lifestyle modifications designed to achieve and maintain a 7% weight loss and 150 minutes of exercise a week	DB, MC, PC, RCT Nondiabetic patients ≥25 years of age at high risk with elevated fasting and post-load plasma glucose concentrations, BMI ≥24 kg/m^2 or ≥22 kg/m^2 for Asian patients, a plasma glucose concentration 95 to 125 mg/dL, and 140 to 199 mg/dL two hours after a 75 gram oral glucose load	N=3,234 3.2 years (mean)	Primary: Prevalence of the metabolic syndrome at baseline in the Diabetes Prevention Program and the incidence of new cases after intensive lifestyle intervention and metformin Secondary: Not reported	Primary: Fifty-three percent of the patients fulfilled the criteria for the metabolic syndrome; this proportion was relatively constant by age. Incidence of the metabolic syndrome was reduced by 41% in the intensive lifestyle group (P<0.001) and by 17% in the metformin group (P=0.03) compared to the placebo group. Resolution of metabolic syndrome in participants who had the syndrome at baseline was significant for intensive lifestyle interventions vs placebo (P=0.002). The prevalence at three years varied significantly by treatment group (P<0.001): 18% of the placebo group, 23% of the metformin group, and 38% of the intensive lifestyle group no longer had the syndrome. Prevalence of the metabolic syndrome in all participants increased from 55% at baseline to 61% after three years in the placebo group (P=0.003) and from 54% to 55% in the metformin group (P>0.2), but decreased in the intensive lifestyle group from 51 to 43% (P<0.001). Three-year cumulative incidences of the metabolic syndrome were 51% for placebo, 45% for metformin, and 34% for intensive lifestyle groups. Secondary: Not reported
Diabetes Prevention Program Research Group[122] (2015) Metformin 850 mg BID vs	DB, MC, PC, RCT Nondiabetic patients ≥25 years of age at high risk with elevated fasting and post-load plasma glucose concentrations, BMI ≥24 kg/m^2 or ≥22	N=2,776 15 years (mean)	Primary: Development of diabetes Secondary: Aggregate microvascular disease (including nephropathy,	Primary: Diabetes incidence rates after an average follow-up of 15 years were significantly lower by 27 and 18% with lifestyle intervention (HR, 0.73; CI, 0.65 to 0.83) and metformin (HR, 0.82; CI, 0.72 to 0.93), respectively, compared with the placebo group. Secondary: The average prevalence of the microvascular outcomes did not differ significantly among the three treatment groups, despite the group differences in diabetes incidence. However, in women (n=1,887) lifestyle

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo with standard lifestyle recommendations vs intensive lifestyle modifications designed to achieve and maintain a 7% weight loss and 150 minutes of exercise a week	kg/m^2 for Asian patients, a plasma glucose concentration 95 to 125 mg/dL, and 140 to 199 mg/dL 2 hours after a 75 g oral glucose load		retinopathy, and neuropathy)	intervention was associated with a lower prevalence (8.7%) than in the placebo (11%) and metformin (11.2%) groups, with 21% (P=0.03) and 22% (P=0.02) reductions with lifestyle compared with placebo and metformin, respectively. Compared with participants who progressed to diabetes, those who didn't progress had a 28% lower prevalence of microvascular complications (P<0.0001).
Zinman et al.[123] CANOE Rosiglitazone 2 mg/day plus metformin 500 mg BID vs placebo	DB, RCT Patients with impaired glucose tolerance	N=207 3.9 years (median duration)	Primary: Time to development of diabetes Secondary: Insulin sensitivity, β cell function, safety	Primary: Incident diabetes occurred in significantly fewer patients receiving combination therapy compared to placebo (14 vs 39%; P<0.0001). The relative risk reduction was 66% (95% CI, 48 to 80) and the absolute risk reduction was 26% (95% CI, 14 to 37), yielding a number needed to treat of 4 (95% CI, 2.70 to 7.14). Seventy patients (80%) receiving combination therapy regressed to normal glucose tolerance compared to 52 patients (53%) receiving placebo (P=0.0002). Secondary: Insulin sensitivity decreased by trial end in patients receiving placebo (median, -1.24) and remained unchanged in patients receiving combination therapy (median, -0.39; P=0.0006 vs placebo). Change in β cell function did not differ between the two treatments (P=0.28). Significantly more patients receiving combination therapy experienced diarrhea compared to placebo (P=0.0253).
Van de Laar et al.[124] (2006)	MA (5 trials)	N=2,360 1 to 6 years	Primary: Occurrence of type 2 diabetes	Primary: In the comparison of acarbose to placebo, the incidence of or conversion to type 2 diabetes was reduced (RR, 0.78; 95% CI, 0.68 to 0.90).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Metformin vs acarbose, placebo, diet and exercise, or both	Patients with impaired glucose tolerance or impaired fasting blood glucose		Secondary: Cardiovascular morbidity and mortality, glycemic control, lipids, BP, body weight	Neither acarbose nor metformin had significant effects on the incidence of type 2 diabetes when compared to one another. However, when compared to diet and exercise, acarbose had beneficial effects on the incidence of type 2 diabetes (RR, 0.40; 95% CI, 0.17 to 0.96). Secondary: There were no significant effects on total mortality or mortality due to cardiovascular causes in trials comparing acarbose to placebo. In one trial (STOP-NIDDM), a decreasing effect on the incidence of cardiovascular disease as a combined end point (MI, angina, revascularization procedures, cardiovascular death, congestive heart failure, cerebrovascular events, and peripheral vascular disease) was reported (RR, 0.47; 95% CI, 0.26 to 0.86). Acarbose decreased PPG by 0.61 mmol/L (95% CI, 0.27 to 0.95) compared to placebo. In the EDIT study, acarbose significantly decreased FPG and PPG in comparison to placebo (P=0.0043 and P=0.0075, respectively). In comparison to metformin, acarbose showed a decreasing effect on PPG (1.40 mmol/L; 95% CI, 0.55 to 2.25). Similarly, acarbose vs diet and exercise also showed significant reductions in FPG and PPG (-1.37 [95% CI, -0.50 to -2.24] and -2.79 mmol/L [95% CI, -1.79 to -3.79]). There were no significant effects on DBP and SBP in trials comparing acarbose to placebo. However, metformin showed significant decreases in both TC and DBP in comparison to acarbose (0.90 mmol/L [95% CI, 0.19 to 1.61] and 6 mm Hg [95% CI, 2.81 to 9.19], respectively). Acarbose decreased body weight by 1.2 kg (95% CI, 0.5 to 1.8) and BMI by 0.3 kg/m^2 (95% CI, 0.1 to 0.5) compared to placebo.
Salpeter et al.[125] (2008) Metformin (variable doses) vs	MA (31 RCTs) Patients at risk for type 2 diabetes mellitus	N=4,570 Duration varied	Primary: BMI, fasting glucose, fasting insulin, calculated insulin resistance, HDL-C, LDL-C,	Primary: Pooled results showed that metformin reduced BMI (-5.3%; 95% CI, -6.7 to -4.0), fasting glucose (-4.5%; 95% CI, -6.0 to -3.0), fasting insulin (-14.4%; 95% CI, -19.9 to -8.9), insulin resistance (-22.6%; 95% CI, -27.3 to -18.0), TG (-5.3%; 95% CI, -10.5 to -0.03), and LDL-C (-5.6%; 95% CI, -8.3 to -3.0%), and increased HDL-C (5.0%; 95% CI, 1.6 to 8.3) compared to placebo or no treatment.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo or no treatment			TG, incidence of new-onset diabetes Secondary: Not reported	The incidence of new-onset diabetes was reduced by 40% (OR, 0.6; 95% CI, 0.5 to 0.8), with an absolute risk reduction of 6% (95% CI, 4 to 8) during a mean trial duration of 1.8 years. Secondary: Not reported
Gestational Diabetes				
Moore et al.[126] (2010) Metformin 500 to 2,000 mg daily (divided doses) vs glyburide 2.5 to 10 mg BID Insulin was started in treatment failures and oral medication was discontinued.	DB, PG, RCT Women with gestational diabetes between 11 and 33 weeks gestation at the time of randomization	N=149 Variable duration	Primary: Glycemic control Secondary: Medication failure rate, macrosomia, admission to the neonatal intensive care unit, five-minute Apgar score <7, birth trauma, preeclampsia, maternal and neonatal hypoglycemia, and route of delivery	Primary: There was no difference between the glyburide or metformin groups in mean fasting (P=0.23) or two-hour PPG concentrations (post-breakfast, P=0.15; post-lunch, P=0.28; post-dinner, P=0.32). Secondary: Twenty-six patients (34.7%) in the metformin group and 12 patients (16.2%) in the glyburide group did not meet glycemic goals and required insulin therapy (P=0.01). The failure rate of metformin was 2.1 times higher than the failure rate of glyburide (95% CI, 1.2 to 3.9, OR, 2.7). Macrosomia occurred in 5.4% of patients in the glyburide group and 1.3% of patients in the metformin group (P=0.20). The mean birth weight of babies in the metformin group was smaller than the mean birth weight of babies in the glyburide group (P=0.02). Other neonatal outcomes did not differ between the two groups. There were four neonatal intensive care unit admissions in the metformin group and one neonatal intensive care unit admission in the glyburide group (P=0.37). There were no 5-minute Apgar scores <7 in either group. There was one shoulder dystocia in the glyburide group and one third-degree tear in the metformin group (P=0.49). The incidence of maternal hypoglycemia and preeclampsia was not different between the two treatment groups (P=0.56 and P>0.50,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				respectively). One infant in the metformin group experienced hypoglycemia with blood glucose less than 40 mg/dL. Excluding elective repeat cesarean deliveries, there were 11 cesarean deliveries in the metformin group compared with two cesarean deliveries in the glyburide group (P=0.02).
Nachum et al.[127] (2017) Metformin 850 to 2,550 mg daily (divided doses) vs glyburide 2.5 to 20 mg daily If optimal glycemic control was not achieved, the other drug was added	OL, PRO, RCT Women 18 to 45 years of age with gestational diabetes diagnosed between 13 to 33 weeks gestation and whose blood glucose was poorly controlled by diet	N=104 Recruitment until delivery	Primary: Rate of treatment failure (defined as patients needing additional oral hypoglycemic or a second-line therapy either because of poor glycemic control or adverse effects of the first-line medication) Secondary: The rate of participants requiring second-line therapy as a result of poor glycemic control or medication-associated adverse effects, the rate of participants requiring third-line therapy with insulin, preprandial and postprandial glucose values, obstetric outcomes,	Primary: Rates of treatment failure were comparable between the groups (glyburide, 34%; metformin, 29%; P=0.6). Secondary: The rate of adverse effects did not differ significantly between the treatments (P=0.11). The adverse effect requiring medication discontinuation was hypoglycemia in the glyburide group and gastrointestinal discomfort in the metformin group. Treatment success after second-line therapy was higher in the metformin group than in the glyburide group (13 of 15 patients [87%] vs 9 of 18 patients [50%], respectively; P=0.03). In the glyburide group, nine (17%) patients eventually were treated with insulin compared with two (4%) in the metformin group (P=0.03). Mean daily blood glucose and other obstetrical and neonatal outcomes were comparable between groups, including macrosomia, neonatal hypoglycemia, and electrolyte imbalance.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			and neonatal hypoglycemia and metabolic complications	
Ibrahim et al.[128] (2013) Group I: oral metformin (500 mg TID) without increasing the insulin dose vs group II: increased insulin dose	NI, RCT Pregnant women with gestational or pre-existing DM at gestations between 20 and 34 weeks who showed insulin resistance (defined as poor glycemic control at a daily dose of ≥1.12 units/kg)	N=90 Variable duration	Primary: Maternal glycemic control Secondary: Maternal hypoglycemia, hospital admissions, neonatal outcomes	Primary: Glycemic control was achieved in 76.1% of patients in group I and 100% of patients in group II (P=0.001). Secondary: Readmission for poor glycemic control was not significantly different between groups (P=0.471). Bouts of maternal hypoglycemia occurred in 6.5% of patients in group I and 22.7% in group II (P=0.029). Only two neonatal/delivery outcomes showed a statistical difference: Neonatal hypoglycemia occurred in 7.0% of cases in group I vs 38.5% in group II (P=0.001). Neonatal Intensive Care Unit admission occurred in 18.6% of group I neonates and 41% of group II neonates (P=0.026).
Spaulonci et al.[129] (2013) Metformin vs insulin	PRO, RCT Women with gestational diabetes with singleton pregnancy, use of diet and exercise for a minimum period of 1 week without satisfactory glycemic control, absence of risk factors for lactic acidosis, and absence of anatomic and/or chromosome anomalies of the conceptus detected by ultrasonography.	N=92 Variable duration	Primary: Maternal glycemic control Secondary: Neonatal outcomes	Primary: Higher mean glucose levels were observed in the insulin group (P=0.020), mainly because of higher levels observed after dinner (P=0.042). Twenty-one percent of women using insulin and 27% of women using metformin achieved adequate glycemic control in the first week of treatment (P=0.11). Twelve (26.08%) of the 46 women in the metformin group required supplemental insulin for adequate glycemic control. Secondary: No significant differences between the two groups were observed regarding the following neonatal outcomes: gestational age at birth, 1-minute Apgar score, 5-minute Apgar score, umbilical artery pH at birth, or newborn weight. There were no fetuses with macrosomia in the group metformin vs three (6.5%) cases in the insulin group (P=0.242). A higher frequency of neonatal hypoglycemia was observed in cases treated with insulin (22.2%) compared with newborns from the metformin group (6.5%) (P=0.032).
Niromanesh et al.[130]	RCT, SB	N=160	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2012) Metformin vs insulin	Gestational diabetes mellitus women with singleton pregnancy and gestational age between 20 and 34 weeks who did not achieve glycemic control on diet	Variable duration	Maternal glycemic control, birth weight Secondary: Neonatal and obstetric complications	The two groups were comparable with respect to mean fasting blood sugar and postprandial measurements throughout pregnancy after randomization until delivery. The mean fasting blood sugar was <95 mg/dL in 74% and 79% of women in the metformin and insulin groups, respectively (P=0.457). Neonates from the metformin group had a significantly lower circumference of head, arm and chest (P<0.05) and had lower birth weight (P=0.005) and height (P=0.033). The frequency rate of SGA (small for gestational age; birth weight < 10th percentile) was 3.8% in the metformin group and 2.5% in the insulin group. The relative risk of LGA (large for gestational age; birth weight > 90th percentile) in the metformin group was half that of the insulin group (RR, 0.5; 95% CI, 0.3 to 0.9, P=0.012). Secondary: The relative risk of emergency cesarean and preterm delivery was 1.6 and 2.2 times higher, respectively, in the metformin group; however, this was not statistically significant. The two groups were not statistically different in terms of need for phototherapy, incidence of hypoglycemia, and birth defects. The two groups were comparable with respect to umbilical artery pH, Apgar score at 5 min, and hospitalization days. Neonatal Intensive Care Unit admission and respiratory distress syndrome was nonsignificantly more frequent in the metformin group (RR, 2.5; 95% CI, 0.5 to 12.5, P=0.443).
Poolsup et al.[131] (2014) Pool A: metformin vs insulin Pool B: glyburide vs insulin	MA Women with gestational diabetes mellitus	N=2,151 (13 RCTs) Variable duration	Primary: Safety and efficacy of oral antidiabetic agents compared to insulin Secondary: Not reported	Primary: <u>Pool A</u> There was a nonsignificant difference in the risk of macrosomia (RR, 0.93; 95% CI, 0.61 to 1.41) and large for gestational age (LGA) births (RR, 0.88; 95% CI, 0.70 to 1.12) between the two study groups. A significant increase in the risk of preterm births occurred in the metformin group as compared to insulin (RR, 1.51; 95% CI, 1.04 to 2.19; P=0.03). Rate of neonatal/perinatal mortality was very low in both groups and results remained statistically non-significant. Risk of shoulder dystocia, neonatal hypoglycemia, congenital abnormality, and small for gestational age (SGA) births tended to be lower with metformin but statistical significance was not achieved. A non-significant decrease in risk of caesarean section, pre-eclampsia, and labor induction was noticed with

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				metformin compared to insulin. A significant decrease in the risk of gestational hypertension was observed in the metformin arm (RR, 0.54; 95% CI, 0.31 to 0.91; P=0.02). A significant decrease in PPG levels occurred (mean difference, -2.47 mg/dL; 95% CI, -4.00 to -0.94, P=0.002) in metformin group compared to insulin, while results were statistically nonsignificant between the two groups for FPG levels (mean difference, 0.74 mg/dL; 95% CI, -0.52 to -2.01). <u>Pool B</u> Glyburide significantly increased the risk of macrosomia (RR, 3.07; 95% CI, 1.14 to 8.23; P=0.03) and neonatal hypoglycemia (RR, 2.30; 95% CI, 1.28 to 4.11; P=0.005) compared to insulin. There was no difference between glyburide and insulin with regard to risk for LGA births; statistically significant heterogeneity was detected for this outcome. There were no significant differences in the risk of preterm births, neonatal mortality, congenital abnormality, or SGA births for glyburide versus insulin. None of the maternal outcomes (caesarean section, pre-eclampsia, maternal hypoglycemia, glycemic levels) displayed a significant difference between glyburide and insulin. The effect estimate for fasting glucose levels (mean difference, 1.90 mg/dL; 95% CI, -0.38 to 4.18) and postprandial glucose levels (mean difference, 3.42 mg/dL; 95% CI, -1.17 to 8.02) favored the insulin group, but results remained nonsignificant. Secondary: Not reported

*Synonym for glyburide.
†Agent not available in the United States.
Drug regimen abbreviations: BID=twice daily, ER=extended-release, IR=immediate-release, QD=once daily, QID=four times daily, SC=subcutaneous, TID=three times daily, XR=extended-release
Study abbreviations: AC=active-comparator, DB=double-blind, DD=double-blind, ES=extension study, MA=meta-analysis, MC=multicenter, NI=non-inferiority, OL=open-label, OS=observational, PC=placebo-controlled, PG=parallel-group, PM=post-marketing, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, SB=single blind, SR=systematic review, XO=cross-over
Miscellaneous abbreviations: apo=apolipoprotein, AUC=area under the curve, BMI=body mass index, BP=blood pressure, CI=confidence interval, CRP=C-reactive protein, DBP=diastolic blood pressure, FFA=free fatty acid, FPG=fasting plasma glucose, GLP-1=glucagon-like peptide-1, HbA_{1c}=glycosylated hemoglobin, HDL-C=high density lipoprotein cholesterol, HOMA-B=homeostasis model assessment-beta cell function, HOMA-S=homeostasis model assessment-insulin sensitivity, HR=hazard ratio, IU=international units, LDL-C=low density lipoprotein cholesterol, MI=myocardial infarction, NPH=neutral protamine Hagedorn, NYHA=New York Heart Association, OR=odds ratio, PPG=postprandial plasma glucose, QOL=quality of life, RR=relative risk, SBP=systolic blood pressure, TC=total cholesterol, TG=triglyceride, TNF=Tumor necrosis factor, TZD=thiazolidinedione, WMD=weighted mean difference

Additional Evidence

Dose Simplification
Schwartz et al. compared the efficacy, tolerability, and safety of metformin immediate-release tablets and metformin extended-release tablets. Patients received a dose of 1,500 mg once daily, 1,500 mg twice daily, or 2,000 mg once daily of metformin extended-release or 1,500 mg daily of metformin immediate-release given in two divided doses. The investigators demonstrated that once-daily extended-release metformin was as effective as twice-daily immediate-release metformin.[16]

Donnan et al. evaluated the patterns and predictors of adherence in patients with type 2 diabetes receiving treatment with a single antidiabetic agent. Adherence was ≥90% in 31.3% of the patients prescribed sulfonylureas and 33.9% of patients prescribed metformin. Patients with better adherence tended to be younger and had a shorter duration of diabetes. There were linear trends of poorer adherence with each increase in the daily number of tablets taken for both sulfonylurea (P=0.001) and metformin (P=0.074) indices. There were significant trends of decreasing adherence with the number of co-medications for the sulfonylurea group (P=0.0001) and metformin group (P=0.007). This study did not measure the impact of adherence on clinical outcomes.[132]

Stable Therapy
Fujioka et al. evaluated glycemic control in patients with type 2 diabetes mellitus switched from twice-daily immediate-release metformin to a once-daily extended-release formulation. The investigators found comparable efficacy and tolerability among the treatment groups.[15] Bhansali et al. demonstrated similar results when patients were switched from an immediate-release metformin product to an extended-release product. The investigators found that patients receiving immediate-release metformin achieved comparable glycemic control when treatment was switched to a once- or twice-daily metformin extended-release product.[13]

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

IX. Cost

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

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

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

Rx=prescription

Table 10. Relative Cost of the Biguanides

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Metformin	extended-release suspension, extended-	Glumetza ER®*, Riomet®*, Riomet ER®	$$$$$	$

	release tablet, solution, tablet			

*Generic is available in at least one dosage form or strength.

X. Conclusions

Metformin in the only biguanide that is currently available and it is approved for use as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.[1-5] Metformin is available in generic formulations.

According to current clinical guidelines, metformin remains the cornerstone to most antidiabetic treatment regimens. Metformin is the initial agent recommended in the glucose-centric algorithm for glycemic control.[9] The goal of treatment for type 2 diabetes is to control hyperglycemia and reduce the risk of long-term complications. A notable new theme in diabetes treatment guidelines is an emphasis on a complication-centric approach, beyond glucose levels, to frame decisions regarding first-line pharmacologic choices for the treatment of persons with diabetes. Pharmacologic therapy should be guided by person-centered treatment factors, including comorbidities and treatment goals. In adults with type 2 diabetes and established/high risk of atherosclerotic cardiovascular disease, heart failure, and/or chronic kidney disease, the treatment regimen should include agents that reduce cardiorenal risk. Pharmacologic approaches that provide adequate efficacy to achieve and maintain treatment goals should be considered, such as metformin or other agents, including combination therapy.[6-9]

Numerous clinical trials have established the efficacy/safety of metformin as monotherapy, as well as in combination with other antidiabetic agents.[12-130] Studies directly comparing immediate-release and sustained-release formulations of metformin have demonstrated similar efficacy.[13-18]

The most common adverse events with metformin are gastrointestinal in nature and include diarrhea, flatulence, nausea/vomiting, abdominal discomfort, and indigestion. There is also a risk of lactic acidosis with metformin. Although it occurs rarely, it can be fatal in approximately 50% of cases. Patients with renal insufficiency, congestive heart failure, hepatic impairment, history of lactic acidosis, decreased tissue perfusion, hemodynamic instability, hypoxic states, or serious acute illness are at increased risk of lactic acidosis.[1-3]

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

Therefore, all brand products 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 biguanide 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 Dipeptidyl Peptidase-4 (DPP-4) Inhibitors
AHFS Class 682005
November 8, 2023

I. Overview

Diabetes mellitus is a chronic condition which results in hyperglycemia. It is differentiated into four main classes: 1) type 1 diabetes; 2) type 2 diabetes; 3) gestational diabetes; and 4) other types (drug- or chemical-induced, genetic defects in β-cell function or insulin action, and diseases of the exocrine pancreas). Type 2 diabetes is the most prevalent form of the disease in the United States. Inadequate glycemic control may lead to both acute and long-term complications, including microvascular and macrovascular events. There are a variety of oral and injectable antidiabetic agents currently available to treat diabetes. The antidiabetic agents are categorized into 12 different American Hospital Formulary Service (AHFS) classes, which differ with regards to their mechanism of action, efficacy, safety profiles, tolerability, and ease of use.

The dipeptidyl peptidase-4 (DPP-4) inhibitors are approved for use as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are human incretin hormones that are released from the small intestine in response to food intake. These hormones have multiple effects on the stomach, liver, pancreas, and brain to control glucose concentrations; however, they are inactivated by the DPP-4 enzyme within minutes. Endogenous GLP-1 levels have been shown to be reduced in patients with type 2 diabetes. The DPP-4 inhibitors slow the inactivation of the incretin hormones and increase their concentration in the bloodstream. This effect enhances glucose-dependent insulin secretion by pancreatic beta cells and suppresses glucagon secretion from pancreatic alpha cells.[1-4]

Alogliptin, linagliptin, saxagliptin, and sitagliptin are also available in combination with metformin. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization.[5-10] Alogliptin is also available in combination with pioglitazone, a thiazolidinedione. The thiazolidinediones increase the insulin sensitivity of adipose tissue, skeletal muscle, and the liver. This results in increased glucose uptake and metabolism, suppression of hepatic glucose production, and decreased plasma free fatty acid concentrations.[11] In general, all of the combination DPP-4 inhibitor products are available for use when treatment with both drug components is appropriate.[5-11]

The DPP-4 inhibitors that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Alogliptin and alogliptin combination products are available in a generic formulation; metformin and pioglitazone are also available generically in separate formulations. This class was last reviewed in November 2021.

Table 1. Dipeptidyl Peptidase-4 (DPP-4) Inhibitors Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Single Entity Agents			
Alogliptin	tablet	Nesina®*	Nesina®*
Linagliptin	tablet	Tradjenta®	Tradjenta®
Saxagliptin	tablet	Onglyza®	Onglyza®
Sitagliptin	tablet	Januvia®	Januvia®
Combination Products			
Alogliptin and metformin	tablet	Kazano®*	Kazano®*
Alogliptin and pioglitazone	tablet	Oseni®*	Oseni®*
Linagliptin and metformin	extended-release tablet, tablet	Jentadueto®, Jentadueto XR®	Jentadueto®, Jentadueto XR®
Saxagliptin and metformin	extended-release tablet	Kombiglyze XR®	Kombiglyze XR®
Sitagliptin and metformin	extended-release, tablet, tablet	Janumet®, Janumet XR®	Janumet®, Janumet XR®

PDL=Preferred Drug List

II. Evidence-Based Medicine and Current Treatment Guidelines

Current clinical guidelines are summarized in Table 2. Please note that guidelines addressing the treatment of type 2 diabetes are presented globally, addressing the role of various medication classes.

Table 2. Treatment Guidelines Using the Dipeptidyl Peptidase-4 (DPP-4) Inhibitors

Clinical Guideline	Recommendation(s)
American Diabetes Association: **Standards of Care in Diabetes (2023)**[12]	Current criteria for the diagnosis of diabetes • The following are the criteria for a diagnosis of diabetes: glycosylated hemoglobin (HbA_{1c}) ≥6.5%, or a fasting plasma glucose (FPG) ≥126 mg/dL, or a two-hour plasma glucose ≥200 mg/dL during an oral glucose tolerance test or patients with classic symptoms of hyperglycemia, or classic symptoms of hyperglycemia or hyperglycemic crisis (random plasma glucose ≥200 mg/dL). Prevention or delay of type 2 diabetes • Refer adults with overweight/obesity at high risk of type 2 diabetes, as typified by the Diabetes Prevention Program (DPP), to an intensive lifestyle behavior change program to achieve and maintain a weight reduction of at least 7% of initial body weight through healthy reduced-calorie diet and ≥150 minutes/week of moderate-intensity physical activity. • A variety of eating patterns can be considered to prevent diabetes in individuals with prediabetes. • Metformin therapy for prevention of type 2 diabetes should be considered in adults at high risk of type 2 diabetes, as typified by the DPP, especially those aged 25 to 59 years with BMI ≥35 kg/m^2, higher FPG) (e.g., ≥110 mg/dL), and higher A1C (e.g., ≥6.0%), and in individuals with prior gestational diabetes mellitus (GDM). • Long-term use of metformin may be associated with biochemical vitamin B12 deficiency; consider periodic measurement of vitamin B12 levels in metformin-treated individuals, especially in those with anemia or peripheral neuropathy. Glycemic goals in adults • An A1C goal for many nonpregnant adults of <7% (53 mmol/mol) without significant hypoglycemia is appropriate. • If using ambulatory glucose profile (AGP)/glucose management indicator (GMI) to assess glycemia, a parallel goal for many nonpregnant adults is time in range (TIR) of >70% with time below range (TBR) <4% and time <54 mg/dL <1%. For those with frailty or at high risk of hypoglycemia, a target of >50% TIR with <1% TBR is recommended. • On the basis of health care provider judgment and patient preference, achievement of lower A1C levels than the goal of 7% may be acceptable and even beneficial if it can be achieved safely without significant hypoglycemia or other adverse effects of treatment. • Less stringent A1C goals (such as <8% [64 mmol/mol]) may be appropriate for patients with limited life expectancy or where the harms of treatment are greater than the benefits. HCPs should consider deintensification of therapy if appropriate to reduce the risk of hypoglycemia in patients with inappropriate stringent A1C targets. Pharmacologic therapy for type 1 diabetes • Most individuals with type 1 diabetes should be treated with multiple dose insulin injections (three to four injections per day of basal and pre-prandial insulin) or continuous subcutaneous (SC) insulin infusion therapy.

Clinical Guideline	Recommendation(s)
	• Most patients should use rapid-acting insulin analogs to reduce hypoglycemia risk. • Patients with type 1 diabetes should receive education on how to match prandial insulin doses to carbohydrate intake, premeal blood glucose, and anticipated physical activity. Pharmacologic therapy for type 2 diabetes • Healthy lifestyle behaviors, diabetes self-management education and support, avoidance of clinical inertia, and social determinants of health should be considered in the glucose-lowering management of type 2 diabetes. Pharmacologic therapy should be guided by person-centered treatment factors, including comorbidities and treatment goals. • In adults with type 2 diabetes and established/high risk of atherosclerotic cardiovascular disease, heart failure, and/or chronic kidney disease, the treatment regimen should include agents that reduce cardiorenal risk. • Pharmacologic approaches that provide adequate efficacy to achieve and maintain treatment goals should be considered, such as metformin or other agents, including combination therapy. • Weight management is an impactful component of glucose-lowering management in type 2 diabetes. The glucose-lowering treatment regimen should consider approaches that support weight management goals. • Metformin should be continued upon initiation of insulin therapy (unless contraindicated or not tolerated) for ongoing glycemic and metabolic benefits. • Early combination therapy can be considered in some individuals at treatment initiation to extend the time to treatment failure. • The early introduction of insulin should be considered if there is evidence of ongoing catabolism (weight loss), if symptoms of hyperglycemia are present, or when A1C levels (>10% [86 mmol/mol]) or blood glucose levels (≥300 mg/dL [16.7 mmol/L]) are very high. • A person-centered approach should guide the choice of pharmacologic agents. Consider the effects on cardiovascular and renal comorbidities, efficacy, hypoglycemia risk, impact on weight, cost and access, risk for side effects, and individual preferences. • Among individuals with type 2 diabetes who have established atherosclerotic cardiovascular disease or indicators of high cardiovascular risk, established kidney disease, or heart failure, a sodium–glucose cotransporter 2 inhibitor and/or glucagon-like peptide 1 receptor agonist with demonstrated cardiovascular disease benefit is recommended as part of the glucose-lowering regimen and comprehensive cardiovascular risk reduction, independent of A1C and in consideration of person-specific factors. • In adults with type 2 diabetes, a glucagon-like peptide 1 receptor agonist is preferred to insulin when possible. • If insulin is used, combination therapy with a glucagon-like peptide 1 receptor agonist is recommended for greater efficacy, durability of treatment effect, and weight and hypoglycemia benefit. • Recommendation for treatment intensification for individuals not meeting treatment goals should not be delayed. • Medication regimen and medication-taking behavior should be reevaluated at regular intervals (every three to six months) and adjusted as needed to incorporate specific factors that impact choice of treatment. • Clinicians should be aware of the potential for over-basalization with insulin therapy. Clinical signals that may prompt evaluation of over-basalization include basal dose more than ~0.5 units/kg/day, high bedtime–morning or post-preprandial glucose differential, hypoglycemia (aware or unaware), and high

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	glycemic variability. Indication of over-basalization should prompt reevaluation to further individualize therapy.
American Diabetes Association/ European Association for the Study of Diabetes: **Management of Hyperglycemia in Type 2 Diabetes. A consensus report by the American Diabetes Association and the European Association for the Study of Diabetes (2022)**[13]	Consensus recommendations • All people with type 2 diabetes should be offered access to ongoing diabetes self-management education and support programs. • Providers and health care systems should prioritize the delivery of person-centered care. • Optimizing medication adherence should be specifically considered when selecting glucose-lowering medications. • Medical nutrition therapy focused on identifying healthy dietary habits that are feasible and sustainable is recommended in support of reaching metabolic and weight goals. • Physical activity improves glycemic control and should be an essential component of type 2 diabetes management. • Adults with type 2 diabetes should engage in physical activity regularly (>150 min/week of moderate- to vigorous-intensity aerobic activity) and be encouraged to reduce sedentary time and break up sitting time with frequent activity breaks. • Aerobic activity should be supplemented with two to three resistance, flexibility, and/or balance training sessions/week. Balance training sessions are particularly encouraged for older individuals or those with limited mobility/poor physical function. • Metabolic surgery should be considered as a treatment option in adults with type 2 diabetes who are appropriate surgical candidates with a BMI ≥40.0 kg/m^2 (BMI ≥37.5 kg/m^2 in people of Asian ancestry) or a BMI of 35.0 to 39.9 kg/m^2 (32.5 to 37.4 kg/m^2 in people of Asian ancestry) who do not achieve durable weight loss and improvement in comorbidities (including hyperglycemia) with nonsurgical methods. • In people with established CVD, a GLP-1 RA with proven benefit should be used to reduce MACE, or an SGLT2i with proven benefit should be used to reduce MACE and HF and improve kidney outcomes. • In people with CKD and an eGFR ≥20 ml/min per 1.73 m^2 and a urinary albumin/creatinine ratio >3.0 mg/mmol (>30 mg/g), an SGLT2i with proven benefit should be initiated to reduce MACE and HF and improve kidney outcomes. Indications and eGFR thresholds may vary by region. If such treatment is not tolerated or is contraindicated, a GLP-1 RA with proven cardiovascular outcome benefit could be considered to reduce MACE and should be continued until kidney replacement therapy is indicated. • In people with HF, SGLT2i should be used because they improve HF and kidney outcomes. • In individuals without established CVD but with multiple cardiovascular risk factors (such as age ≥55 years, obesity, hypertension, smoking, dyslipidemia, or albuminuria), a GLP-1 RA with proven benefit could be used to reduce MACE, or an SGLT2i with proven benefit could be used to reduce MACE and HF and improve kidney outcomes. • In people with HF, CKD, established CVD, or multiple risk factors for CVD, the decision to use a GLP-1 RA or SGLT2i with proven benefit should be independent of background use of metformin. • SGLT2i and GLP-1 RA reduce MACE, which is likely to be independent of baseline HbA1c. In people with HF, CKD, established CVD, or multiple risk factors for CVD, the decision to use a GLP-1 RA or an SGLT2i with proven benefit should be independent of baseline HbA1c. • In general, selection of medications to improve cardiovascular and kidney outcomes should not differ for older people. • In younger people with diabetes (<40 years), consider early combination therapy.

Clinical Guideline	Recommendation(s)
	• In women with reproductive potential, counseling regarding contraception and taking care to avoid exposure to medications that may adversely affect a fetus are important.
American Association of Clinical Endocrinologists/ American College of Endocrinology: **Clinical Practice Guidelines for Developing a Diabetes Mellitus Comprehensive Care Plan (2022)**[14]	Antihyperglycemic Pharmacotherapy for Persons with Type 2 Diabetes • Individualized pharmacotherapy for persons with T2D should be prescribed based on evidence for benefit that includes glucose lowering, avoidance of hypoglycemia and weight gain, and reduction of cardio-renal risk. • Persons with T2D and their health care professionals should use patient-centered shared decision-making to agree on therapy targets and treatments as well as a regimen for glucose monitoring (i.e., BGM, structured BGM, or CGM). • Glycemic targets include A1C, BGM, and, for those using CGM, achievement of CGM targets such as time in range (TIR), percentage in low and very low range, time above range, and glycemic variability. Nonglycemic targets include avoidance of hypoglycemia, control of BP, lipids, other CVD risk factors, and achieving and maintaining a healthy body weight. • Independent of glycemic control, targets, or treatment, if there is established or high risk for ASCVD, HF, and/or CKD, clinicians should prescribe a GLP-1 RA or an SGLT2i with proven efficacy for the specific condition(s) of the person with T2D being treated. • DM therapy should be individualized based on level of glycemia and the presence of comorbidities, complications, and access. Metformin is often the preferred initial therapy. Other agents may be appropriate as first line or in addition to metformin to reduce BG and/or to address specific comorbidities (such as ASCVD, HF, CKD, obesity, NAFLD), independent of glucose-lowering effects. • For some recently diagnosed individuals with T2D and more severe hyperglycemia (A1C ≥7.5%), unlikely to attain the A1C target with a single agent, early combination pharmacotherapy should be considered, usually to include metformin plus another agent that does not cause hypoglycemia, especially a GLP-1 RA, SGLT2i, or dipeptidyl peptidase 4 (DPP-4) inhibitor. • For newly diagnosed persons with T2D and an entry A1C >9.0% and/or ≥1.5% above target, one should initiate, along with lifestyle modifications, dual- or possibly triple-combination pharmacotherapy usually including metformin. Basal insulin along with noninsulin therapy is recommended if there are significant signs or symptoms of hyperglycemia, especially including catabolism (e.g., weight loss) or a very high A1C >10% (86 mmol/mol) or BG levels (≥300 mg/dL [16.7 mmol/L]). • Clinicians should discuss with persons with T2D the likelihood that most persons with T2D ultimately require a combination of multiple complementary antihyperglycemic agents, in addition to lifestyle interventions, to attain and maintain optimal glycemic control. • The DM care team should assess medication adherence and safety and glycemic control in persons with T2D quarterly or more frequently as needed. Subsequent visits will depend upon the metabolic targets achieved and the stability of metabolic control. • Persons with T2D who start on metformin should continue it unless intolerance or contraindications occur. When intensification of antihyperglycemic treatment is needed, other agents should be added to metformin. • Most persons with T2D who require intensification of antihyperglycemic therapy with a GLP-1 RA or insulin should initially be prescribed a GLP-1 RA. If further intensification is required, one should prescribe a basal insulin or a switch to a fixed-ratio combination of a basal insulin and a GLP-1 RA (insulin

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	glargine U100 + lixisenatide [GlarLixi] or insulin degludec + liraglutide [IdegLira]). • Insulin should be prescribed for persons with T2D when noninsulin antihyperglycemic therapy fails to achieve target glycemic control or when a person has symptomatic hyperglycemia. • Long-acting basal insulin analogs are the recommended initial choice of insulin therapy for persons with T2D. The insulin analogs glargine (U100 or U300), degludec (U100 or U200), or detemir are preferred over intermediate-acting Neutral Protamine Hagedorn (NPH) insulin because analog insulins have demonstrated less hypoglycemia in some studies. Glargine U300 and degludec can be associated with less hypoglycemia than glargine U100 or detemir. • Many persons with T2D receiving basal insulin and not at goal A1C can have significantly improved glycemia by the addition of a GLP-1 RA or being switched to a fixed-ratio combination basal insulin–GLP-1 RA (GlarLixi or IdegLira). One of these changes should be considered before adding a meal-time insulin for postprandial glycemic control. • When control of postprandial hyperglycemia is needed and a basal insulin and a GLP-1 RA are already being used, preference should be given to rapid-acting insulins (the analogs lispro, aspart, and glulisine or the rapid-acting inhaled human insulin powder) over regular human insulin. The former have a more consistent and a more rapid onset and offset of action with less risk of hypoglycemia. • Ultra-rapid-acting insulins (faster-acting insulin aspart, lispro aabc, and [human insulin] inhalation powder) may allow a decrease in the time between insulin administration and food intake and reduce the postprandial peak of PG as compared with rapid-acting insulins. The significance of this on long-term complications is unknown. • Basal-bolus insulin regimens or continuous subcutaneous insulin infusion (CSII) (i.e., insulin pump) allow for adjustment of insulin doses according to carbohydrate intake and activity levels and are recommended for intensive insulin therapy in persons with T2D. • Premixed insulin formulations (fixed combinations of shorter- and longer-acting components) of human or analog insulin may be considered for persons with T2D who have consistent dietary and exercise patterns and in whom adherence to more intensive insulin regimens is problematic. However, these preparations have reduced dosage flexibility and may increase the risk of hypoglycemia compared with basal insulin or basal-bolus regimens. • In persons with T2D who are treated with basal-bolus insulin therapy, adding a GLP-1 RA, or switching to a fixed-ratio combination of a GLP-1 RA and a basal insulin, or adding an SGLT2i or pramlintide (less commonly used) may be able to reduce postprandial hyperglycemia, A1C, and weight. GLP-1 RAs may also allow reduction or discontinuation of bolus insulin in some individuals. <u>How should insulin therapy be used for management of persons with type 1 diabetes?</u> • Insulin must be used to treat all persons with T1D. • Physiologic insulin replacement regimens, which provide both basal and prandial (meal-related or bolus) insulin, are recommended for most persons with T1D. • Achievement of glucose targets using either MDI of insulin or CSII, is needed to prevent development of life-threatening crises, such as acute hyperglycemic crises (DKA and hyperglycemic hyperosmolar state) and catabolic state. • A multi-component self-management DM education program is recommended for persons with T1D. Ideally, this is provided by a professional with expertise (i.e., certified diabetes care and education specialist) in the topics of healthy lifestyle, insulin technique including prandial insulin dosing guided by

Clinical Guideline	Recommendation(s)
	carbohydrate counting and diet adjustments for special situations, such as physical activity and prolonged fasting. Instruction is also needed in how to deal with sick days and prevention of DKA and hypoglycemia, and other relevant issues. Due to changes in DM self-management practices and each individual's medical history, personal and cultural background, and educational needs, specific education topics may need to be repeated at regular intervals. • The ideal insulin regimen should be personalized to an individual's needs and glycemic targets, attempting to better emulate physiological insulin replacement to maintain near normoglycemia, to prevent the development and progression of DM complications, while minimizing hypoglycemia and providing flexibility for specific daily life situations/scenarios such as: exercise, sleep, acute illness, psychological stress, etc. • Insulin regimens usually should involve the use of insulin analogs for most persons with T1D and include the following approaches: o MDI, which usually involve 1 to 2 subcutaneous injections daily of basal insulin to suppress ketogenesis and gluconeogenesis and to control glycemia between meals and overnight, and subcutaneous injections of prandial insulin or use of inhaled insulin before each meal to control meal-related glycemic excursions. CGM is the preferred method of glucose monitoring for all individuals with T1D. o Insulin pump therapy (CSII) provides constant/continuous infusion of fast-acting insulin driven by mechanical force and delivered via a cannula inserted under the skin. CSII can improve (or enhance) glycemic control and should be an option for insulin delivery for appropriate persons with DM. Ideally, these individuals should also use CGM as stated in R13.6.a. o Automated insulin delivery systems (AIDs), which include an insulin pump, an integrated CGM, and computer software algorithm, aim to better emulate physiological insulin replacement and achieve glycemic targets. This technology is recommended for many persons with T1D since its use has been shown to increase TIR while often reducing hypoglycemia or at least without causing increased hypoglycemia. o Open-loop (use of a pump and sensor which do not communicate) and sensor-augmented pump (SAP) systems: (CGM communicates with pump facilitating needed adjustments to basal rate; temporary interruption of insulin delivery when glucose levels are low or forecast to be low within 30 min). Insulin pump with a CGM or an SAP is recommended to manage persons with DM treated with intensive insulin management who prefer not to use AIDs or have no access to them. <u>How should diabetes mellitus in pregnancy be managed?</u> • For women with GDM, the following treatment goals are recommended: preprandial glucose concentration ≤95 mg/dL and either a 1-h post-meal glucose ≤140 mg/dL or a 2-h post-meal glucose ≤120 mg/dL to decrease adverse fetal outcomes. • All women with preexisting DM (T1D, T2D, or previous GDM) need access to preconception care and counseling to ensure adequate nutrition, healthy weight, and glucose control before conception, during pregnancy, and in the postpartum period. • Rapid-acting insulin analogs (insulin-lispro, insulin-aspart) should be used to treat postprandial hyperglycemia in pregnant women. • Options for basal insulin include long-acting insulin (e.g., NPH, detemir, or glargine) or rapid-acting insulin via a CSII. Regular insulin, although not recommended as first-line therapy, is acceptable to use in managing pregnant women with DM when rapid-acting insulin analogs are not available. • Insulin is the preferred therapeutic choice for pregnant women with GDM or T2D, but metformin has been given a category B for pregnancy with

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	accumulating clinical evidence of metformin's safety during the first trimester and beyond. Metformin has been shown to improve pregnancy and fetal outcomes except for increased rates of infants with SGA and later onset of obesity. The prescriber should discuss the potential risks and benefits of oral agent therapy during pregnancy as well as the need for longer-term outcome studies.
American Association of Clinical Endocrinologists/ American College of Endocrinology: **Consensus Statement on the Comprehensive Type 2 Diabetes Management Algorithm (2023)**[15]	Principles underlying the algorithm • Lifestyle modification underlies all therapy. • Maintain or achieve optimal weight. • Choice of antihyperglycemic therapy reflects glycemic targets, atherosclerotic cardiovascular disease (ASCVD), congestive heart failure (CHF), chronic kidney disease (CKD), overweight/obesity, and nonalcoholic fatty liver disease (NAFLD). • Choice of therapy includes ease of use and access. • Optimal hemoglobin A1c (A1C) is ≤6.5% or as close to normal as is safe and achievable for most patients. • Individualize all glycemic targets (A1C, glucose management indicator [GMI], time in range [TIR], fasting blood glucose [FBG], and PPG). • Get to goal as soon as possible (adjust ≤3 months). • Avoid hypoglycemia. Hypoglycemia, defined as blood glucose (BG) <70 mg/dL, is associated with an increased risk for adverse outcomes including mortality. • CGM is highly recommended to assist persons with diabetes in reaching goals safely. • Comorbidities must be managed for comprehensive care. Algorithm summative information • The algorithm is intended as a more concise document than the guideline, providing easily accessible, visual guidance for decision-making in the clinic setting. • In this 2023 algorithm, there continues to be an emphasis on lifestyle modification and treatment of overweight/obesity as key pillars of the management of prediabetes and DM. • The importance of appropriate management of the atherosclerotic risk factors of dyslipidemia and hypertension is highlighted. • One notable new theme is an obvious emphasis on a complication-centric approach, beyond glucose levels, to frame decisions regarding first-line pharmacologic choices for the treatment of persons with diabetes. • The algorithm is divided into discrete graphic sections that outline the principles for management of T2D and guide management of adiposity-based chronic disease (ABCD), prediabetes, and atherosclerotic risk factors of dyslipidemia and hypertension. In addition, the algorithms for antihyperglycemic agents include both complication-centric and glucose-centric approaches, and there is direction for insulin initiation and titration. Tables summarizing the benefits and risks of antihyperglycemic medications (updated) and weight-loss pharmacotherapy (new) are provided.

American Academy of Pediatrics: **Management of Newly Diagnosed Type 2 Diabetes Mellitus (T2DM) in Children and Adolescents (2013)**[16]	• Clinicians must ensure that insulin therapy is initiated for children and adolescents with T2DM who are ketotic or in diabetic ketoacidosis and in whom the distinction between types 1 and 2 diabetes mellitus is unclear and, in usual cases, should initiate insulin therapy for patients.
	  ○ Who have random venous or plasma blood glucose (BG) concentrations ≥250 mg/dL.
	  ○ Whose HbA_{1c} is >9%.

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	• In all other instances, clinicians should initiate a lifestyle modification program, including nutrition and physical activity, and start metformin as first-line therapy for children and adolescents at the time of diagnosis of T2DM.
	• Monitoring of HbA_{1c} concentrations is recommended every three months and intensifying treatment is recommended if treatment goals for finger-stick BG and HbA_{1c} concentrations are not being met.
	• Advise patients to monitor finger-stick BG concentrations in patients who:
	  o Are taking insulin or other medications with a risk of hypoglycemia; or
	  o Are initiating or changing their diabetes treatment regimen; or
	  o Have not met treatment goals; or
	  o Have intercurrent illnesses.
	• Incorporate the Academy of Nutrition and Dietetics' *Pediatric Weight Management Evidence-Based Nutrition Practice Guidelines* in dietary or nutrition counseling of patients with T2DM at the time of diagnosis and as part of ongoing management.
	• Encourage children and adolescents with T2DM to engage in moderate-to-vigorous exercise for at least 60 minutes daily and to limit nonacademic "screen time" to less than two hours a day.

American Diabetes Association: **Type 1 Diabetes in Children and Adolescents: A Position Statement by the American Diabetes Association (2018)[17]**	<u>Blood Glucose Management: Monitoring and Treatment</u> • Most children with type 1 diabetes should be treated with intensive insulin regimens via either multiple daily injections of prandial insulin and basal insulin or continuous subcutaneous insulin infusion. • An HbA_{1c} target of <7.5% should be considered in most children and adolescents but should be individualized based on the needs and situation of the patient and family. • Children and adolescents with type 1 diabetes should have blood glucose levels monitored up to six to ten times/day including premeal, pre-bedtime, and as needed for safety (e.g., exercise, driving, illness, or the presence of symptoms of hypoglycemia). • Continuous blood glucose monitoring should be considered in all children and adolescents whether using insulin injections or an insulin pump. • In pediatric patients with type 1 diabetes automated insulin delivery systems can improve glycemic control and reduce hypoglycemia. <u>Lifestyle Management</u> • Individualized medical nutrition therapy is recommended for children and adolescents with type 1 diabetes. • Monitoring carbohydrate intake, whether by carbohydrate counting or experience-based estimation, is key to achieving optimal glycemic control. • Exercise if recommended for all children and adolescents with type 1 diabetes. The suggested goal is 60 minutes of moderate to vigorous aerobic activity daily with muscle-strengthening and bone-strengthening activities three times a week. • Children and adolescents with type 1 diabetes should be educated about prevention and management of potential hypoglycemia during and after exercise. • Strategies to prevent hypoglycemia during exercise, after exercise, and overnight following exercise include reducing prandial insulin dosing for the meal/snack preceding exercise, increasing carbohydrate intake, eating bedtime snacks, using continuous blood glucose monitoring, and/or reducing basal insulin doses. <u>Behavioral Aspects of Self-Management</u> • Children and adolescents with diabetes should be assessed for psychosocial issues and family stresses that could impact diabetes management at diagnosis and routine follow-up. • Consider including children in consent processes as early as cognitive development indicates understanding of health consequences of behavior.

Clinical Guideline	Recommendation(s)
	• Offer adolescents time by themselves with their care provider(s) starting at age 12 years, or when developmentally appropriate. <u>Complications and Comorbidities</u> • Diabetic Ketoacidosis o All individuals with type 1 diabetes should have access to an uninterrupted supply of insulin. Lack of access and insulin omissions are major causes of diabetic ketoacidosis. o Patients with type 1 diabetes should have continuous access to medical support for sick-day management. • Hypoglycemia o The recommended treatment of hypoglycemia (blood glucose <70 mg/dL) in conscious patients is 15 g of glucose, although any form of carbohydrate can be used. If hypoglycemia continues after 15 minutes, treatment should be repeated. Once blood glucose has returned to normal patients should consider consuming a meal/snack and/or reduce insulin. o All individuals with type 1 diabetes should be prescribed glucagon and families/caregivers should be educated on administration. o Treatment regimens should be reevaluated in those with hypoglycemia unawareness or one or more episodes of severe hypoglycemia. • Diabetic Kidney Disease o Annual screening for albuminuria with a random spot urine sample for albumin-to-creatinine ratio should be considered at puberty or at age >10 years, whichever is earlier, once the child has had diabetes for 5 years. o An angiotensin-converting-enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB), titrated to normalization of albumin excretion, may be considered when elevated urinary albumin-to-creatinine ratio is documented. • Retinopathy o An initial dilated and comprehensive eye examination is recommended at age 10 years or after puberty has started, whichever is earlier, once the patient has had diabetes for three to five years. o Annual routine follow-up is recommended but may be given every two years based on the advice of an eye care professional. • Neuropathy o Consider an annual comprehensive foot exam for adolescents at the start of puberty or at age 10 years, whichever is earlier, once the patient has had type 1 diabetes for 5 years. • Hypertension o Children and adolescents with type 1 diabetes should have blood pressure monitored at each visit. Elevated blood pressure should be confirmed on three separate days. o Initial treatment of high-normal blood pressure should include dietary modification and increased exercise. Pharmacologic treatment should be considered if blood pressure is not controlled after three to six months. o In patients with conformed hypertension pharmacologic treatment should be added to lifestyle modification at diagnosis. o ACE inhibitors and ARBs should be considered for initial treatment. • Dyslipidemia o A fasting lipid profile should be taken in children ≥10 years of age or older after the diagnosis of diabetes. Obtain a fasting lipid profile in children 10 years of age or older as soon as convenient after the diagnosis of diabetes o If lipids are abnormal, initial therapy should consist of optimizing glucose control and medical nutrition therapy using a Step 2 American Heart Association diet that restricts saturated fat to 7% of total calories and dietary cholesterol to 200 mg/day.

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	○ If lipids remain abnormal after six months of lifestyle intervention, consider adding a statin in children at least 10 years of age.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the dipeptidyl peptidase-4 (DPP-4) inhibitors are noted in Table 3.

Table 3. FDA-Approved Indications for the DPP-4 Inhibitors[1-11]

Generic Name(s)	Adjunct to Diet and Exercise to Improve Glycemic Control in Adults with Type 2 Diabetes	Monotherapy or Combination Therapy as Adjunct to Diet and Exercise to Improve Glycemic Control in Adults with Type 2 Diabetes
Alogliptin		✔
Linagliptin		✔
Saxagliptin		✔
Sitagliptin		✔
Alogliptin and metformin	✔ [a]	
Alogliptin and pioglitazone	✔ [b]	
Linagliptin and metformin	✔ [c]	
Saxagliptin and metformin	✔ [d]	
Sitagliptin and metformin	✔ [e]	

[a]When treatment with both alogliptin and metformin is appropriate.
[b]When treatment with both alogliptin and pioglitazone is appropriate.
[c]When treatment with both linagliptin and metformin or metformin extended-release is appropriate.
[d]When treatment with both saxagliptin and metformin is appropriate.
[e]When treatment with both sitagliptin and metformin or metformin extended-release is appropriate.

IV. Pharmacokinetics

The pharmacokinetic parameters of the dipeptidyl peptidase-4 (DPP-4) inhibitors are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the DPP-4 Inhibitors[18]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Single Entity Agents					
Alogliptin	100	20	Liver, limited (% not reported)	Renal (76), Feces (13)	21
Linagliptin	30	70 to 99	Not reported	Renal (5 to 7), Bile (80)	>100
Saxagliptin	Not reported	Negligible (% not reported)	Liver (% not reported)	Renal (60), Feces (22)	2.5
Sitagliptin	87	38	Liver, minimal (% not reported)	Renal (87), Feces (13)	12.4
Combination Products					
Alogliptin and metformin	100/50 to 60	20/ Negligible (% not reported)	Liver, limited (% not reported)/None	Renal (76), Feces (13)/ Renal (90)	21/6.2
Alogliptin and pioglitazone	100/50*	20/ >99	Liver, limited (% not reported)/ Liver, extensive (% not reported)	Renal (76), Feces (13)/ Renal (15 to 30)	21/3 to 7

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Linagliptin and metformin	30/50 to 60	70 to 99/ Negligible (% not reported)	Minimal (% not reported)/None	Renal (5 to 7), Bile (80)/ Renal (90)	>100/6.2
Saxagliptin and metformin	Not reported/ 50 to 60	Negligible (% not reported)/ Negligible (% not reported)	Liver (% not reported)/None	Renal (60), Feces (22)/ Renal (90)	2.5/6.2
Sitagliptin and metformin	87/50 to 60	38/Negligible (% not reported)	Liver, minimal (% not reported)/None	Renal (87), Feces (13)/ Renal (90)	12.4/6.2

*Animal studies.

V. Drug Interactions

Major drug interactions with the dipeptidyl peptidase-4 (DPP-4) inhibitors are listed in Table 5.

Table 5. Major Drug Interactions with the DPP-4 Inhibitors[18]

Generic Name(s)	Interaction	Mechanism
Linagliptin	Tipranavir	Concurrent use of linagliptin and tipranavir may result in decreased linagliptin exposure.
Linagliptin	Strong CYP3A4 inducers	Coadministration of linagliptin (a CYP3A4 substrate) with strong CYP3A4 inducers may reduce linagliptin exposure and lead to a loss of linagliptin efficacy.
Metformin	Iodinated contrast materials, parenteral	Iodinated contrast materials-induced renal failure can interfere with the renal elimination of metformin; therefore, there is an increased risk of metformin-induced lactic acidosis.
Pioglitazone	Ifosfamide	Concurrent use of ifosfamide and pioglitazone may result in increased neurotoxic and nephrotoxic effects.
Pioglitazone	Tolvaptan	Concurrent use of pioglitazone and tolvaptan may result in decreased tolvaptan plasma concentrations.

VI. Adverse Drug Events

The most common adverse drug events reported with the dipeptidyl peptidase-4 (DPP-4) inhibitors are listed in Table 6. The boxed warning for DPP-4 inhibitor combination products containing metformin is listed in Table 7 and for alogliptin with pioglitazone in Table 8. There have been postmarketing reports of serious hypersensitivity reactions in patients taking DPP-4 inhibitors. These reactions include anaphylaxis, angioedema and exfoliative skin conditions including Stevens-Johnson syndrome. There have also been postmarketing reports of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, in patients taking DPP-4 inhibitors.[1-11] A warning has also been added to the labeling of DPP-4 inhibitors to inform of the potential increased risk of heart failure in high-risk populations.[1-11]

Table 6. Adverse Drug Events (%) Reported with the DPP-4 Inhibitors[1-11,19]

Adverse Event	Single Entity Agents*				Combination Products*				
	Alogliptin	Linagliptin	Saxagliptin	Sitagliptin	Alogliptin and Metformin†	Alogliptin and Pioglitazone†	Linagliptin and Metformin†	Saxagliptin and Metformin†	Sitagliptin and Metformin†
Abdominal pain	-	-	1.7 to 2.4	2.3	-	-	-	-	2.2 to 3.0
Anaphylaxis	✔	✔	✔	✔	-	-	-	-	-
Angioedema	✔	✔	✔	✔	-	-	-	-	-
Arthralgia	✔	5.7	-	✔	-	-	-	-	-
Back pain	-	6.4	-	✔	4.3	4.2	-	-	-
Cardiac failure	4	-	-	-	-	-	-	-	-
Constipation	✔	-	-	✔	-	-	-	-	-
Cough	-	2.7	-	-	-	-	✔	-	-
Decreased appetite	-	-	-	-	-	-	✔	-	-
Diarrhea	✔	-	-	3	5.5	-	6.3	5.8 to 9.9	2.4 to 7.5
Fracture	-	-	✔ ‡	-	-	-	-	-	-
Gastroenteritis	-	-	1.9 to 2.3	-	-	-	-	-	-
Headache	4.2	5.7	6.5 to 7.5	1.1 to 5.9	5.3	-	-	7.5	2.7 to 5.9
Hepatic failure	✔	-	-	-	-	-	-	-	-
Hyperlipidemia	-	2.7	-	-	-	-	-	-	-
Hypersensitivity	✔	✔	1.5	✔	-	-	✔	-	✔
Hypertension	-	-	-	-	5.5	-	-	-	-
Hypertriglyceridemia	-	2.4	-	-	-	-	-	-	-
Hypoglycemia	1.5	7.6 to 22.9	2.7 to 20.0	0.6 to 15.5	1.9 to 5.3	0 to 3.8	1.4 to 22.9	3.4 to 7.8	15.3 to 16.4
Infection	-	-	✔	-	-	-	-	-	-
Lymphopenia	-	-	0.5 to 1.5	-	-	-	-	-	-
Myalgia	-	✔	-	✔	-	-	-	-	-
Nasopharyngitis	4.4	7	6.9	5.2 to 11.0	6.8	4.9	6.3	6.9	6.1 to 11.0
Nausea	✔	-	-	1.4	-	-	✔	-	1.6 to 4.8
Pancreatitis	0.2	✔	✔	✔	-	-	✔	-	-

Adverse Event	Single Entity Agents*				Combination Products*				
	Alogliptin	Linagliptin	Saxagliptin	Sitagliptin	Alogliptin and Metformin†	Alogliptin and Pioglitazone†	Linagliptin and Metformin†	Saxagliptin and Metformin†	Sitagliptin and Metformin†
Peripheral edema	-	-	1.2 to 8.1	8.3	-	-	-	-	8.3
Pruritus	-	-	-	✔	-	-	✔	-	-
Rash	✔	✔	0.2 to 0.3	✔	-	-	-	-	-
Renal function abnormality	3 to 23	-	-	✔	-	-	-	-	-
Sinusitis	-	-	2.6 to 2.9	-	-	-	-	-	-
Thrombocytopenia	-	-	✔	-	-	-	-	-	-
Upper respiratory tract infection	4.2	-	7.7	4.5 to 15.5	8	4.1	-	-	5.5 to 6.2
Uric acid increased	-	3	-	-	-	-	-	-	-
Urinary tract infection	-	-	6.8	-	4.2	-	-	-	-
Urticaria	✔	-	-	✔	-	-	-	-	-
Vomiting	-	-	2.2 to 2.3	✔	-	-	✔	-	1.1 to 2.2
Weight gain	-	2.3	-	-	-	-	-	-	-

-Event not reported or incidence <1%.
✔ Percent not specified.
*Administered as monotherapy or in combination with other antidiabetic agents.
†Adverse reactions for combination therapy only are reported.
‡ Incidence rate of 1 per 100 patient-years (pooled analysis of 2.5, 5, and 10 mg) compared to placebo (0.6 per 100 patient-years).

Table 7. Boxed Warning for DPP-4 Inhibitor Combination Products Containing Metformin[5-10]

WARNING
WARNING: LACTIC ACIDOSIS • Postmarketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias. The onset of metformin-associated lactic acidosis is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, somnolence, and abdominal pain. Metformin-associated lactic acidosis was characterized by elevated blood lactate levels (greater than 5 mmol/L), anion gap acidosis (without evidence of ketonuria or ketonemia), an increased lactate/pyruvate ratio; and metformin plasma levels generally greater than 5 mcg/mL. Risk factors for metformin-associated lactic acidosis include renal impairment, concomitant use of certain drugs (e.g., carbonic anhydrase inhibitors such as topiramate), age 65 years old or greater, having a radiological study with contrast, surgery and other procedures, hypoxic states (e.g., acute congestive heart failure), excessive alcohol intake, and hepatic impairment. • If metformin-associated lactic acidosis is suspected, immediately discontinue therapy and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended.

Table 8. Boxed Warning for Alogliptin and Pioglitazone[11]

WARNING
WARNING: CONGESTIVE HEART FAILURE • Thiazolidinediones, including pioglitazone, which is a component of alogliptin-pioglitazone, cause or exacerbate congestive heart failure in some patients. • After initiation of alogliptin-pioglitazone and after dose increases, monitor patients carefully for signs and symptoms of heart failure (e.g., excessive, rapid weight gain, dyspnea and/or edema). If heart failure develops, it should be managed according to current standards of care and discontinuation or dose reduction of pioglitazone in alogliptin-pioglitazone must be considered. • Alogliptin-pioglitazone is not recommended in patients with symptomatic heart failure. Initiation of alogliptin-pioglitazone in patients with established New York Heart Association (NYHA) Class III or IV heart failure is contraindicated.

VII. Dosing and Administration

The usual dosing regimens for the dipeptidyl peptidase-4 (DPP-4) inhibitors are listed in Table 9.

Table 9. Usual Dosing Regimens for the DPP-4 Inhibitors[1-11,18]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Single-Entity Agents			
Alogliptin	Monotherapy or combination therapy as adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes: Tablet: 25 mg QD	Safety and efficacy in children have not been established.	Tablet: 6.25 mg 12.5 mg 25 mg
Linagliptin	Monotherapy or combination therapy as adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes: Tablet: 5 mg QD	Safety and efficacy in children have not been established.	Tablet: 5 mg
Saxagliptin	Monotherapy or combination therapy as adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes: Tablet: 2.5 or 5 mg QD	Safety and efficacy in children have not been established.	Tablet: 2.5 mg 5 mg
Sitagliptin	Monotherapy or combination therapy as adjunct to diet and exercise to improve	Safety and efficacy in children have not been established.	Tablet: 25 mg 50 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	glycemic control in adults with type 2 diabetes: Tablet: 100 mg QD		100 mg
Combination Products			
Alogliptin and metformin	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes when treatment with both alogliptin and metformin is appropriate: Tablet: initial, individualized based on the patient's current regimen and administered BID; maximum, 25-2,000 mg/day	Safety and efficacy in children have not been established.	Tablet: 12.5-500 mg 12.5-1,000 mg
Alogliptin and pioglitazone	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes when treatment with both linagliptin and pioglitazone is appropriate: Tablet: initial, individualized based on the patient's current regimen and glycemic control and administered QD; maximum, 25-45 mg/day	Safety and efficacy in children have not been established.	Tablet: 12.5-30 mg 25-15 mg 25-30 mg 25-45 mg
Linagliptin and metformin	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes when treatment with both linagliptin and metformin is appropriate: Extended-release tablet: initial, individualized on the basis of both effectiveness and tolerability; maximum, 5-2,000 mg QD Tablet: initial, individualized on the basis of both effectiveness and tolerability; maximum, 2.5-1,000 mg BID	Safety and efficacy in children have not been established.	Extended-release tablet: 2.5-1,000 mg 5-1,000 mg Tablet: 2.5-500 mg 2.5-850 mg 2.5-1,000 mg
Saxagliptin and metformin	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes when treatment with both saxagliptin and metformin is appropriate: Extended-release tablet: initial, individualized on the basis of the patient's current regimen, effectiveness, and tolerability and administered QD; maximum, 5-2,000 mg/day	Safety and efficacy in children have not been established.	Extended-release tablet: 5-500 mg 2.5-1,000 mg 5-1,000 mg
Sitagliptin and metformin	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes when treatment with both sitagliptin and metformin or metformin extended-release is appropriate: Extended-release tablet: initial, individualized based on the patient's current regimen and administered QD; maximum, 100-2,000 mg/day Tablet: initial, individualized based on the patient's current regimen and administered BID; maximum, 100-2,000 mg/day	Safety and efficacy in children have not been established.	Extended-release tablet: 50-500 mg 50-1,000 mg 100-1,000 mg Tablet: 50-500 mg 50-1,000 mg

BID=twice daily, QD=once daily

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the dipeptidyl peptidase-4 (DPP-4) inhibitors are summarized in Table 10.

Table 10. Comparative Clinical Trials with the DPP-4 Inhibitors

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Type 2 Diabetes – Monotherapy				
DeFronzo et al.[20] (2008) Alogliptin Study 010 Alogliptin 12.5 mg QD vs alogliptin 25 mg QD vs placebo All patients received counseling on diet and exercise.	DB, MC, PC, RCT Treatment naïve patients 18 to 80 years of age with type 2 diabetes, an HbA_{1c} value 7.0 to 10.0%, a BMI 23 to 45 kg/m^2, exercise for ≥1 month and BP ≤180/110 mm Hg	N=329 26 weeks	Primary: Mean change from baseline in HbA_{1c} at week 26 Secondary: Changes in FPG, hyperglycemic rescue, incidence of marked hyperglycemia, changes in body weight and safety endpoints.	Primary: Mean HbA_{1c} decreased significantly more with 12.5 mg (-0.56%; P<0.001) and 25 mg (-0.59%; P<0.001) alogliptin than with placebo (-0.02%) by week 26. Secondary: FPG reductions were significantly greater with alogliptin 12.5 and 25 mg than with placebo at week 26 (-10.3 and -16.4 vs 11.3 mg/dL, respectively; P<0.001 for both comparisons). The percentage of patients who required hyperglycemic rescue was significantly less with alogliptin 12.5 and 25 mg compared to placebo (9.8 and 7.6 vs 29.7%, respectively; P=0.001 and P<0.001, respectively). Differences between treatment and placebo of most other secondary endpoints, including weight loss, were not significant. Most common adverse events occurred with similar or lower frequency in those given alogliptin vs placebo. However, headache occurred more frequently with alogliptin (6.8 to 7.5%) than with placebo (4.7%).
Rosenstock et al.[21] (2008) <u>Low-dose</u> Saxagliptin 2.5 to 40 mg QD vs placebo	DB, MC, PC, PG, RCT Type 2 diabetics ≥21 to ≤70 years of age with an HbA_{1c} ≥6.8 to ≤9.7%, BMI ≤37 kg/m^2, and a screening fasting or random C-peptide >0.5 ng/mL	N=338 12 weeks (saxagliptin 2.5, 5, 10, 20, and 40 mg); 6 weeks (saxagliptin 100 mg)	Primary: Change in baseline HbA_{1c} Secondary: Analyses of each dose vs placebo for decreasing HbA_{1c}, FPG, and PPG at 60 minutes from baseline	Primary: With low-dose saxagliptin, the test for log-linear trend across the treatment groups did not demonstrate a significant dose-response relationship in decreasing HbA_{1c}. Placebo-subtracted adjusted mean changes from baseline to week 12 with saxagliptin ranged from -0.45 to -0.63%, with no apparent significant dose-response relationship (P=0.9888). Secondary: After 12 weeks, HbA_{1c} was significantly decreased with low-dose saxagliptin compared to placebo (all doses P<0.007), with similar and clinically meaningful decreases in HbA_{1c} achieved with all doses of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<u>High-dose</u> Saxagliptin100 mg QD vs placebo				saxagliptin. Adjusted mean baseline decreases exceeded 0.70% with each saxagliptin dose compared to 0.27% with placebo. With high-dose saxagliptin, HbA_{1c} was significantly decreased compared to placebo (-1.09 vs -0.36%; P value not reported). With both low- and high-dose saxagliptin, decreases in FPG were evident after two weeks of treatment, and ranged from -11.0 to -22.0 mg/dL with low-dose saxagliptin compared to 3.0 mg/dL with placebo, and -26.3 mg/dL with high-dose saxagliptin compared to -3.3 mg/dL with placebo (P values not reported). With low-dose saxagliptin decreases in PPG at 60 minutes during a liquid meal tolerance test ranged from -24.0 to -41.0 mg/dL compared to -1.0 mg/dL with placebo (P value not reported). With high-dose saxagliptin it was -45.0 mg/dL compared to -17.0 mg/dL with placebo (P value not reported).
Rosenstock et al.[22] (abstract) (2009) <u>Randomized cohort</u> Saxagliptin 2.5 to 10 mg QD vs placebo <u>Open-label cohort</u> Saxagliptin 10 mg QD vs placebo	OL, PC, RCT Treatment-naïve type 2 diabetics with inadequate glycemic control, and an $HbA_{1c} \geq 7.0$ and $\leq 10.0\%$	N=401 (N=66 in the OL cohort) 24 weeks	Primary: Change in baseline HbA_{1c} Secondary: Change in baseline FPG and PPG, proportion of patients achieving an $HbA_{1c} < 7.0\%$	Primary: In the main treatment cohort, saxagliptin significantly decreased HbA_{1c} compared to placebo (-0.43, -0.46, and -0.54 vs 0.19% for placebo; all P<0.0001). Secondary: Saxagliptin significantly decreased FPG compared to placebo (-15, -9, and -17 vs 6 mg/dL; P=0.0002, P=0.0074, and P<0.0001). The decrease in PPG AUC with saxagliptin 2.5 (-6,868 [mg/minute]/[dL], 5 (-6,896 [mg/minute]/[dL], and 10 mg (-8,804 [mg/minute]/[dL] compared to placebo (-647 [mg/minute]/[dL] was only significant with saxagliptin 5 (P=0.0002) and 10 mg (P<0.0001). Greater proportions of patients receiving saxagliptin achieved an HbA_{1c} <7.0% compared to patients receiving placebo (35 [P value not significant], 38 [P=0.0443], and 41 [P=0.0133] vs 24%). Decreases in HbA_{1c}, FPG, and PPG AUC were observed in the OL cohort.
Scircia et al.[23] (2013)	RCT	N=16,492	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
SAVOR-TIMI Saxagliptin 5 mg QD (2.5 mg daily in patients with an estimated glomerular filtration rate ≤50 mL per minute) vs placebo	Type 2 diabetics ≥40 years of age with an HbA_{1c} ≥6.5 to ≤12% and either a history of established cardiovascular disease or multiple risk factors for vascular disease	2.1 years	A composite of cardiovascular death, myocardial infarction or ischemic stroke Secondary: A composite endpoint (cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, coronary revascularization, or heart failure), hospitalization rate for heart failure and cases of pancreatitis	A primary end-point event occurred in 613 patients in the saxagliptin group and in 609 patients in the placebo group (7.3 and 7.2%, respectively; HR, 1.00; 95% CI, 0.89 to 1.12; P=0.99 for superiority; P<0.001 for noninferiority); the results were similar in the "on-treatment" analysis (HR, 1.03; 95% CI, 0.91 to 1.17). Secondary: The major secondary end point of a composite of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, coronary revascularization, or heart failure occurred in 1,059 patients in the saxagliptin group and in 1,034 patients in the placebo group (12.8 and 12.4%, respectively; HR, 1/09; 95% CI, 0.94 to 1.11; P=0.66). More patients in the saxagliptin group than in the placebo group were hospitalized for heart failure (3.5 vs. 2.8%; HR, 1.27; 95% CI, 1.07 to 1.51; P=0.007). Rates of adjudicated cases of acute and chronic pancreatitis were similar in the two groups (acute pancreatitis, 0.3% in the saxagliptin group and 0.2% in the placebo group; chronic pancreatitis, <0.1 and 0.1% in the two groups, respectively).
Aschner et al.[24] (2006) Sitagliptin 100 mg QD vs sitagliptin 200 mg QD vs placebo	DB, MC, PC, RCT Type 2 diabetics 18 to 75 years of age, either receiving or naïve to oral antihyperglycemic agents, and an HbA_{1c} 8.0%	N=741 24 weeks	Primary: Change in baseline HbA_{1c}, FPG, PPG, fasting insulin, proinsulin, fasting lipids, β cell function, and insulin resistance Secondary: Safety and tolerability	Primary: Sitagliptin significantly decreased HbA_{1c} compared to placebo (100 mg treatment difference, -0.79% [95% CI, -0.96 to -0.62] and 200 mg treatment difference, -0.94% [95% CI, -1.11 to -0.77]; a significantly greater proportion of patients receiving sitagliptin achieved an HbA_{1c} <7.0% compared to patients receiving placebo (41 and 45 vs 17%; P<0.001 for both). Sitagliptin significantly decreased FPG compared to placebo (100 mg treatment difference, -17.1 mg/dL and 200 mg treatment difference, -21.3 mg/dL; P<0.001 for both). Sitagliptin significantly reduced two-hour PPG compared to placebo (-48.9 and -56.3 vs -2.2 mg/dL; P<0.001 for both).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				There were no significant effects on fasting insulin and proinsulin with either treatment. Sitagliptin also had no significant effects on fasting lipids. HOMA-B was significantly increased and the proinsulin:insulin ratio was significantly decreased with sitagliptin compared to placebo, indicating improved β cell function (P≤0.001 and P≤0.01, respectively). Secondary: There were fewer sitagliptin-treated patients compared to placebo-treated patients that required rescue therapy (8.8 and 4.8 vs 20.6%; P<0.001). No meaningful differences in clinical adverse effects were noted between the two treatments. The incidence of hypoglycemia was similar among the two treatments. Both doses of sitagliptin were well tolerated.
Hanefeld et al.[25] (2007) Sitagliptin 25 mg QD vs sitagliptin 50 mg QD vs sitagliptin 50 mg BID vs sitagliptin 100 mg QD vs	DB, MC, PC, PG, RCT Type 2 diabetics 23 to 74 years of age and an HbA_{1c} 7.6 to 7.8%	N=555 12 weeks	Primary: Change in baseline HbA_{1c}, FPG, mean daily glucose, HOMA-B, QUICKI, and HOMA-IR Secondary: Adverse events, body weight	Primary: Sitagliptin significantly decreased HbA_{1c} by -0.39 to -0.56% compared to placebo (P<0.05). Sitagliptin significantly decreased FPG by -11.0 to -17.2 mg/dL compared to placebo (P<0.05), and the largest decrease was achieved with sitagliptin 100 mg QD. Sitagliptin significantly improved mean daily glucose (-14.0 to -22.6 mg/dL; P<0.05). HOMA-B was significantly increased (11.3 to 15.2; P<0.05) with sitagliptin, whereas there was no significant changes in QUICKI and HOMA-IR with sitagliptin compared to placebo. Secondary: Overall, there was a low frequency of hypoglycemia observed with sitagliptin. There was no change in body weight observed with any treatment.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo				
Raz et al.[26] (2006) Sitagliptin 100 mg QD vs sitagliptin 200 mg QD vs placebo	DB, MC, PC, PG, RCT Type 2 diabetics 18 to 75 years of age with an HbA_{1c} 7.0 to 10.0%	N=521 18 weeks	Primary: Change in baseline HbA_{1c} Secondary: Change in baseline FPG, fasting insulin, proinsulin, and lipids; safety and tolerability	Primary: Sitagliptin (100 mg, -0.60% [95% CI, -0.82 to -0.39] and 200 mg, -0.48% [95% CI, -0.70 to -0.26]) significantly decreased HbA_{1c} compared to placebo (P<0.001). Secondary: Sitagliptin (100 mg, -1.1 mmol/L [95% CI, -1.7 to -0.5] and 200 mg, -0.9 mmol/L [95% CI, -1.5 to -0.3]) significantly decreased FPG compared to placebo (P<0.001). There were no significant effects on fasting insulin, proinsulin, or fasting lipids with either treatment. Rescue therapy was required for 8.8, 11.7, and 17.3% of patients receiving sitagliptin 100 mg, sitagliptin 200 mg, and placebo (P value not reported). Treatment with sitagliptin was well tolerated, and no significant differences between treatments in the incidence of adverse effects were observed. The incidence of hypoglycemia and gastrointestinal side effects was similar between the two treatments.
Nonaka et al.[27] (2007) Sitagliptin 100 mg QD vs placebo	DB, MC, PC, RCT Japanese patients with type 2 diabetics, HbA_{1c} ≥6.5 to <10.0%, and FPG ≥126 to ≤240 mg/dL	N=151 12 weeks	Primary: Change in baseline HbA_{1c}, FPG, PPG, body weight; adverse effects Secondary: Not reported	Primary: Sitagliptin (-0.65%; 95% CI, -0.80 to -0.50) significantly decreased HbA_{1c} compared to placebo (0.41%; 95% CI, 0.26 to 0.56; treatment difference, -1.05%; 95% CI, -1.27 to -0.84; P <0.001). A significantly greater proportion of patients receiving sitagliptin achieved HbA_{1c} <7.0% compared to patients receiving placebo (P<0.001). Sitagliptin (-22.5 mg/dL; 95% CI, -28.0 to -17.0) significantly decreased FPG compared to placebo (9.4 mg/dL; 95% CI, 3.9 to 14.9; treatment difference, -31.9 mg/dL; 95% CI, -39.7 to -24.1; P<0.001). Sitagliptin (-69.3 mg/dL; 95% CI, -85.3 to -53.4) significantly decreased PPG compared to placebo (12.0 mg/dL; 95% CI, -6.5 to 30.5; treatment difference, -81.3 mg/dL; 95% CI, -105.8 to -56.9; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Body weight was unchanged compared to baseline with sitagliptin (-0.1 kg), but significantly (P<0.01) different compared to placebo (-0.7 kg). No notable difference in adverse events, including hypoglycemia, was observed between the two treatments. Secondary: Not reported
Hartley et al.[28] (2015) Sitagliptin vs glimepiride	DB, MC, NI, RCT Patients ≥65 and ≤85 years of age with type 2 diabetes that was inadequately controlled with diet and exercise alone	N=480 30 weeks	Primary: Change in baseline HbA_{1c}, FPG, and body weight; incidence of symptomatic hypoglycemia Secondary: Not reported	Primary: After 30 weeks, the least squares (LS) mean change in HbA_{1c} baseline was −0.32% with sitagliptin and −0.51% with glimepiride, for a between-group difference of 0.19% (95% CI, 0.03 to 0.34). This result met the pre-specified criterion for declaring non-inferiority. The LS mean change in FPG from baseline was −14.5 mg/dL with sitagliptin and −21.2 mg/dL with glimepiride, for a between-group difference of 6.7 mg/dL (95% CI, 0.7 to 12.7). The percentages of patients with adverse events of symptomatic hypoglycemia were 0.8% in the sitagliptin group and 4.7% in the glimepiride group (between-treatment difference, −3.9 %; P=0.009). The LS mean change in body weight from baseline was 0.4 kg with sitagliptin and 1.1 kg with glimepiride, for a between-group difference of −0.7 kg (P=0.011). Secondary: Not reported
Scott et al.[29] (2007) Sitagliptin 5 mg BID vs sitagliptin 12.5 mg BID vs	AC, DB, PC, RCT Type 2 diabetics 21 to 75 years of age, inadequately controlled (HbA_{1c} 7.9%) with diet and exercise	N=743 12 weeks	Primary: Change in baseline HbA_{1c}, FPG, mean daily glucose, and body weight; adverse effects Secondary: Not reported	Primary: Sitagliptin (-0.38 to -0.77%) significantly decreased HbA_{1c} compared to placebo (P<0.001). Sitagliptin 50 mg achieved the greatest decrease. The placebo subtracted difference in HbA_{1c} of glipizide was -1.00%. Sitagliptin significantly decreased FPG and mean daily glucose compared to placebo (P values not reported). There was no difference between sitagliptin and placebo with changes in body weight. Glipizide resulted in a modest weight gain compared to placebo (P value not reported).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
sitagliptin 25 mg BID vs sitagliptin 50 mg BID vs glipizide 5 to 20 mg daily vs placebo				The incidence of hypoglycemia was highest with glipizide (17%) compared to placebo (2%) and sitagliptin (0 to 4%, not dose-dependent). Secondary: Not reported
Chan et al.[30] (2008) <u>Phase I</u> Sitagliptin 25 to 50 mg QD vs placebo <u>Phase II</u> Sitagliptin 25 to 50 mg daily and placebo vs glipizide 2.5 to 20 mg daily and placebo	DB, PC, PG, RCT Patients ≥18 years of age with type 2 diabetes, baseline HbA_{1c} of 6.5 to 10.0%, and renal insufficiency	N=91 54 weeks (Phase I was 12 weeks; Phase II was 42 weeks)	Primary: Safety and tolerability Secondary: Efficacy	Primary: Adverse events were similar among patients receiving sitagliptin and placebo/glipizide, including serious adverse events (30.8 and 38.5%, respectively), drug-related serious adverse events (1.5 and 0.0%, respectively), and adverse events leading to discontinuation. Incidences of adverse events by body systems and specific clinical adverse events were also similar between the sitagliptin and placebo/glipizide groups, with the exception of hypoglycemia and anemia. Hypoglycemia occurred in 4.6% of patients receiving sitagliptin and 23.1% of patients receiving placebo/glipizide. Anemia occurred in 3.1% of patients receiving sitagliptin and 15.4% of patients receiving placebo/glipizide. There was a higher incidence of MI (4.6 and 0.0%) and heart failure (7.7 and 3.8%) in the sitagliptin group compared to the placebo/glipizide group, respectively. The number of patients experiencing cardiovascular events per 100 patient-years was similar between groups. There were six deaths (7.7%) in the sitagliptin group and one death (3.8%) in the placebo/glipizide group. This represents an overall mortality rate of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				7.3 deaths per 100 patient-years, with 8.8 and 4.0 deaths per 100 patient-years in the sitagliptin and placebo/glipizide groups, respectively. No clinically meaningful differences were observed for laboratory safety measures, including alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, creatine phosphokinase, uric acid, electrolytes, white blood cell count or absolute neutrophil count between groups. At week 54, the mean change from baseline in serum creatinine for patients with moderate renal insufficiency was -0.02 and 0.69 mg/dL in the sitagliptin and placebo/glipizide groups, respectively. At week 54, small (2 mm Hg) mean decreases in systolic, diastolic and mean arterial BPs were observed for patients on sitagliptin compared to those on placebo/glipizide. At week 54, there was a small mean decrease in body weight from baseline in the sitagliptin group (-0.9 kg) compared with no mean change in the placebo/glipizide group (0.0 kg). Secondary: At week 12, the mean change from baseline in HbA_{1c} was -0.6% (95% CI, -0.8 to -0.4%) in the sitagliptin group compared with -0.2% (95% CI, -0.4 to 0.1%) in the placebo group At week 12, the mean change from baseline in FPG was -25.5 mg/dL (95% CI, -38.2 to -12.8 mg/dL) with sitagliptin and -3.0 mg/dl (95% CI, -15.7 to 9.6) with placebo. At week 54, the mean and least squares mean change from baseline in HbA_{1c} with sitagliptin was -0.7% in the prespecified analysis and in the ANCOVA analysis. The mean and least squares mean changes from baseline were -1.0 and -0.8%, respectively in the placebo/glipizide group. Between-group testing for efficacy was not performed at the week 54 time point.

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				At week 54, the mean percent changes in lipids were as follows for sitagliptin: TC (+4.3%; 95% CI, -1.5 to 10.1), LDL-C (+11.9%; 95% CI, 1.6 to 22.2), and non-HDL-C (+7.1%; -1.2 to 15.3), TGs (-0.7%; 95% CI, -13 to 11.5), and HDL-C (+0.9%; 95% CI, -5.9 to 7.7). The mean percent changes in lipids in the placebo/glipizide group were as follows: TC (-0.2%; 95% CI, -10.5 to 10.0), LDL-C (3.3%; 95% CI, -8.6 to 15.2), non-HDL-C (-1.6%; 95% CI, -13.7 to 10.5), TG (+0.9%; 95% CI, -27.5 to 29.3), and HDL-C (+6.6%; 95% CI, -5 to 18.2).
DeFronzo et al.[31] (2008) Sitagliptin 100 mg QD for 2 weeks vs exenatide 5 µg SC BID for 1 week, then 10 µg SC BID for 1 week	DB, MC, RCT, XO Patients 18 to 70 years of age with type 2 diabetes who were treated with a stable regimen of metformin, HbA_{1c} 7.0 to 11.0%, FPG <280 mg/dL, and BMI 25 to 45 kg/m^2	N=95 4 weeks	Primary: 2-hour PPG Secondary: Postprandial insulin, glucagon, active GLP-1 and TG concentrations, and safety	Primary: The 2-hour PPG concentration (least square mean) was lower for exenatide compared to sitagliptin (133 vs 208 mg/dL; P<0.0001). In the intent-to-treat population, the 2-hour PPG concentration was lower with exenatide compared to sitagliptin (166 vs 210 mg/dL, respectively; P<0.0001). The change in 2-hour PPG concentration (least square mean) from baseline was -112 mg/dL for exenatide compared to -37 mg/dL for sitagliptin (P<0.0001). FPG was similar following treatment with exenatide (-15 mg/dL) and sitagliptin (-19 mg/dL; P=0.3234). Following crossover to the alternate therapy, patients switched from exenatide to sitagliptin experienced an increase in mean 2-hour PPG +73 mg/dL. Patients switched from sitagliptin to exenatide treatment experienced a reduction in the mean 2-hour PPG concentration -76 mg/dL. Secondary: The acute insulin response was greater for exenatide compared to sitagliptin (P=0.0017). Both exenatide and sitagliptin reduced the mean postprandial plasma glucagon concentration compared to baseline; however, the reduction was greater with exenatide compared to sitagliptin (P=0.0011).

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				Both exenatide and sitagliptin both reduced mean postprandial TG concentrations compared to baseline; however, the decrease was greater with exenatide compared to sitagliptin (P=0.0118). Exenatide reduced the rate of gastric emptying compared to baseline and to sitagliptin (P<0.0001). Sitagliptin had no effect on gastric emptying). Adverse events with exenatide and sitagliptin were mild-to-moderate. The most common adverse events were gastrointestinal with both treatments. Nausea was experienced by 34% of patients treated with exenatide and 12% of patients treated with sitagliptin. Vomiting was experienced by 24% of patients treated with exenatide and 3% of patients treated with sitagliptin. No serious treatment-emergent adverse events were reported during the study.
Aschner et al.[32] (2010) Sitagliptin 100 mg QD vs metformin 1,000 mg BID	AC, DB, RCT Patients 18 to 78 years of age with type 2 diabetes mellitus who were treatment naïve with an HbA_{1c} 6.5 to 9.0%	N=1,050 24 weeks	Primary: Change in HbA_{1c} from baseline Secondary: Proportions of patients with HbA_{1c} <7.0% or <6.5%, change in FPG, fasting serum insulin, fasting serum proinsulin, and lipid parameters	Primary: In the per protocol population, the change in HbA_{1c} (least square mean) from baseline at week 24 was −0.43% in the sitagliptin group and −0.57% in the metformin group (difference, 0.14%; 95% CI, 0.06 to 0.21), which demonstrated the non-inferiority of sitagliptin to metformin. In the full analysis set, the HbA_{1c} change from baseline at week 24 was −0.38% (95% CI, −0.43 to −0.32) in the sitagliptin group and −0.55% (95% CI, –0.61 to −0.50) in the metformin group (difference, 0.18%; 95% CI, 0.10 to 0.25), which demonstrated the non-inferiority of sitagliptin to metformin. Secondary: The proportion of patients with an HbA_{1c} <7.0% at week 24 was greater with metformin (76%) compared with sitagliptin (69%; difference, -7.1%; 95% CI, −12.9 to −1.2). The proportion of patients with an HbA_{1c} <6.5% was not statistically different between the metformin (39%) and sitagliptin (34%) groups (difference, −5.6%; 95% CI, −11.8 to 0.8). The change from baseline in FPG was greater with metformin (–19.4 mg/dl compared with sitagliptin (–11.5 mg/dL).

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				The reduction in fasting proinsulin was greater in the metformin group, which resulted in a larger reduction in the proinsulin/insulin ratio at week 24. Both treatments produced similar increases in β-cell function and reductions in insulin resistance over 24 weeks. HDL-C was improved with both treatments. TGs were slightly reduced with sitagliptin. Small increases in TC were observed for each group, with a slightly greater increase for sitagliptin. Modest increases in LDL-C and non-HDL-C were observed with sitagliptin, but not metformin over 24 weeks. The incidence of drug-related adverse events was lower in the sitagliptin group than in the metformin group. The incidence of gastrointestinal adverse events overall was lower in the sitagliptin group compared with the metformin group (11.6 vs 20.7%, respectively). Hypoglycemia occurred at a low rate in both groups (1.7% with sitagliptin and 3.3% with metformin; P=0.116). Body weight was reduced from baseline in both the sitagliptin (−0.6 kg) and metformin (−1.9 kg; P<0.001).
Russell-Jones et al.[33] (2012) DRUATION-4 Exenatide ER 2 mg SC once weekly vs metformin 2,000 mg/day vs pioglitazone 45 mg/day	DB, DD, MC, PG, RCT Drug-naïve (patients excluded if treated with any antihyperglycemic drug for >7 days within 3 months of screening) adult type 2 diabetics with HbA_{1c} 7.1 to 11.0%, BMI 23 to 45 kg/m^2, and stable weight	N=820 26 weeks	Primary: Change in baseline HbA_{1c} Secondary: Proportion of patients achieving HbA_{1c} <7.0 and ≤6.5%, fasting serum glucose, seven-point self-monitored glucose concentrations, weight, lipid profile, insulin profile, safety and	Primary: Decreases in HbA_{1c} were -1.53±0.07, -1.48±0.07, -1.63±0.08, and -1.15±0.08% with exenatide ER, metformin (P=0.620 vs exenatide ER), pioglitazone (P=0.328 vs exenatide ER), and sitagliptin (P<0.001 vs exenatide ER). The HbA_{1c} at trial end was 6.94±0.07, 6.99±0.07, 6.84±0.08, and 7.32±0.08% with exenatide ER, metformin, pioglitazone, and sitagliptin, respectively. Secondary: Similar proportions of patients receiving exenatide ER and metformin achieved HbA_{1c} <7.0% (63 vs 55%; P value not reported). A significantly greater proportion of patients receiving exenatide ER achieved HbA_{1c} <7.0% compared to patients receiving sitagliptin (63 vs 43%; P<0.001), and ≤6.5% compared to patients receiving metformin (49 vs 36%; P=0.004) and sitagliptin, respectively (49 vs 26%; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs sitagliptin 100 mg/day			tolerability, patient-reported QOL	Decreases in fasting serum glucose at weeks 16 and 26 were significantly greater with exenatide ER compared to sitagliptin (P<0.001 for both). There were no differences observed with exenatide ER compared to metformin (P=0.155 at week 26) and pioglitazone (P=0.153 at week 26). Seven-point self-monitored glucose concentrations demonstrated similar decreases with exenatide ER, metformin, and pioglitazone. Exenatide ER demonstrated greater decreases at all time points compared to sitagliptin. Mean decreases in post-meal excursions after 26 weeks were similar among all treatments. Decreases in weight were significantly greater with exenatide ER compared to pioglitazone and sitagliptin by weeks four and eight, and the effect was sustained through 26 weeks (P≤0.003 for all). There was no difference between exenatide ER and metformin after 26 weeks (-2.0 vs -2.0 kg; P=0.892). No clinically significant changes in serum lipids were observed with any treatment. Mean HOMA-B was significantly improved with exenatide ER compared to metformin, pioglitazone, and sitagliptin (P<0.001 for all). HOMA-S significantly improved with metformin and pioglitazone compared to exenatide ER (P<0.001 for both), and the change with exenatide ER was similar to sitagliptin (P=0.329). Serious adverse events were reported in 1.6, 5.3, 5.5, and 1.8% of patients receiving exenatide ER, metformin, pioglitazone, and sitagliptin, respectively. No serious adverse event was reported by more than one patient. Treatment-emergent adverse events reported by at least five percent of patients in any group included headache (highest with metformin), diarrhea (highest with metformin), injection site nodule (highest with exenatide ER), nasopharyngitis (highest with sitagliptin), nausea (highest with exenatide ER), dyspepsia (highest with exenatide ER), constipation (highest with exenatide ER), back pain (highest with metformin), arthralgia (highest with exenatide ER), hypertension (highest with pioglitazone), and peripheral edema (highest with pioglitazone). No

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				major hypoglycemia was reported. One patient receiving sitagliptin with elevated lipase at screening experienced moderate chronic pancreatitis after eight days and discontinued from study treatment. All treatments resulted in improvements in perceived treatment satisfaction, weight-related QOL, and binge eating behavior. All treatments, except pioglitazone, resulted in significant improvements in health status. Significant improvements in weight-related quality of life, binge eating behavior, and health status were reported with exenatide ER compared to pioglitazone (P values not reported).
Monami et al.[34] (2011) DPP-4 inhibitors (linagliptin, alogliptin*, sitagliptin, saxagliptin, vildagliptin*) vs placebo or active comparator (oral hypoglycemic agents and/or insulin)	MA (53 trials) Patients with type 2 diabetes who were receiving a DPP-4 inhibitor	N=33,881 ≥24 weeks	Primary: Incidence of cancer Secondary: Incidence of pancreatitis, all-cause and cardiovascular mortality, incidence of major cardiovascular events	Primary: There were 176 cases of cancer (107 and 69 in patients receiving DPP-4 inhibitors and comparators, respectively); 12.5% were gastrointestinal, 5.7% were pancreatic, 6.2% were pulmonary, 14.7% were mammary gland/female genital tract, 11.3% were male urogenital tract, 3.4% were thyroid, and 26.1% were of another origin. There was no difference in the proportion of cases between patients receiving DPP-4 inhibitors or a comparator (P=0.90). Secondary: The risk of pancreatitis with DPP-4 inhibitors was 0.786 (P=0.55). The number of reported deaths was 28 and 31 with DPP-4 inhibitors and comparators, respectively. Cardiovascular deaths occurred in 10 patients receiving DPP-4 inhibitors and 20 patients receiving comparators. The risk for all-cause death and cardiovascular death in patients receiving DPP-4 inhibitors was 0.668 (P=0.149 and P=0.054, respectively). There were 137 and 120 major cardiovascular events reported with DPP-4 inhibitors and comparators, respectively. DPP-4 inhibitors were associated with a significantly lower risk of major cardiovascular events (OR, 0.689; P=0.006).
Fakhoury et al.[35] (2010) Incretin-based therapies (exenatide,	MA (38 RCTs: 8, exenatide; 7, liraglutide; 12, sitagliptin; 11, vildagliptin)	N=Not reported Duration varied	Primary: Change in baseline HbA_{1c} and weight, hypoglycemia	Primary: Sitagliptin (WMD, -0.79; 95% CI, -0.93 to -0.65; P<0.001) significantly decrease HbA_{1c} compared to placebo.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
liraglutide, vildagliptin*, and sitagliptin) vs placebo	Type 2 diabetics ≥18 years of age	(4 to 52 weeks	Secondary: Not reported	Exenatide (WMD, -0.75; 95% CI, -0.83 to -0.67; P<0.001) and liraglutide (WMD, -1.03; 95% CI, -1.16 to -0.90; P<0.0010) significantly decreased baseline HbA_{1c}. In the adjusted analyses for exenatide, controlling for whether exenatide was given as monotherapy or in combination with another treatment provided the most variability, but even this estimate fell within the boundaries of the unadjusted model CI (WMD, -0.84; 95% CI, -0.95 to -0.73; P<0.001). In the adjusted analyses for liraglutide, no covariates were found to be significant. There was significant weight gain with sitagliptin (WMD, 0.60; 95% CI, 0.33 to 0.87; P<0.001) compared to placebo. Exenatide (WMD, -1.10; 95% CI, -1.32 to -0.88; P<0.001) and liraglutide (WMD, -0.82; 95% CI, -1.92 to -0.27; P=0.142) both exhibited reduction in weight. The most remarkable result is the average weight reduction of 1.10 kg observed with exenatide. Sitagliptin-treated patients were 156% more likely to experience some hypoglycemia compared to placebo treated patients (RR, 2.56; 95% CI, 1.23 to 5.33; P=0.01). When adjusted for covariates, age was the only variable found to be significant (RR, 1.84; 95% CI, 1.02 to 3.34; P=0.044). Exenatide-treated patients were 140% more likely to experience some hypoglycemia compared to placebo treated patients (RR, 2.40; 95% CI, 1.39 to 4.11; P=0.002). Liraglutide-treated patients were 69% more likely to experience some hypoglycemia compared to placebo treated patients (RR, 1.69; 95% CI, 1.00 to 2.86; P=0.050). Secondary: Not reported
Amori et al.[36] (2007) Incretin therapy (exenatide, liraglutide, sitagliptin and vildagliptin*)	MA (29 RCTs) Type 2 diabetics	N=12,996 Duration varied (12 to 52 weeks)	Primary: Change in baseline HbA_{1c} Secondary: FPG, proportion of patients achieving an HbA_{1c} <7.0%	Primary: Pooled analysis of trials comparing GLP-1 analogues to placebo demonstrated a significant difference in the decrease in HbA_{1c} favoring GLP-1 analogues (WMD, -0.97; 95% CI, -1.13 to -0.81). Specifically, no difference in the HbA_{1c} was found in OL, non-inferiority trials between exenatide and insulin glargine or biphasic aspart (WMD, -0.06; 95% CI, -0.22 to 0.10). Liraglutide demonstrated similar HbA_{1c}

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vs non-incretin-based therapy (placebo or hypoglycemic agent)				efficacy compared to OL glimepiride titrated to glycemic goals or DB maximum dose metformin (data not reported). Secondary: Compared to placebo, FPG was significantly decreased with GLP-1 analogues (WMD, -27 mg/dL; 95% CI, -33 to -21). Exenatide-treated patients were more likely to achieve an HbA_{1c} <7.0% compared to placebo treated patients (45 vs 10%, respectively; RR, 4.2; 95% CI, 3.2 to 5.5), while no difference in the proportions of patients achieving this goal was observed between exenatide and insulin therapy in NI trials (39 vs 35%, respectively; RR, 1.1; 95% CI, 0.8 to 1.5). Data with liraglutide were not reported.
Shyangdan et al.[37] (2011) GLP-1 receptor agonist based therapies (albiglutide, exenatide ER, liraglutide, lixisenatide*, semaglutide*, and taspoglutide*) vs non-GLP-1 receptor based therapies (placebo, TZDs, DPP-4 inhibitors, insulin glargine, and sulfonylureas)	MA (RCTs) Type 2 diabetics ≥18 years of age	N=not reported 8 to 26 weeks	Primary: Change in baseline HbA_{1c}, incidence of hypoglycemia, weight change Secondary: Health-related QOL, safety, mortality, morbidity, BP, FPG, PPG, lipid profile, β cell function	Primary: Change in baseline HbA_{1c} Exenatide ER significantly decreased HbA_{1c} compared to TZDs (-1.5 vs -1.2%; P=0.02), DPP-4 inhibitors (-1.5 vs -0.9%; P<0.0001), and insulin glargine (-1.5 vs -1.3%; treatment difference, -0.2%; 95% CI, -0.35 to -0.05; P=0.03). There was no difference in the proportion of patients achieving an HbA_{1c} <7.0% between exenatide ER and TZDs (60 vs 52%; P=0.15). A significantly greater proportion of patients receiving exenatide ER achieved an HbA_{1c} <7.0% compared to patients receiving DPP-4 inhibitors (60 vs 35%; P<0.0001) and patients receiving insulin glargine (60 vs 48%; P=0.03). Compared to placebo, treatment with liraglutide 1.2 mg significantly decreased HbA_{1c} (-1.15%; 95% CI, -1.33 to -0.96; P<0.00001). Patients receiving liraglutide 1.2 mg were more likely to achieve an HbA_{1c} <7.0% compared to patients receiving placebo (OR, 2.91; 95% CI, 1.74 to 4.87; P<0.05). Liraglutide 1.2 mg decreased HbA_{1c} to a greater extent compared to TZDs (-0.64%; 95% CI -0.83 to -0.45; P value not reported). The likelihood of achieving an HbA_{1c} <7.0% was greater with liraglutide 1.2 mg compared to TZDs (OR, 1.60; 95% CI, 1.18 to 2.15; P value not reported). Liraglutide 1.2 mg decreased HbA_{1c} to a greater extent compared to DPP-4 inhibitors (-0.34%; 95% CI, -0.53 to -0.15; P value not reported). The likelihood of achieving an HbA_{1c} <7.0% was greater with liraglutide 1.2 mg compared to DPP-4 inhibitors (OR, 2.56; 95% CI,

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				1.94 to 3.37; P value not reported). Liraglutide 1.2 mg was not associated with a decrease in HbA_{1c} compared to sulfonylureas (-0.01%; 95% CI -0.27 to 0.29; P value not reported). The likelihood of achieving an HbA_{1c} <7.0% was not greater with liraglutide 1.2 mg compared to sulfonylureas (OR, 0.98; 95% CI, 0.84 to 1.14; P=0.78). Compared to placebo, liraglutide 1.8 mg significantly decreased an HbA_{1c} (-1.15%; 95% CI, -1.31 to -0.99; P<0.05). Patients receiving liraglutide 1.8 mg were more likely to achieve HbA_{1c} <7.0% compared to patients receiving placebo (OR, 3.25; 95% CI, 1.97 to 5.36; P<0.05). Liraglutide 1.8 mg decreased HbA_{1c} to a greater extent compared to TZDs (-0.69%; 95% CI -0.88 to -0.50%; P value not reported). The likelihood of achieving an HbA_{1c} <7.0% was greater with liraglutide 1.8 mg compared to TZDs (OR, 1.91; 95% CI, 1.43 to 2.53; P value not reported). Liraglutide 1.8 mg decreased HbA_{1c} to a greater extent compared to DPP-4 inhibitors (-0.60%; 95% CI -0.78 to -0.42; P value not reported). The likelihood of achieving HbA_{1c} <7.0% was greater with liraglutide 1.8 compared to DPP-4 inhibitors (OR, 1.99; 95% CI, 1.48 to 2.66; P value not reported). Liraglutide 1.8 mg was not associated with a reduction in HbA_{1c} compared to sulfonylureas (-0.02%; 95% CI -0.30 to 0.26; P value not reported). The likelihood of achieving an HbA_{1c} <7.0% was not greater with liraglutide 1.8 mg compared to sulfonylureas (OR, 1.09; 95% CI, 0.94 to 1.26; P=0.27). Liraglutide decreased HbA_{1c} to a greater extent compared to insulin glargine (-0.24%; 95% CI, -0.49 to 0.01; P value not reported). The likelihood of achieving an HbA_{1c} <7.0% was not different between insulin glargine and liraglutide (OR, 1.16; 95% CI, 0.96 to 1.40; P value not reported). Liraglutide 1.2 mg was associated with a non-significant increase in HbA_{1c} compared to 1.8 mg (0.10%; 95% CI, -0.03 to 0.23; P=0.13). Patients receiving liraglutide 1.2 mg were not more likely to achieve an HbA_{1c} <7.0% compared to the 1.8 mg dose (P=0.92). Incidence of hypoglycemia

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				The incidence of minor hypoglycemia was similar between exenatide ER and TZDs. The incidence of minor hypoglycemia was higher with DPP-4 inhibitors (five vs two patients) and insulin glargine (26 vs 8%) compared to exenatide ER. The incidence of major hypoglycemia was higher with insulin glargine compared to exenatide ER (two vs one patients). Overall, there was no difference in the incidence of minor hypoglycemia between liraglutide 1.2 mg and placebo (P=0.42), and there was significantly more hypoglycemia with liraglutide 1.8 mg (OR, 1.66; 95% CI, 1.15 to 2.40; P=0.007). The incidence of minor hypoglycemia was higher with insulin glargine compared to liraglutide (29 vs 27%). Liraglutide was associated with a significantly higher rate of minor hypoglycemia compared to TZDs (P=0.048), and similar rates compared to DPP-4 inhibitors (P values not reported). Liraglutide was associated with a significantly lower incidence of hypoglycemia compared to sulfonylureas (P<0.00001). Weight loss Exenatide ER significantly decreased weight compared to TZDs (-2.3 vs 2.8 kg; P<0.00001), DPP-4 inhibitors (-2.3 vs -0.8 kg; P=0.0009), and insulin glargine (-2.6 vs 1.4 kg; P<0.00001). Patients receiving liraglutide 1.2 mg experienced an average weight loss of -0.75 kg (95% CI, -1.95 to 0.45; P=0.22). Liraglutide 1.2 mg was associated with a greater decrease in weight compared to insulin glargine (-3.40 kg; 95% CI, -4.31 to -2.49; P value not reported), TZDs (-3.40 kg; 95% CI, -4.31 to -2.49; P value not reported), DPP-4 inhibitors (-1.90 kg; 95% CI, -2.65 to -1.15; P value not reported), and sulfonylureas (-3.60 kg; 95% CI, -4.15 to -3.05; P value not reported). Patients receiving liraglutide 1.8 mg experienced a significant weight loss compared to placebo (-1.33 kg; 95% CI, -2.38 to 0.27; P=0.0014). Liraglutide 1.8 mg was associated with a greater decrease in weight compared to TZDs (-2.30 kg; 95% CI, -2.85 to -1.75; P value not reported), DPP-4 inhibitors (-2.42 kg; 95% CI, -3.17 to -1.67; P value not reported), and sulfonylureas (-3.80 kg; 95% CI, -4.35 to -3.25; P value not reported).

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				Patients were more likely to experience weight gain with liraglutide 1.2 compared to 1.8 mg (0.48 kg; 95% CI, 0.16 to 0.80; P value not reported). Secondary: Data on mortality and morbidity were not reported for any treatment. QOL Exenatide ER significantly improved weight-related quality of life and IWQOL total scores compared to TZDs (IWQOL treatment difference, 3.94; 95% CI, 1.28 to 6.61; P=0.0038). Both exenatide ER (IWQOL total score, 5.15; 95% CI, 3.11 to 7.19) and DPP-4 inhibitors (4.56; 95% CI, 2.56 to 6.57) resulted in significant improvements in weight-related quality of life and IWQOL total scores. Treatment satisfaction was significantly greater with exenatide ER compared to DPP-4 inhibitors (treatment difference, 1.61; 95% CI, 0.07 to 3.16; P=0.0406). Exenatide ER significantly improved the self-esteem IWQOL domain and one EQ-5D dimensions compared to insulin glargine. Data for liraglutide were not reported. Safety Withdrawals due to adverse events were greater with exenatide ER compared to TZDs (6.9 vs 3.6%), DPP-4 inhibitors (6.9 vs 3.0%), and insulin glargine (4.7 vs 0.9%). More serious adverse events occurred with TZDs (6 vs 3%) compared to exenatide ER. The incidence of serious adverse events was similar between exenatide ER and DPP-4 inhibitors (3 vs 3%) and insulin glargine (5 vs 4%). Compared to placebo, withdrawals due to adverse events were between 5 and 10% with liraglutide 1.2 mg and between 4 and 15% with liraglutide 1.8 mg. Withdrawals were also higher with liraglutide compared to sulfonylureas (9.4 to 12.9 vs 1.3 to 3.0%). Liraglutide was associated with more gastrointestinal adverse events (nausea, vomiting, and diarrhea) compared to insulin glargine, TZDs, DPP-4 inhibitors, and sulfonylureas. BP

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				There was no difference in the decreases in SBP and DBP between exenatide ER and TZDs. Exenatide ER significantly decreased SBP compared to DPP-4 inhibitors (treatment difference, -4 mm Hg; 95% CI, -6 to -1; P=0.0055). There was no difference in the decrease in DBP between treatments. Data comparing exenatide ER and insulin glargine were not reported. Liraglutide 1.2 mg did not significantly decrease SBP (P=0.15) compared to placebo (P=0.15) and DPP-4 inhibitors (P=0.76). Liraglutide 1.8 mg significantly decreased SBP (P=0.05) compared to placebo, but not DPP-4 inhibitors (P=0.86). Liraglutide also significantly decreased SBP compared to insulin glargine (P=0.0001) and sulfonylureas (P value not reported). No difference in SBP was observed between liraglutide and DPP-4 inhibitors. There was no difference between liraglutide in the decrease in DBP compared to placebo, insulin glargine, or sulfonylureas. DPP-4 inhibitors significantly decreased DBP compared to liraglutide 1.8 mg (P value not reported). Data comparing liraglutide and TZDs were not reported. FPG There was no difference in the decrease in FPG between exenatide ER and TZDs (-1.8 vs -1.5 mmol/L; P=0.33). Exenatide ER significantly decreased FPG compared to DPP-4 inhibitors (-0.90 mmol/L; 95% CI, -1.50 to -0.30; P=0.0038), and insulin glargine significantly decreased FPG compared to exenatide ER (-0.70 mmol/L; 95% CI, 0.14 to 1.26; P=0.01). Liraglutide significantly decreased FPG compared to placebo (1.2 mg; P<0.0001 and 1.8 mg; P<0.00001), TZDs (P≤0.006), and DPP-4 inhibitors (P<0.00001). There was no difference between liraglutide and insulin glargine or sulfonylureas in decreases in FPG (P value not reported). PPG There was no difference in the decrease in PPG between exenatide ER and TZDs. Exenatide ER significantly decreased PPG at all measurements on a six-point self-monitored glucose concentrations profile compared to DPP-4 inhibitors (P<0.05). Both exenatide ER and insulin glargine decreased PPG at all eight time points, with significant difference in favor of

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				exenatide ER after dinner (P=0.004) and insulin glargine at 03000 hour (P=0.022) and before breakfast (P<0.0001). Liraglutide significantly decreased PPG compared to placebo (P value not reported), TZDs (P<0.05), and sulfonylureas (liraglutide 1.8 mg; P<0.0001). There was no difference between liraglutide and insulin glargine in decreases in PPG (P value not reported). It was reported that PPG recorded in trials comparing liraglutide and DPP-4 inhibitors was highly variable. Lipid profile TZDs significantly decreased TG compared to exenatide ER. Exenatide ER decreased TC and LDL-C, while TZDs and DPP-4 inhibitors increased these measures. All treatments increased HDL-C. Data comparing exenatide ER and insulin glargine were not reported. Compared to placebo, liraglutide 1.2 decreased TG (P<0.05) and LDL-C (P<0.05), and no difference was observed with liraglutide 1.8 mg. Data comparing liraglutide to insulin glargine, TZDs, DPP-4 inhibitors, and sulfonylureas were not reported. β cell function Data for exenatide ER are not reported. Liraglutide significantly improved HOMA-B compared to placebo (P value not reported), TZDs (P<0.05), and DPP-4 inhibitors (P value not reported); and proinsulin:insulin ratio compared to placebo (P value not reported), insulin glargine (P=0.0019), and TZDs (P≤0.02). There was no difference between liraglutide and sulfonylureas in the improvements in HOMA-B and proinsulin:insulin ratio.
Pinelli et al.[38] (2011) GLP-1 receptor agonist, long-acting formulations at maximum doses (liraglutide,	MA, SR (5 RCTs) Adult type 2 diabetics	N=not reported Duration varied (not reported)	Primary: Change in baseline HbA_{1c}, FPG, PPG, weight, BP, and lipid profile; safety Secondary: Not reported	Primary: Pooled analysis demonstrates modest decreases in HbA_{1c} favoring long-acting GLP-1 receptor agonists over exenatide (WMD, -0.47%; 95% CI, -0.69 to -0.25) and sitagliptin (WMD, -0.60%; 95% CI, -0.75 to -0.45). Long-acting GLP-1 receptor agonists were significantly more likely to achieve HbA_{1c} <7.0% compared to exenatide (OR, 2.14; 95% CI, 1.38 to 3.34) and sitagliptin (OR, 3.84; 95% CI, 2.78 to 5.31).

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exenatide ER, albiglutide*, and lixisenatide*) vs exenatide and sitagliptin				Pooled analysis demonstrates significant decreases in FPG favored long-acting GLP-1 receptor agonists compared to exenatide (WMD, -18.39 mg/dL; 95% CI, -24.67 to -12.10) and sitagliptin (WMD, -20.96; 95% CI, -27.88 to -14.04). In one trial, exenatide achieved significantly greater decreases in PPG compared to exenatide ER (-124 vs -95 mg/dL; P=0.01). In another trial, exenatide achieved significantly greater decreases in PPG after breakfast (treatment difference, -24 mg/dL; P<0.0001) and dinner (-18 mg/dL; P=0.0005) compared to liraglutide. There was no difference between treatments after lunch. In a third trial, exenatide ER significantly decreased PPG after each meal compared to sitagliptin (P<0.05). Pooled analysis demonstrates significant decreases in weight with long-acting GLP-1 receptor agonists compared to sitagliptin (WMD, -1.99 kg; 95% CI, -2.69 to -1.09), but not exenatide (WMD, -0.48 kg; 95% CI, -1.11 to 0.44). In one trial, exenatide ER significantly decreased SBP compared to sitagliptin (treatment difference, -4 mm Hg; P=0.006), but results were not significant in the three other trials (P values not reported). One trial demonstrated sitagliptin significantly decreased DBP compared to liraglutide (-1.78 vs 0.07 mm Hg; P=0.02). Between-group differences were not significant in the other three trials (P values not reported). Long-acting GLP-1 receptor agonists significantly improved TC compared to other incretin-based therapy in two of four trials. Exenatide ER significantly decreased TC (-12.0 vs -3.9 mg/dL; P value not reported) and LDL-C (-5.0 vs 1.2 mg/dL) compared to exenatide. Liraglutide significantly decreased TC compared to sitagliptin (-6.60 vs -0.77 mg/dL; P=0.03). In one trial, long-acting GLP-1 receptor agonists significantly improved TG compared to incretin-based therapy (-36 with liraglutide vs -20 mg/dL with exenatide ER; P=0.05). No episodes of severe hypoglycemia were reported in four of the trials. In another trial, two patients receiving exenatide experienced severe hypoglycemia. Non-severe hypoglycemia occurred infrequently and in

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				similar amounts among the treatments. The most commonly reported adverse events with long-acting GLP-1 receptor agonists were gastrointestinal-related. Compared to exenatide, the incidence of vomiting was significantly decreased with long-acting GLP-1 receptor agonists (OR, 0.55; 95% CI, 0.34 to 0.89), there was a trend towards decreased nausea (OR, 0.58; 95% CI, 0.32 to 1.06), and no difference in diarrhea (OR, 1.03; 95% CI, 0.67 to 1.58). Nausea (OR, 4.70; 95% CI, 1.81 to 12.24), vomiting (OR, 3.22; 95% CI, 1.63 to 6.36), and diarrhea (OR, 2.32; 95% CI, 1.42 to 3.81) with long-acting GLP-1 receptor agonists were increased compared to sitagliptin. Compared to exenatide, exenatide ER caused more injection site pruritus in two trials (17.6 vs 1.4%), in another trial exenatide had a similar rate of injection site reactions compared to placebo injection (10 vs 7%). Acute pancreatitis was not reported in any trial. One patient receiving liraglutide experienced mild pancreatitis after 88 days of treatment. Secondary: Not reported
Type 2 Diabetes – Combination Therapy				
Nauck et al.[39] (2009) Alogliptin Study 008 Alogliptin 12.5 mg QD vs alogliptin 25 mg QD vs placebo All patients were stabilized on	DB, PC, RCT Treatment naïve patients 18 to 80 years of age with type 2 diabetes, an HbA_{1c} value 7.0 to 10% (despite a stable metformin regimen ≥3 months in duration), a BMI 23 to 45 kg/m^2, C-peptide concentration ≥0.26 nmol/L and SCR <1.5 mg/dL (men) or <1.4 mg/dL (women)	N=527 26 weeks	Primary: Mean change from baseline in HbA_{1c} at week 26 Secondary: HbA_{1c} and FPG changes from baseline at each study visit, incidence of marked hyperglycemia, hyperglycemic rescue, C-peptide, proinsulin, insulin and proinsulin/insulin ratio,	Primary: The 25 mg combination arm compared to metformin monotherapy resulted in statistically significant improvements from baseline in HbA_{1c} (-0.6 vs -0.1%, respectively; P<0.001). Similar results were found with the 12.5 mg combination arm (P<0.001). Secondary: The 25 mg combination arm compared to metformin monotherapy resulted in statistically significant improvements from baseline in FPG (-17 vs 0 mg/dL, respectively; P<0.01). In addition, comparisons at all time points for measures of HbA_{1c} and FPG favored the combination arms. Fewer patients in the alogliptin treatment groups experienced marked hyperglycemia compared to the placebo group at each time point and the difference in overall incidence was statistically significant for both the 12.5 mg (P<0.001) and 25 mg (P=0.003). In addition, the incidence of hyperglycemic rescue was significantly lower (P≤0.004) for patients in the alogliptin treatment groups compared to the placebo group.

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metformin and continued this agent throughout treatment at a dose ≥1,500 mg/day or the highest tolerated daily dose.			achievement of glycemic goals, changes in body weight and safety evaluations	There were no statistically significant differences between the alogliptin groups and placebo changes from baseline to week 26 in fasting plasma proinsulin and insulin levels. Relative to patients in the placebo group, a significantly greater percentage of patients in both the alogliptin 12.5 and 25 mg groups achieved HbA_{1c} levels of ≤7.0% (P<0.001) and ≤6.5% (P< 0.05). Adverse events were similar across all treatment arms. In addition, the incidence of hypoglycemia was low in all treatment groups; there were no severe hypoglycemic events and no clinically significant hypoglycemic episodes reported.
Pratley et al.[40] (2009) Alogliptin Study 009 Alogliptin 12.5 mg QD vs alogliptin 25 mg QD vs placebo Concomitant therapy with metformin or sulfonylurea at pre-study doses was permitted.	DB, MC, PC, PG, RCT Patients 18 to 80 years of age with type 2 diabetes, an HbA_{1c} value 7.5% to 10.0% inadequately controlled on a thiazolidinedione alone or in combination with metformin or a sulfonylurea	N=493 26 weeks	Primary: Mean change from baseline in HbA_{1c} at week 26 Secondary: HbA_{1c} and FPG changes from baseline at each study visit, hyperglycemic rescue, C-peptide, proinsulin, insulin and proinsulin/ insulin ratio, HOMA-B, achievement of glycemic goals, changes in body weight and safety evaluations	Primary: The addition of alogliptin 25 mg daily to pioglitazone therapy resulted in significant improvements from baseline compared to placebo in HbA_{1c} (-0.8 vs -0.2%, respectively; P<0.01). Significant improvements from baseline compared to placebo were observed with the 12.5 mg arm. Secondary: The addition of alogliptin 25 mg daily to pioglitazone therapy resulted in significant improvements from baseline compared to placebo FPG (-20 vs -6 mg/dL, respectively; P<0.01). Significant decreases from baseline were observed with the 12.5 mg arm compared to placebo. A significantly larger proportion of patients achieved HbA_{1c} ≤7.0% with alogliptin 12.5 or 25 mg than with placebo (44.2 and 49.2 vs 34.0%, respectively; P≤0.016). The percentage of patients with marked hyperglycemia was significantly lower for alogliptin than placebo (≤25% for both alogliptin groups vs 44.3%, respectively; P<0.001). The incidences of overall adverse events and hypoglycemia were similar across treatment groups, but cardiac events occurred more often with active treatment than placebo.
Pratley et al.[41]	DB, MC, PC, RCT	N=500	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2009) Alogliptin Study 007 Alogliptin 12.5 mg QD vs alogliptin 25 mg QD vs placebo All patients received glyburide at a dose ≥10 mg QD.	Patients 18 to 80 years of age with type 2 diabetes, an HbA_{1c} value 7.0 to 10.0%, FPG<15.3 mmol/L, BMI 23 to 45 kg/m^2 who were inadequately controlled on a sulfonylurea for ≥3 months	26 weeks	Mean change from baseline in HbA_{1c} at week 26 Secondary: Evaluation of the safety of alogliptin and the effects of alogliptin on additional measures of glycemic control, β-cell function, plasma lipids, weight and adverse events	The addition of alogliptin 25 mg to glyburide therapy resulted in statistically significant improvements from baseline in HbA_{1c} at week 26 when compared to placebo (-0.5 vs 0%, respectively; P<0.01). Significant decreases with the 12.5 mg strength compared to placebo were also noted. Secondary: Improvements observed in FPG with alogliptin 12.5 and 25 mg were not statistically significant compared to placebo (-5 and -8 vs 2 mg/dL, respectively; P>0.07). More patients in the alogliptin groups achieved HbA_{1c} levels ≤7.0% at week 26 compared to patients in the placebo group. However, only the comparison between alogliptin 25 mg (and not the 12.5 mg strength) and placebo reached statistical significance (34.8 and 29.6 vs 18.2%, respectively; P=0.002 and P=0.057). Fewer patients in the alogliptin (12.5 and 25 mg) groups required hyperglycemia rescue (14.9 and 15.7 vs 28.3%, respectively; P<0.05 for both comparisons). Modest improvements were observed in fasting insulin concentration, proinsulin: insulin ratio and HOMA-b with alogliptin treatment, however these differences were not considered significant. Minor nonsignificant increases in body weight were also observed with alogliptin. Adverse events were similar across all treatment groups. The incidences of hypoglycemia for placebo, alogliptin 12.5 mg and alogliptin 25 mg groups were 11.1, 15.8 and 9.6% respectively.
Rosenstock et al.[42] (2009) Alogliptin 12.5 mg QD vs alogliptin 25 mg QD	DB, MC, PC, RCT Patients 18 to 80 years of age with type 2 diabetes, an HbA_{1c} value ≥8.0%, FPG<15.3 mmol/L, BMI 23 to 45 kg/m^2 who were	N=390 26 weeks	Primary: Mean change from baseline in HbA_{1c} at week 26 Secondary: Evaluation of the safety of alogliptin and the effects of	Primary: The addition of alogliptin 25 mg once daily to insulin therapy compared to placebo resulted in statistically significant improvements from baseline at week 26 in HbA_{1c} (-0.7 vs -0.1, respectively; P<0.05). Similar decreases were observed with the 12.5 mg strength compared to placebo. Secondary: The addition of alogliptin 25 mg once daily to insulin therapy compared to placebo resulted in statistically significant improvements from baseline at

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vs placebo All patients received insulin therapy with or without metformin.	inadequately controlled on insulin at a dose≥15 units and ≤100 units per day for at least 8 weeks		alogliptin on additional measures of glycemic control, β-cell function, plasma lipids and weight.	week 26 in FPG (-12 vs 6 mg/dL, respectively; P<0.05). Decreases in FPG and HbA_{1c} compared to placebo with alogliptin were generally observed at all time points. The overall incidences of hyperglycemic rescue were significantly lower in the alogliptin 12.5 and 25 mg groups (21 and 20% respectively) than in the placebo group (40%; P<0.001 for both comparisons). Differences in other secondary endpoints including change in weight and lipid parameters from baseline did not differ significantly between treatment groups. Incidences of overall adverse events, and of gastrointestinal, dermatological and infection-related events, were similar among groups. There were no differences in the proportions of patients experiencing hypoglycemia among placebo (24%), alogliptin 12.5 mg (27%) and alogliptin 25 mg (27%).
Zannad et al.[43] (2015) EXAMINE post-hoc analysis Alogliptin vs placebo	DB, MC, RCT Patients with type 2 diabetes receiving antidiabetic therapy (with the exception of a DPP-4 inhibitor or GLP-1 analogue), and had had an acute coronary syndrome event within 15 to 90 days before randomization	N=5,380 Median 533 days	Primary: Composite major adverse cardiac events (MACE) endpoint was cardiovascular death, non-fatal acute myocardial infarction, and non-fatal stroke Secondary: Exploratory extended MACE composite endpoint that combined the first occurrence of all-cause mortality, non-fatal	Primary: Alogliptin was non-inferior to placebo in lowering the risk of the composite primary endpoint (11.3 vs 11.8%; HR, 0.96; upper boundary of the one-sided 95% CI, 1.16). Secondary: The exploratory extended MACE endpoint was seen in 433 (16.0%) patients assigned to alogliptin and in 441 (16.5%) assigned to placebo (HR, 0.98; 95% CI, 0.86 to 1.12). Hospital admission for heart failure was the first event in 85 (3.1%) patients taking alogliptin compared with 79 (2.9%) taking placebo (HR, 1.07; 95% CI, 0.79 to 1.46). Alogliptin had no effect on composite events of cardiovascular death and hospital admission for heart failure in the post hoc analysis (HR, 1.00; 95% CI, 0.82 to 1.21) and results did not differ by baseline BNP concentration. NT-pro-BNP concentrations decreased significantly and similarly in the two groups.

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			myocardial infarction, non-fatal stroke, urgent revascularization due to unstable angina, and hospital admission for heart failure	
Rosenstock et al.[44] (2013) Alogliptin 25 mg QD vs glipizide 5 mg (titrated to 10 mg if needed)	AC, DB, PRO, RCT Patients aged 65 to 90 years of age with type 2 diabetes on diet and exercise therapy alone during the 2 months prior to screening with HbA_{1c} level of 6.5 to 9.0% or on oral antidiabetic monotherapy with HbA_{1c} of 6.5 to 8.0%	N=441 52 weeks	Primary: HbA_{1c} changes at week 52 from baseline. Secondary: Changes from baseline in HbA_{1c} at all time points, changes in FPG, 2-hour PPG, weight and lipid changes, and adverse events	Primary: Glycemic control with alogliptin was comparable to that with glipizide, with no statistically significant treatment-group differences for any of the corresponding efficacy endpoints. Secondary: Treatment with alogliptin resulted in modest body weight decreases throughout the study, which were significant when compared with the increases observed with glipizide, −0.62 vs 0.60 kg, respectively, by week 52 (P<0.001). Triglycerides also significantly improved with alogliptin (8.0% decrease) compared with glipizide (1.2% increase; P=0.046), whereas no significant differences were noted for total cholesterol (0.4 vs 0.3% decrease), high-density lipoprotein cholesterol (1.7 vs 0.6% increase) or low-density lipoprotein cholesterol (0.8% increase vs 1.3% decrease). Fewer patients discontinued from alogliptin because of adverse events (8.6 vs 12.3% from glipizide).
Del Prato et al.[45] (2014) Alogliptin 12.5 mg QD vs alogliptin 25 mg QD vs	DB, MC, RCT Patients 18 to 80 years of age with type 2 diabetes inadequately controlled on stable-dose metformin	N=2,639 104 weeks	Primary: Mean change from baseline in HbA_{1c} Secondary: Changes over time in HbA_{1c} and FPG, incidence of clinical response (HbA_{1c} ≤6.5 and	Primary: From baseline HbA_{1c} values of 7.6% in all three treatment groups, changes up to weeks 52 and 104 showed sustained glycemic response. In the analysis of mean differences between the treatment groups at week 104, the criteria for non-inferiority to glipizide were satisfied for both alogliptin 12.5 mg (P<0.001) and alogliptin 25 mg (P<0.001), and the criteria for superiority to glipizide were satisfied for alogliptin 25 mg (P=0.010). Secondary: FPG concentration decreased by 0.05 and 0.18 mmol/l for alogliptin 12.5 and 25 mg, respectively, and increased by 0.30 mmol/l for glipizide

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glipizide 5 mg QD, titrated to a maximum of 20 mg			≤7.0%), changes in body weight, incidence of hyperglycemic rescue, and changes in 2-h PPG over time	(P<0.001 for both comparisons with glipizide). Mean weight changes were −0.68, −0.89 and 0.95 kg for alogliptin 12.5 and 25 mg and glipizide, respectively (P<0.001 for both comparisons with glipizide). Hypoglycemia occurred in 23.2% of patients in the glipizide group vs 2.5 and 1.4% of patients in the alogliptin 12.5 and 25 mg groups, respectively.
Rosenstock et al.[46] (2010) Alogliptin 25 mg QD vs alogliptin 12.5 mg QD and pioglitazone 30 mg QD vs alogliptin 25 mg QD and pioglitazone 30 mg QD vs pioglitazone 30 mg QD	DB, PG, RCT Treatment naïve patients 18 to 80 years of age with type 2 diabetes, an HbA_{1c} value 7.0 to 11.0%, a BMI 23 to 45 kg/m^2, who failed diet and exercise interventions for ≥2 months	N=655 26 weeks	Primary: Mean change from baseline in HbA_{1c} at week 26 Secondary: HbA_{1c} and FPG changes from baseline at each study visit, percentage of patients achieving specific HbA_{1c} goals, frequency of glycemic rescue and safety evaluations	Primary: Coadministration of the 25 mg dose with pioglitazone compared to 25 mg alone and to pioglitazone 30 mg alone resulted in statistically significant improvements from baseline in HbA_{1c} (-1.7 vs -1.0 and -1.2%, respectively; P<0.01 for both comparisons). Similar reductions were observed with the combination therapy arm involving the 12.5 mg strength. Secondary: Coadministration of the 25 mg dose with pioglitazone compared to 25 mg alone and to pioglitazone 30 mg alone resulted in statistically significant improvements from baseline in FPG (-50 vs -26 and -37 mg/dL, respectively; P<0.01 for both comparisons). In addition, each treatment resulted in prompt and progressive reductions in HbA_{1c} and FPG that were sustained throughout the 26 weeks. In addition, both combination therapy groups were associated with significantly greater percentage of patients meeting glycemic goals compared to monotherapy. Fewer patients in the combination therapy groups required hyperglycemic rescue (3.7 and 2.4% with combination alogliptin 12.5 and 25 mg groups, respectively) than with either pioglitazone (6.1%) or alogliptin monotherapy (11.0%). The safety profile of combination therapy was consistent with that of the individual components. The most frequently reported adverse events included headache, back pain, urinary tract infection and peripheral edema.
DeFronzo et al.[47] (2012)	DB, MC, PC, PG, RCT	N=1,554 26 weeks	Primary: Mean change from baseline in	Primary:

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Alogliptin 12.5 mg QD vs alogliptin 25 mg QD vs pioglitazone 15 mg QD vs pioglitazone 30 mg QD vs pioglitazone 45 mg QD vs alogliptin 12.5 mg QD and pioglitazone 15 mg QD vs alogliptin 12.5 mg QD and pioglitazone 30 mg QD vs	Patients 18 to 80 years of age with type 2 diabetes, an HbA_{1c} value 7.5% to 10.0%, FPG <16.7 mmol/L, BMI 23 to 45 kg/m^2, blood pressure ≤160/110 mm Hg, HGB ≥12 g/dL (men) or ≥10 g/dL (women), ALT ≤2.5 X ULN, TSH ≤ULN, SCR <133 µmol/L (men) or <124 µmol/L (women), and C-peptide concentration ≥0.26 nmol/L who were inadequately controlled on metformin at a dose of ≥1,500 mg/day for ≥2 months		HbA_{1c} at week 26 Secondary: HbA_{1c} and FPG changes from baseline at each study visit, hyperglycemic rescue, C-peptide, proinsulin, insulin and proinsulin/insulin ratio, HOMA-B, achievement of glycemic goals, changes in body weight and safety evaluations	Coadministration of alogliptin and pioglitazone provided significant improvements in HbA_{1c} and FPG compared to placebo, or either treatment as a single agent added to metformin therapy (P<0.01 for all comparisons). Secondary: More patients in the placebo group (41 of 129; 31.8%) required hyperglycemic rescue than in any active treatment group. The alogliptin and pioglitazone therapy groups had a higher percentage of patients requiring hyperglycemic rescue (8.5 to 14.7%) than any combination therapy (1.5 to 4.6%). Measures of β-cell function found a greater decrease in alogliptin 25 mg/pioglitazone compared to pioglitazone alone. However, the decrease in the alogliptin 12.5 mg/pioglitazone arms were similar to the pioglitazone arms alone. Body weight decreased slightly in patients receiving placebo (-0.7 kg) or alogliptin (-0.02 and -0.7 kg for the 12.5 and 25 mg groups, respectively), whereas there were modest but significant increases in body weight in all groups receiving pioglitazone (P values not reported). In general, the combination of alogliptin and pioglitazone was well tolerated. In addition, the incidence of adverse events was similar across treatment groups.

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alogliptin 12.5 mg QD and pioglitazone 45 mg QD vs alogliptin 25 mg QD and pioglitazone 15 mg QD vs alogliptin 25 mg QD and pioglitazone 30 mg QD vs alogliptin 25 mg QD and pioglitazone 45 mg QD vs placebo Patients received metformin at a dose of 1,500 mg/day.				
Bosi et al.[48] (2011) Alogliptin 25 mg QD and pioglitazone 30 mg QD vs	AC, DB, MC, PG, RCT Patients 18 to 80 years of age with type 2 diabetes, an HbA_{1c} value 7.0 to 10%, FPG <15.3	N=803 52 weeks	Primary: Mean change from baseline in HbA_{1c} at weeks 26 and 52 Secondary:	Primary: In combination with pioglitazone and metformin, alogliptin was associated with a significantly greater decrease compared to the titration of pioglitazone in HbA_{1c} (-0.7 vs -0.3%, respectively; P=0.025) and FPG (-15 vs -4 mg/L, respectively; P<0.001) at 52 weeks. Similar, the decrease was greater with the alogliptin group at 26 weeks (P<0.001). Secondary:

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pioglitazone 45 mg QD All members received metformin at a dose ≥1,500 mg throughout the study.	mmol/L, BMI 23 to 45 kg/m^2, blood pressure ≤160/110 mm Hg, and C-peptide concentration ≥0.26 nmol/L who were inadequately controlled on metformin at a dose of ≥1,500 mg/day and pioglitazone 30 mg daily for ≥2 months		Mean change from baseline in HbA_{1c} and FPG at all other visits, proportions of patients achieving glycemic goals, proinsulin: insulin ratio, C-peptide, HOMA-B, HOMA insulin resistance, body weight, serum triglycerides, cholesterol, and safety endpoints	In combination with pioglitazone and metformin, alogliptin was associated with a significantly greater decrease compared to the titration of pioglitazone in FPG (-15 vs -4 mg/L, respectively; P<0.001) at 52 weeks. Decreases favored alogliptin for HbA_{1c} and FPG at 26 weeks and other time points. At week 52, the proportions of patients achieving HbA_{1c} levels ≤7.0 (33.2 vs 21.3%, respectively) and ≤6.5% (8.7 vs 4.3%, respectively) were significantly higher in the alogliptin group than in the pioglitazone titration group (P<0.001 for all comparisons). Proinsulin: insulin ratio (-0.048 vs -0.007, respectively) and HOMA β-cell function (15.02 vs 2.06, respectively) were significantly improved in the alogliptin group compared to the pioglitazone titration group at 52 weeks (P< 0.001 for all comparisons). However, no statistically significant differences in mean change from baseline in C-peptide, HOMA insulin, in body weight, total cholesterol, HDL cholesterol, LDL-C, triglycerides or free fatty acids resistance were observed between the treatment groups at week 52 (P>0.05 for all comparisons). No meaningful differences in incidences of individual adverse events were observed between treatments.
Leiter et al.[49] (2014) Albiglutide 30 mg once weekly (uptitrated if needed) vs sitagliptin (dosed based on the eGFR value)	DB, MC, RCT Renally impaired patients with type 2 diabetes	N=507 52 weeks	Primary: Change in HbA_{1c} from baseline to 26 weeks Secondary: FPG, weight, achievement of treatment targets, hyperglycemic rescue, and safety.	Primary: The model-adjusted LS mean for the primary end point of change from baseline in HbA_{1c} at week 26 was −0.83% in the albiglutide group and −0.52% in the sitagliptin group, with similar results across all three baseline eGFR groups. The treatment difference (albiglutide vs sitagliptin) was −0.32% (95% CI, −0.49 to −0.15). The upper bound of the CI was below the prespecified noninferiority margin of 0.4%, indicating noninferiority of albiglutide to sitagliptin. A superiority test conducted in accordance with a prespecified, step-wise procedure indicated that albiglutide was statistically superior to sitagliptin (P=0.0003). The treatment effect of albiglutide seen at week 26 was maintained through week 52. Secondary:

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Patients continued to receive their prescribed oral antihyperglycemic medication regimen (metformin, thiazolidinedione, sulfonylurea, or any combination of these oral antihyperglycemic medications)				The change in FPG from baseline at week 26 was −1.42 mmol/L in the albiglutide group and −0.22 mmol/L in the sitagliptin group. At week 26, the difference in LS means (albiglutide vs sitagliptin) was −1.20 mmol/L (P<0.0001). A higher percentage of patients in the albiglutide treatment group achieved the treatment targets of HbA_{1c} <6.5% and <7.0% at week 26 (albiglutide 15.3% and 42.6%, respectively, compared with sitagliptin 12.3% and 30.5%, respectively). The treatment difference between albiglutide and sitagliptin was statistically significant (P=0.0077) for the treatment target of HbA_{1c} <7.0% at week 26. There was a statistically significant difference between albiglutide and sitagliptin (P=0.0017) in the mean time to hyperglycemia rescue through week 52. The proportion of patients who had required hyperglycemia rescue was lower in the albiglutide group than in the sitagliptin group at week 26 (6.1% [15 patients] vs 12.1% [29 patients]) and at week 52 (17.9% [44 patients] vs. 28.3% [68 patients]). Patients in both treatment groups showed a modest mean loss in body weight through week 26, with a model-adjusted LS mean weight change from baseline of −0.79 kg for albiglutide and −0.19 kg for sitagliptin (P<0.05). The incidence of any adverse event and the event rates of on-therapy adverse events over the course of the study were similar between the two treatment groups (83.5% and 347 AEs/100 person-years with albiglutide and 83.3% and 331 AEs/100 person-years with sitagliptin).
Del Prato et al.[50] (2011) Linagliptin 5 mg/day vs placebo	DB, MC, PC, PG, RCT Type 2 diabetics 18 to 80 years of age with BMI ≤40 kg/m^2, and either treatment-naïve or had previously received 1 oral antidiabetic agent (excluding TZDs)	N=503 24 weeks	Primary: Change in baseline HbA_{1c} Secondary: Proportion of patients achieving an HbA_{1c} <7.0 or <6.5%, change in baseline HbA_{1c} by visit over time, proportion of patients with an HbA_{1c} decrease ≥0.5%, change in	Primary: Adjusted mean differences of the change in HbA_{1c} significantly favored linagliptin compared to placebo (-0.69%; P<0.0001). Secondary: The proportion of patients with a baseline HbA_{1c} ≥7.0% who achieved an HbA_{1c} <7.0% receiving linagliptin and placebo were 25.2 vs 11.6% (OR, 2.9; P=0.0006). The difference between linagliptin and placebo in HbA_{1c} decreases from baseline increased over time and favored linagliptin (-0.46% at week six to -0.69% at week 24; P<0.0001 for all). The proportion of patients who achieved an HbA_{1c} decrease ≥0.5% was 47.1 vs 19.0% with linagliptin and placebo (OR, 4.2; P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			baseline FPG, and two-hour PPG, safety	Adjusted mean differences of the decrease in FPG significantly favored linagliptin compared to placebo (-1.3 mmol/L; P<0.0001). Adjusted mean differences of the decrease in two-hour PPG significantly favored linagliptin compared to placebo (-3.2 mmol/L; P<0.0001). Linagliptin was well tolerated. In the total population, 6.6% of patients discontinued treatment prematurely, most frequently due to adverse events (1.8%) or a refusal to continue medication (2.0%). A greater proportion of patients receiving placebo reported at least one adverse event (58.7 vs 52.4%) or serious adverse event (4.2 vs 3.0%). Hyperglycemia was the most frequently reported adverse event (8.6 vs 22.8%). Other more commonly reported adverse events with linagliptin included headache (2.7 vs 1.2%), hypertension (3.6 vs 1.2%), and back pain (2.7 vs 1.8%). No clinically significant findings emerged regarding laboratory analyses or vital signs.
Taskinen et al.[51] (2011) Linagliptin 5 mg/day vs placebo All patients also received metformin ≥1,500 mg/day.	DB, MC, PC, PG, RCT Type 2 diabetics 18 to 80 years of age with BMI ≤40 kg/m^2, who had inadequate glycemic control on metformin ≥1,500 mg/day (HbA_{1c} 7.0 to 10.0%) or metformin in combination with ≤1 other oral antidiabetic agent (HbA_{1c} 6.5 to 9.0%) for ≥10 weeks prior to trial entry	N=701 24 weeks	Primary: Change in baseline HbA_{1c} Secondary: Change in baseline FPG, two-hour PPG, body weight, and β cell function; change in baseline HbA_{1c} and FPG over time; proportion of patients achieving an HbA_{1c} <7.0 and <6.5%; proportion of patients with an HbA_{1c} decrease ≥0.5%; proportion of patients who	Primary: Linagliptin decreased HbA_{1c} by -0.49% compared to 0.15% with placebo (treatment difference, -0.64%; 95% CI, -0.78 to -0.50; P<0.0001). Secondary: Linagliptin significantly decreased FPG compared to placebo (-0.6 vs 0.6 mmol/L; treatment difference, -1.2 mmol/L; P<0.0001). Linagliptin significantly decreased PPG compared to placebo (-2.7 vs 1.0 mmol/L; treatment difference, -3.7 mmol/L; P<0.0001). Neither treatment was associated with a significant change in body weight (-0.4 vs -0.5 kg; P value not reported). HOMA-B demonstrated a clinically relevant difference between treatments in adjusted mean change from baseline at 24 weeks in favor of linagliptin of 11.9 (mU/L)/(mmol/L), for a relative change of 1.26 (mU/L)/(mmol/L) (P=0.0005).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			required rescue medication; safety	The significant difference between the two treatments in decreases in HbA_{1c} increased over time from six to 18 weeks (-0.43 to -0.65%), and then remained stable until trial end (-0.64%). Decreases in FPG over time were similar, with linagliptin-treated patients achieving decreases over time. The difference between the two treatments in terms of adjusted mean change from baseline in FPG increased overtime (-0.9 to -1.2 mmol/L; P<0.0001 for all). Among patients with a baseline HbA_{1c} ≥7.0%, 26.0 vs 9.0% of those receiving linagliptin and placebo achieved an HbA_{1c} <7.0% (OR, 4.4; 95% CI, 2.4 to 8.0; P=0.0001). A significant difference was also observed in achieving HbA_{1c} <6.5% for those with a baseline HbA_{1c} ≥6.5% (10 vs 2%; OR, 5.5; 95% CI, 1.9 to 15.6; P=0.0016). Fifty and 22% of patients receiving linagliptin and placebo achieved a reduction in HbA_{1c} ≥0.5% at 24 weeks (OR, 3.8; 95% CI, 2.5 to 5.7; P<0.0001). More than twice as many patients receiving placebo required rescue medication (19 vs 8%; OR, 0.28; P=0.0001). Overall, linagliptin was well tolerated and adverse events occurred at a similar rate with both treatments. Most adverse events were mild or moderate in intensity. All hypoglycemic events were of mild intensity and assistance was not required by any patient. The incidence of treatment-related adverse events was slightly higher among placebo-treated patients (10.7 vs 6.9%). No clinically significant findings emerged regarding laboratory analyses or vital signs.
Owens et al.[52] (2011) Linagliptin 5 mg QD vs placebo	DB, MC, PC, PG, RCT Type 2 diabetics ≥18 to ≤80 years of age, BMI ≤40 kg/m^2, and HbA_{1c} ≥7.0 and ≤10.0% despite receiving	N=1,058 24 weeks	Primary: Change in baseline HbA_{1c} Secondary: Proportion of patients achieving an HbA_{1c} <6.5 or <7.0%; proportion	Primary: Linagliptin significantly decreased HbA_{1c} compared to placebo (treatment difference, -0.62%; 95% CI, -0.73 to 0.50; P<0.0001). Secondary: A significantly greater proportion of patients with baseline HbA_{1c} ≥7.0% achieved an HbA_{1c} <7.0% with linagliptin compared to placebo (29.2 vs 8.1%; P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Patients were also receiving metformin and a sulfonylurea.	metformin ≥1,500 mg/day and the maximum tolerated dose of a sulfonylurea		of patients achieving an HbA_{1c} decrease ≥0.5%; change in baseline FPG, fasting plasma insulin, HOMA-B, HOMA-IR, body weight, waist circumference, and lipid profile; use of rescue medication; safety	The proportion of patients achieving an HbA_{1c} decrease ≥0.5% was 58.2 and 30.2% with linagliptin and placebo (P value not reported). Linagliptin significantly decreased FPG (treatment difference, -7.0 mmol/L; 95% CI, -1.0 to -0.4; P<0.0001). Linagliptin significantly improved HOMA-B and HOMA-IR compared to placebo (P<0.001). No significant changes in body weight or waist circumference were observed with either treatment. Only placebo-treated patients experienced a meaningful decrease in TG (-12 mg/dL). Changes in TC, HDL-C, and LDL-C were similar between the two treatments. Of the patients receiving linagliptin, 5.4% required rescue medication compared to 13.0% of placebo-treated patients. The likelihood of requiring rescue medication was approximately three times lower with linagliptin (OR, 0.361; P<0.0001). Overall, 66.3 and 59.7% of patients receiving linagliptin and placebo experienced adverse events. The proportion of patients reporting severe adverse events was low with both treatments (2.4 vs 1.5%). Hypoglycemia was the most commonly reported adverse event (22.7 vs 14.8%). Symptomatic hypoglycemia was reported in 16.7 and 10.3% of patients. Hypoglycemia was generally mild or moderate, with severe hypoglycemia reported in 2.7 and 4.8% of patients.
Bajaj et al.[53] (2014) Linagliptin 5 mg QD vs placebo	DB, MC, PC, RCT Type 2 diabetics ≥18 to ≤80 years of age, BMI ≤45 kg/m^2, and HbA_{1c} ≥7.5 and ≤10.0% despite receiving metformin ≥1,500	N=272 24 weeks	Primary: Change in baseline HbA_{1c} Secondary: Change from baseline in FPG, the percentage of	Primary: Linagliptin significantly reduced HbA_{1c} levels: The placebo-corrected adjusted mean change from baseline at week 24 for linagliptin was –6 mmol/mol; 95% CI, –9 to –3 (–0.57%; 95% CI, –0.83 to –0.31; P<0.0001). Secondary: In patients with baseline HbA_{1c} ≥7.0%, 32.4% of patients in the linagliptin group and 13.8% in the placebo group achieved HbA_{1c} <7.0% (OR, 2.94;

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	mg/day and pioglitazone 45 mg/day		patients who attained HbA_{1c} levels <7.0% and <6.5%, the percentage of patients who achieved a reduction of ≥0.5% in HbA_{1c}	P=0.0033). The placebo-corrected adjusted mean change from baseline in FPG at week 24 was –0.57 mmol/l (–10.4 mg/dl; P=0.0280). The incidence of serious adverse events was 2.2% with linagliptin and 3.4% with placebo. Investigator-defined hypoglycemia occurred in 5.5% of the linagliptin group and 5.6% of the placebo group. No meaningful changes in mean body weight were noted for either group.
Rosenstock et al.[54] (2019) CARMELINA Linagliptin 5 mg QD vs placebo Treatment given in addition to usual care (except DPP-4 inhibitors, glucagon-like peptide 1 receptor agonists, and sodium-glucose cotransporter 2 inhibitors)	DB, MC, NI, RCT Adults with type 2 diabetes, HbA_{1c} of 6.5% to 10.0%, high CV risk (history of vascular disease and urine-albumin creatinine ratio >200 mg/g), and high renal risk (reduced eGFR and micro- or macroalbuminuria)	N=6,979 Median of 2.2 years	Primary: Time to first occurrence of the composite of CV death, nonfatal myocardial infarction, or nonfatal stroke Secondary: Time to first occurrence of adjudicated death due to renal failure, ESRD, or sustained 40% or higher decrease in eGFR from baseline	Primary: The primary composite 3-point outcome occurred in 12.4% of patients randomized to linagliptin (5.77 per 100 person-years) and 12.1% of patients randomized to placebo (5.63 per 100 person-years), for an absolute incidence rate difference of 0.13 (95% CI, −0.63 to 0.90) per 100 person-years (HR, 1.02; 95% CI, 0.89 to 1.17; P<0.001 for noninferiority), meeting the criterion for noninferiority. The subsequent testing for superiority according to the prespecified testing procedure was not statistically significant (P=0.74). Secondary: The risk of the secondary kidney composite outcome was not significantly different between the groups randomized to linagliptin (9.4%; 4.89 per 100 person-years) and placebo (8.8%; 4.66 per 100 person-years) (absolute incidence rate difference, 0.22; 95% CI, −0.52 to 0.97 per 100 person-years), and the test for superiority did not achieve statistical significance (HR, 1.04; 95% CI, 0.89 to 1.22; P=0.62).
Forst et al.[55] (2010) Linagliptin 1, 5, or 10 mg/day vs	AC, DB, MC, PC, PG, RCT Type 2 diabetics 21 to 75 years of age with BMI 25 to 40 kg/m^2, who had inadequate glycemic	N=333 12 weeks	Primary: Change in baseline HbA_{1c} Secondary: Change in baseline FPG and body weight, proportion	Primary: Placebo corrected decreases in HbA_{1c} were -0.40±0.14 (P=0.006), -4.40±0.14 (P<0.001), and -8.00±1.50% (P<0.001) with linagliptin 1, 5, and 10 mg, respectively. Treatment with glimepiride significantly decreased HbA_{1c} compared to treatment with placebo -0.68% (P<0.0001). Secondary:

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placebo vs glimepiride (OL) 1 to 3 mg/day Patients were also receiving metformin.	control on metformin alone (HbA_{1c} 7.5 to 10.0%)		of patients achieving an HbA_{1c} ≤7.0%, proportion of patients with an HbA_{1c} decrease ≥0.5%, safety	Decreases in FPG were significantly greater with all doses of linagliptin compared to placebo. The placebo corrected FPG decrease were -1.1 (P=0.0020), -1.9 (P<0.0001), and -1.6 mmol/L (P<0.0001) with linagliptin 1, 5, and 10 mg, respectively. After 12 weeks a small decrease in body weight was observed with all doses of linagliptin (-0.15, -0.57, and -1.27 kg, respectively; P values not reported). Only one (1.4%) patient receiving placebo achieved an HbA_{1c} ≤7.0% compared to ten (approximately 15%), nine (approximately 15%), and 14 (21%) patients receiving linagliptin 1, 5, and 10 mg/day, respectively (P values not reported). A greater proportion of patients receiving linagliptin achieved an HbA_{1c} decrease ≥0.5% compared to patients receiving placebo (43.8 to 53.2 vs 12.9%; P value not reported). In addition, HbA_{1c} decreased by ≥1.0% in 14.1, 27.4, 22.7, and 7.7% with linagliptin 1 mg, linagliptin 5 mg, linagliptin 10 mg, and placebo (P values not reported). Linagliptin was well tolerated. The most commonly reported adverse events were considered to be of mild or moderate intensity; however, ten patients experienced severe adverse events. No episodes of hypoglycemia were reported. Three (4.6%) patients experienced hypoglycemia after dosing with glimepiride.
Haak et al.[56] (2012) Linagliptin 5 mg QD vs metformin 500 mg BID vs	DB, MC, PC, RCT Patients 18 to 80 years of age with type 2 diabetes who were treatment-naïve (HbA_{1c} 7.5 to 11.0%) or who had received one other oral antidiabetic drug (HbA_{1c} 7.0 to 10.5%)	N=791 24 weeks	Primary: Change from baseline in HbA_{1c} at week 24 Secondary: Change from baseline in FPG, change from baseline in HbA_{1c} and FPG over time, proportion of	Primary: After 24 weeks, the mean change in HbA_{1c} was 0.1% with placebo, -0.5% with linagliptin 5 mg QD, -0.6% with metformin 500 mg BID, -1.1% with metformin 1,000 mg BID, -1.2% with linagliptin plus metformin 500 mg, and -1.6% with linagliptin plus metformin 1,000 mg. The adjusted placebo-corrected mean changes in HbA_{1c} were -1.7% (95% CI, -2.0 to -1.4) for linagliptin plus metformin 1,000 mg; -1.3% (95% CI, -1.6 to -1.1) for linagliptin plus metformin 500 mg; -1.2% (95% CI, -1.5 to -0.9) for metformin 1,000 mg; -0.8% (95% CI, -1.0 to -0.5) for metformin 500 mg, and -0.6% (95% CI, -0.9 to -0.3) for linagliptin monotherapy (P<0.0001 for all).

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metformin 1,000 mg BID vs linagliptin 2.5 mg BID and metformin 500 mg BID vs linagliptin 2.5 mg BID and metformin 1,000 mg BID vs placebo			patients requiring rescue therapy after failing to achieve pre-specified glycemic targets or discontinuing because of lack of efficacy, safety	The mean treatment differences for linagliptin plus metformin 1,000 mg vs metformin and linagliptin monotherapy were -0.5% (95% CI, -0.7 to -0.3) and -1.1% (95% CI, -1.4 to -0.9), respectively. For linagliptin plus metformin 500 mg, the respective mean differences were -0.6% (95% CI, -0.8 to -0.4) and -0.8% (95% CI, -1.0 to -0.6; P<0.0001 for all). Secondary: The adjusted placebo-corrected mean changes in FPG from baseline were -3.3 mmol/L (95% CI, -4.0 to -2.6) and -2.4 mmol/L (95% CI, -3.1 to -1.7) in the linagliptin plus metformin 1,000 mg and linagliptin plus metformin 500 mg groups, respectively. This is compared to -2.3 mmol/L (95% CI, -3.0 to -1.7), -1.4 mmol/L (95% CI, -2.1 to -0.8) and -1.0 mmol/L (95% CI, -1.7 to -0.3) in the metformin 1,000 mg, metformin 500 mg, and linagliptin monotherapy groups, respectively (P<0.0001 for all). The proportion of patients requiring rescue therapy for inadequate glycemic control at week 24 was lower in the combination therapy groups (linagliptin plus metformin 1,000 mg, 4.3%; linagliptin plus metformin 500 mg, 7.3%) compared to either monotherapy alone (metformin 1,000 mg, 8.0%; metformin 500 mg, 13.5%; linagliptin, 11.1%). The proportion of patients reporting adverse events were comparable across the active treatment groups.
Haak et al.[57] (2013) linagliptin 2.5 mg plus metformin 500 mg (both twice daily) vs linagliptin	DB, MC, PC, RCT Patients 18 to 80 years of age with type 2 diabetes who were treatment-naïve (HbA_{1c} 7.5 to 11.0%) or who had received one other oral antidiabetic drug (HbA_{1c} 7.0 to 10.5%)	N=566 54 weeks	Primary: Safety Secondary: Change from baseline in HbA_{1c} and FPG, the percentages of patients who achieved target HbA_{1c} levels of < 7.0 or < 6.5%,	Primary: The incidences of treatment-emergent AEs during the extension period were comparable across the groups, ranging between 66 and 77%. Most adverse events were of mild or moderate intensity, with the majority considered unrelated to study drug. Secondary: All three groups maintained the reduction in HbA_{1c} achieved at the end of the six-month trial, with changes of 0.12 ± 0.72%, 0.08 ± 0.74% and 0.13 ± 0.54%, for the metformin 1000 group, linagliptin 2.5 + metformin 500, and linagliptin 2.5 + metformin 1000 groups, respectively.

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2.5 mg plus metformin 1000 mg (both twice daily) vs metformin 1000 mg twice daily monotherapy	(extension study of Haak et al.)		the percentages of patients with a reduction in HbA_{1c} levels of ≥ 0.5%, and use of rescue therapy	The overall incidence of rescue medication use was lower in the linagliptin 2.5 + metformin 1000 treatment group (14.0%) than in the linagliptin 2.5 + metformin 500 (27.6%) and metformin 1000 (24.7%) treatment groups. During the extension study, there were no clinically meaningful changes in weight, with mean ±SD changes of –0.4 ± 2.7 kg, 0.2 ± 3.0 kg and –0.7 ± 3.2 kg in the metformin 1000, linagliptin 2.5 + metformin 500, and linagliptin 2.5 + metformin 1000 groups, respectively.
Gomis et al.[58] (2011) Linagliptin 5 mg/day vs placebo All patients were receiving pioglitazone 30 mg/day.	DB, DD, MC, PC, PG, RCT Type 2 diabetics 18 to 80 years of age with BMI ≤40 kg/m^2, who had inadequate glycemic control (HbA_{1c} 7.5 to 11.0%)	N=389 24 weeks	Primary: Change in baseline HbA_{1c} Secondary: Proportion of patients achieving an HbA_{1c} <7.0%; proportion of patients with an HbA_{1c} decrease ≥0.5%; change in baseline HbA_{1c} over time; change in baseline FPG, β cell function, and body weight; safety	Primary: Combination therapy significantly decreased HbA_{1c} compared to placebo (-1.06±0.06 vs -0.56±0.09%; treatment difference, -0.51%; 95% CI, -0.71 to -0.30; P<0.0001). Secondary: The proportion of patients achieving an HbA_{1c} <7.0% was significantly greater with combination therapy compared to placebo (42.9 vs 30.5%; OR, 2.1; 95% CI, 1.3 to 3.5; P=0.0051). A significantly greater proportion of patients receiving combination therapy had ≥5.0% decrease in HbA_{1c} compared to patients receiving placebo (75.0 vs 50.8%; OR, 3.8; 95% CI, 2.3 to 6.4; P<0.0001). The placebo corrected difference in adjusted mean change from baseline in HbA_{1c} increased over the first 12 weeks (reaching -0.5%), and remained constant until trial end. Combination therapy resulted in a larger decrease in non-adjusted HbA_{1c} over time compared to placebo (P<0.0001 at each visit). Combination therapy significantly decreased FPG compared to placebo (-1.8±0.1 vs -1.0±0.2 mmol/L; treatment difference, -0.8 mmol/L; P<0.0001). There was no difference in decreases in HOMA-IR between the two treatments (-2.90 vs -2.58; treatment difference, -0.32; 95% CI, -0.77 to 0.13; P=0.16). Similar results were observed with HOMA-B (-2.17 vs -1.44; treatment difference, -0.73; 95% CI, -9.16 to 7.70; P=0.86).

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				Both treatments resulted in weight gain, with the increase being significantly greater with combination therapy (2.3 vs 1.2 kg; treatment difference, 1.1 kg; 95% CI, 0.2 to 2.0; P=0.014). Overall, the proportion of patients who experienced at least one adverse event was similar with both treatments (52.5 vs 53.1%). Most adverse events were of mild to moderate intensity. Hypoglycemia occurred in 1.2 and 0.0% of patients receiving combination therapy and placebo, respectively. Laboratory analyses did not reveal any clinically significant findings.
Ledesma et al.[59] (2019) Linagliptin 5 mg daily vs placebo	DB, MC, RCT Type 2 diabetics aged ≥60 years on stable insulin (the only permitted additional glucose-lowering therapies were metformin and/or alpha-glucosidase inhibitors, administered at a stable dose for 12 weeks prior to randomization), with baseline HbA_{1c} 7.0% to 10.0%, and body mass index ≤45 kg/m^2	N=302 24 weeks	Primary: Reduction in HbA_{1c} from baseline to 24 weeks Secondary: Adverse events, achieving HbA_{1c} targets	Primary: The adjusted mean change in HbA_{1c} at 24 weeks compared with placebo was −0.63% (95% CI, –0.81 to −0.46; P <0.001). Secondary: The incidence of hypoglycemia (as defined for the efficacy assessment) was not statistically different between the linagliptin and placebo groups. Linagliptin was overall well tolerated, with similar incidences of adverse events between treatment groups. There appeared to be a numerical increase in the incidence of drug-related adverse events and nasopharyngitis (all mild cases) in the linagliptin group, whereas the incidence of severe adverse events was numerically higher in the placebo group. The incidence of adverse events of special interest was low, without imbalances between the study arms. There were no reported incidents of acute or chronic pancreatitis or pancreatic cancer in either group. The probability of achieving predefined HbA_{1c} targets without hypoglycemia (HbA_{1c} <8.0%: OR, 2.02; P <0.05 and HbA_{1c} <7.0%: OR, 2.44; P <0.01) was improved with linagliptin vs placebo.
Rosenstock et al.[60] (2015) Saxagliptin (SAXA) (5 mg/day) plus dapagliflozin	DB, RCT Type 2 diabetics with HbA_{1c} ≥8.0% and ≤12.0% on background	N=534 24 weeks	Primary: Change in baseline HbA_{1c} Secondary:	Primary: At week 24, the adjusted mean change from the baseline HbA_{1c} was –1.5% with SAXA+DAPA+MET vs –0.9% with SAXA+MET (difference −0.59%, P<0.0001) and –1.2% with DAPA+MET (difference −0.27%, P<0.02).

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(DAPA) (10 mg/day) vs SAXA (5 mg/day) and placebo vs DAPA (10 mg/day) and placebo	metformin extended release ≥1,500 mg/day		Adjusted mean change from baseline in 2-h PPG, FPG, and body weight, adjusted mean proportion of patients achieving a therapeutic glycemic response, defined as HbA_{1c} <7.0%	Secondary: The adjusted mean reduction in FPG was greater in the SAXA+DAPA+MET group (–38 ± 2.8 mg/dL) than in the SAXA+MET group (–14 ± 2.9 mg/dL) but similar to the DAPA+MET group (–32 ± 2.8 mg/dL). SAXA+DAPA+MET also resulted in a significantly greater adjusted mean reduction from baseline in PPG versus SAXA+MET (difference, –44 mg/dL; 95% CI, –53.7 to –34.3; P<0.0001) but not versus DAPA+MET (difference, –9 mg/dL; 95% CI, –18.8 to 0.5; P=0.06). Reduction in body weight of 2.1 kg (2.4%) was observed in the SAXA+DAPA+MET group and 2.4 kg (2.8%) in the DAPA+MET group compared with no change in the SAXA+MET group. The proportion of patients achieving HbA_{1c} <7% was 41% with SAXA+DAPA+MET versus 18% with SAXA+MET and 22% with DAPA+MET. Urinary and genital infections occurred in ≤1% of patients receiving SAXA+DAPA+MET. Hypoglycemia was infrequent, with no episodes of major hypoglycemia.
Chacra et al.[61] (2010) Saxagliptin 2.5 mg QD and glyburide 7.5 to 15 mg daily vs saxagliptin 5 mg QD and glyburide 7.5 to 15 mg daily vs glyburide 2.5 to 15 mg daily and placebo	DB, MC, RCT Type 2 diabetics 18 to 77 years of age with inadequate glycemic control (HbA_{1c} ≥7.5 to ≤10.0%), on a submaximal sulfonylurea dose for ≥2 months before screening, fasting C-peptide ≥1 ng/mL, and BMI ≤40 kg/m^2	N=768 24 weeks	Primary: Change in baseline HbA_{1c} Secondary: Change in baseline FPG and PPG $AUC_{0\text{-}3hr}$, proportion of patients achieving an HbA_{1c} <7.0%, safety	Primary: Saxagliptin significantly decreased HbA_{1c} compared to placebo (-0.54 and -0.64 vs 0.08%; P<0.0001 for both). Secondary: Saxagliptin significantly decreased FPG compared to placebo (2.5 mg; P=0.0218 and 5 mg; P=0.002). Saxagliptin significantly decreased PPG $AUC_{0\text{-}3hr}$ compared to placebo (-4,296 and -5,000 vs 1,196 (mg/minute)/(dL); P<0.0001 for both). A significantly greater proportion of patients receiving saxagliptin achieved an HbA_{1c} <7.0% compared to patients receiving placebo (22.4 and 22.8 vs 9.1%; P<0.0001 for both). Overall saxagliptin was well tolerated. The proportion of patients reporting any adverse event was similar across all treatments; with no evidence of a dose-response relationship. The proportion of patients reporting at least one adverse event and at least one treatment-related adverse event was 75.0 and 19.8, 72.3 and 21.3, and 76.8 and 14.2% with saxagliptin 2.5 mg, saxagliptin 5 mg, and placebo. No events of Stevens-Johnson syndrome or angioedema were reported. Cardiac disorder events

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				were: 2.0, 4.0 and 3.7% with saxagliptin 2.5 mg, saxagliptin 5 mg, and placebo. Hypertension was reported in 3.6, 6.3, and 2.2% with saxagliptin 2.5 mg, saxagliptin 5 mg, and placebo; however, mean SBP and DBP decreased with all treatments. There was no difference in the incidence of reported and confirmed hypoglycemic events with saxagliptin compared to placebo (P>0.05). Confirmed hypoglycemia occurred in 2.4, 0.8, and 0.7% of patients receiving saxagliptin 2.5 mg, saxagliptin 5 mg, and placebo.
Barnett et al.[62] (2012) Saxagliptin 5 mg QD vs placebo All patients also received insulin alone or in combination with metformin.	DB, MC, RCT Type 2 diabetics with inadequate glycemic control (HbA_{1c} 7.5 to 11.0% on stable insulin therapy (30 to 150 U/day alone or in combination with metformin) for at least 8 weeks	N=455 24 weeks	Primary: Change in HbA_{1c} from baseline to week 24 (or rescue), PPG, FPG, body weight, adverse events Secondary: Not reported	Primary: Patients treated with saxagliptin had significantly greater reductions in adjusted mean HbA_{1c} (difference, -0.41%; P<0.0001), PPG 180-minute AUC (-3829.8 mg/minute/dL; P=0.0011), and 120-minute PPG (-23.0 mg/dL; P=0.0016) at 24 weeks compared to placebo. Treatment with saxagliptin resulted in similar reductions in HbA_{1c} relative to placebo, irrespective of metformin treatment. At 24 weeks, difference in adjusted mean FPG for saxagliptin compared to placebo was -4.02 mg/dL (P=0.3958); 17.3 and 6.7% of patients in the saxagliptin and placebo groups, respectively, achieved HbA_{1c} <7.0%. Mean change from baseline in body weight at week 24 was 0.39 kg for saxagliptin and 0.18 kg for placebo. Hypoglycemia was reported in 18.4% and 19.9% of patients in the saxagliptin and placebo groups, respectively. Other adverse events reported in at least 5% of patients were urinary tract infection (5.9 vs 6.0%), influenza (3.0 vs 6.6%), and pain in extremity (1.6 vs6.0%). Secondary: Not reported
Stenlöf et al.[63] (2010) Saxagliptin 5 mg QD vs placebo	DB, MC, PC, RCT Type 2 diabetics with inadequate glycemic control (HbA_{1c} 7.0 to 10.0%), and currently receiving stable doses of	N=93 4 weeks	Primary: Change in baseline 24-hour mean weighted glucose Secondary: Change in baseline four-hour mean weighted PPG,	Primary: Saxagliptin significantly decreased 24-hour mean weighted glucose compared to placebo (-13.8 vs -3.0 mg/dL; P<0.0001). Secondary: Saxagliptin significantly decreased four-hour mean weighted PPG compared to placebo (-30.7 vs 0.4 mg/dL; P<0.0001). Similar results were observed with two-hour mean weighted PPG (-38.2 vs -2.8 mg/dL; P=0.0010).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
All patients also received metformin ER ≥1,500 mg/day.	metformin IR or metformin ER (≥1,500 mg/day) as monotherapy for ≥8 weeks		two-hour PPG (both assessed after the evening meal), three-day average mean daily glucose, and two-day average FPG	Saxagliptin significantly decreased three-day average mean daily glucose compared placebo (-11.7 vs 7.0 mg/dL; P<0.0001). Saxagliptin significantly decreased two-day average FPG compared to placebo (-10.8 vs 4.5 mg/dl; P=0.002).
Barnett et al.[64] (2012) Saxagliptin 5 mg QD vs placebo All patients also received insulin alone or in combination with metformin.	DB, MC, RCT Type 2 diabetics with inadequate glycemic control (HbA_{1c} 7.5 to 11.0% on stable insulin therapy (30 to 150 U/day alone or in combination with metformin) for at least 8 weeks	N=455 24 weeks	Primary: Change in HbA_{1c} from baseline to week 24 (or rescue), PPG, FPG, body weight, adverse events Secondary: Not reported	Primary: Patients treated with saxagliptin had significantly greater reductions in adjusted mean HbA_{1c} (difference, -0.41%; P<0.0001), PPG 180-minute AUC (-3829.8 mg/minute/dL; P=0.0011), and 120-minute PPG (-23.0 mg/dL; P=0.0016) at 24 weeks compared to placebo. Treatment with saxagliptin resulted in similar reductions in HbA_{1c} relative to placebo, irrespective of metformin treatment. At 24 weeks, difference in adjusted mean FPG for saxagliptin compared to placebo was -4.02 mg/dL (P=0.3958); 17.3 and 6.7% of patients in the saxagliptin and placebo groups, respectively, achieved HbA_{1c} <7.0%. Mean change from baseline in body weight at week 24 was 0.39 kg for saxagliptin and 0.18 kg for placebo. Hypoglycemia was reported in 18.4% and 19.9% of patients in the saxagliptin and placebo groups, respectively. Other adverse events reported in at least 5% of patients were urinary tract infection (5.9 vs 6.0%), influenza (3.0 vs 6.6%), and pain in extremity (1.6 vs 6.0%). Secondary: Not reported
Matthaei et al.[65] (2015) Saxagliptin 5 mg/day vs placebo	DB, RCT Patients on stable metformin (≥1,500 mg/day) for ≥8 weeks with HbA_{1c} 8.0 to 11.5%	N=315 24 weeks	Primary: Change in HbA_{1c} from baseline Secondary: FPG, proportion of patients achieving HbA_{1c} <7.0%	Primary: Change from baseline in HbA_{1c} was significantly greater with saxagliptin (–0.51%; 95% CI, –0.63 to –0.39) compared with placebo (–0.16%; 95% CI, –0.28 to –0.04) add-on to dapagliflozin plus metformin (difference –0.35%; 95% CI, –0.52 to –0.18; P<0.0001). Secondary: Reductions in 2-h PPG and FPG were similar between treatment arms. A larger proportion of patients achieved HbA_{1c} <7% with saxagliptin add-on

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
in addition to background dapagliflozin plus metformin IR	At screening patients received open-label dapagliflozin (10 mg/day) plus metformin immediate release (IR) for 16 weeks Patients with inadequate glycemic control (HbA_{1c} 7 to 10.5%) after initial 16 weeks were randomized to receive saxagliptin or placebo			to dapagliflozin plus metformin (35.3%) compared with placebo add-on to dapagliflozin plus metformin (23.1%).
Du et al.[66] (2017) SMART Acarbose 50 mg TID (could be titrated to 100 mg TID after 7 days of treatment) vs saxagliptin 5 mg QD All patients continued on their existing dose and regimen of metformin throughout the study	MC, OL, PG, RCT Chinese patients ≥18 years of age with type 2 diabetes inadequately controlled with metformin monotherapy with an HbA_{1c} between 7.5 and 11.0% at screening, and an HbA_{1c} between 7.0 and 11.0% and an FPG ≤13.3 mmol/L at the pre-randomization visit	N=488 24 weeks	Primary: Absolute change from baseline in HbA_{1c} at week 24 Secondary: Proportion of patients achieving a therapeutic glycemic response (defined as HbA_{1c} <7.0%), the proportion of patients with any gastrointestinal adverse events, the proportion of patients achieving therapeutic glycemic response	Primary: Saxagliptin was non-inferior to acarbose for glycemic control (HbA_{1c} change from baseline, -0.82% and -0.78%, respectively; difference, -0.04; 95% CI, -0.22 to 0.13%). Secondary: At week 24, 38.3% of patients receiving saxagliptin and 41.5% of patients receiving acarbose had achieved a therapeutic glycemic response. In the full analysis set, 5.5% of patients receiving saxagliptin and 24.7% of patients receiving acarbose reported gastrointestinal adverse events (risk ratio, 0.22; P<0.0001). This lower risk of gastrointestinal adverse events was also observed in the per protocol population (saxagliptin, 5.0% vs acarbose, 26.0%; risk ratio, 0.19; P<0.0001). Overall, 37.0% of patients and 28.8% of patients receiving saxagliptin and acarbose, respectively, achieved a therapeutic glycemic response without gastrointestinal adverse events. There was no significant difference between treatment groups for change from baseline to week 24 in FPG, 2-hour PPG and HOMA-β; however,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			without gastrointestinal adverse events, and the change from baseline in FPG, 2-hour PPG, β-cell function, and body weight	greater weight loss was observed with acarbose compared with saxagliptin (P=0.0078).
Müller-Wieland et al.[67] (2018) Dapagliflozin 10 mg plus saxagliptin 5 mg vs dapagliflozin 10 mg vs glimepiride 1 to 6 mg (titrated) Patients on metformin monotherapy (≥1500 mg/day)	DB, MC, RCT Patients with type 2 diabetes 18 to ≥75 years of age on stable metformin (≥1500 mg/day) for ≥8 weeks and HbA_{1c} concentration of 7.5 to 10.5%	N=939 52 weeks	Primary: Absolute change from baseline in HbA_{1c} Secondary: Proportion of patients reporting confirmed hypoglycemic episodes during the 52-week treatment period, changes from baseline in total body weight and FPG at week 52, and the time to rescue during the treatment period	Primary: Adjusted mean change from baseline in HbA_{1c} at 52 weeks was −0.82% for dapagliflozin alone and −1.20% for dapagliflozin plus saxagliptin, compared with −0.99% for glimepiride when added to baseline metformin monotherapy. Non-inferiority, based on a prespecified margin of 0.3%, was demonstrated for both dapagliflozin-containing treatment groups, relative to glimepiride, at Week 52. The change in HbA_{1c} from baseline was statistically significantly greater (P=0.001) with dapagliflozin plus saxagliptin than with glimepiride. Secondary: The proportion of patients experiencing at least one episode of confirmed hypoglycemia was low across all groups (<5%) and was significantly lower in both dapagliflozin-containing treatment groups than in the glimepiride group (P<0.001, both comparisons). Total body weight decreased from baseline in both dapagliflozin-containing treatment groups, whereas it increased in the glimepiride group. Reductions in FPG from baseline were statistically significantly greater with dapagliflozin plus saxagliptin than with glimepiride as add-on therapy, and dapagliflozin was non-inferior to glimepiride as add-on therapy. The proportions of patients who met rescue criteria during the treatment period were 18.6%, 8.3% and 21.4% in the dapagliflozin, dapagliflozin plus saxagliptin and glimepiride add-on to metformin groups, respectively.
Rosenstock et al.[68] (2019) Dapagliflozin 5 mg/day plus saxagliptin 5 mg/day	DB, MC, RCT Patients ≥18 years of age with type 2 diabetes; stable metformin dose	N=883 24 weeks	Primary: Mean change in HbA_{1c} from baseline to week 24	Primary: The adjusted mean ± SE change from baseline in HbA_{1c} at 24 weeks was greater with dapagliflozin plus saxagliptin plus metformin than with either dapagliflozin or saxagliptin plus metformin (−1.03 ± 0.06% vs −0.63 ± 0.06% vs −0.69 ± 0.06%; P<0.0001 for both comparisons).

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vs dapagliflozin 5 mg/day vs saxagliptin 5 mg/day	(≥1500 mg/d) for ≥8 weeks before enrolment; BMI ≤45 kg/m^2; fasting plasma glucose ≤15 mmol/L (≤270 mg/dL); and HbA_{1c} 7.5% to 10.0%		Secondary: Proportion of participants achieving HbA_{1c} <7%, change in body weight, safety	Secondary: The proportion of participants who achieved HbA_{1c} levels of <7.0% was greater with dapagliflozin plus saxagliptin plus metformin than with dapagliflozin or saxagliptin plus metformin (adjusted response rate, 41.6%; 95% CI, 36.0 to 47.1 vs 21.8%; 95% CI, 17.2 to 26.4 vs. 29.8%; 95% CI, 24.9 to 34.8; P<0.0001 and P=0.0018 for comparisons vs dapagliflozin plus metformin and saxagliptin plus metformin, respectively). Reductions in total body weight from baseline were greater with dapagliflozin plus saxagliptin plus metformin than with saxagliptin plus metformin (adjusted mean ± SE change, −2.0 ± 0.2 kg vs −0.4 ± 0.2 kg; P<0.0001). The proportions of participants reporting at least one adverse event were 41.3%, 42.0%, and 39.3% for dapagliflozin plus saxagliptin plus metformin, dapagliflozin plus metformin, and saxagliptin plus metformin, respectively. The most commonly reported adverse events with dapagliflozin plus saxagliptin plus metformin were decreased eGFR (4.1%), urinary tract infection (2.4%), and pollakiuria (2.4%). With dapagliflozin plus metformin, the most commonly reported adverse events were decreased eGFR (3.8%), viral upper respiratory tract infection (3.1%), and influenza (3.1%). With saxagliptin plus metformin, viral or non-viral upper respiratory tract infections (2.7% and 2.0%) were the most commonly reported adverse events. In the triple therapy group, 5.8% of participants experienced at least one hypoglycemic event, compared with 2.7% and 3.4% in the dapagliflozin plus metformin and saxagliptin plus metformin groups, respectively.
Vilsbøll et al.[69] (2020) Dapagliflozin plus saxagliptin (DAPA + SAXA) vs insulin glargine (INS)	OL, PG, RCT Patients ≥18 years of age with type 2 diabetes and inadequate glycemic control (HbA_{1c} ≥8% to ≤12%) receiving stable metformin therapy (≥1500 mg/day)	N=600 52 weeks	Primary: mean change in HbA_{1c} and body weight from baseline and achieving an optimal glycemic response (HbA_{1c} <7.0%) without hypoglycemia	Primary: At 52 weeks, HbA_{1c} decreased more with DAPA + SAXA (adjusted least squares (LS) mean, −1.5%; 95% CI, −1.6% to −1.4%) than with INS (adjusted LS mean, −1.3%; 95% CI, −1.4% to −1.1%); the LS mean difference (95% CI) was −0.25% (−0.4% to −0.1%; P=0.009). Total body weight reduced with DAPA + SAXA (LS mean, -1.8 kg; 95% CI, -2.4 to -1.3) and increased with INS (LS mean, +2.8 kg; 95% CI, 2.2 to 3.3). More patients on DAPA + SAXA (17.6%) achieved HbA_{1c} <7.0% without hypoglycemia versus those on INS (9.1%). Secondary:

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	with or without sulphonylurea (≥50% of maximal dose) for at least 8 weeks before screening		Secondary: Proportion of patients requiring rescue medication or discontinuing due to lack of glycemic control and change from baseline in the average postprandial glucose values; safety	Overall, 174 patients required rescue medication or discontinued the study due to lack of glycemic control: 77 (23.8%) in the DAPA + SAXA group and 97 (30.4%) in the INS group at week 52. The adjusted percentage of patients requiring rescue medication or discontinuation at week 52 was 21.0% (95% CI, 16.7% to 26.1%) and 27.7% (95% CI, 22.8% to 33.3%) in the DAPA + SAXA and INS groups, respectively (OR, 0.7; 95% CI, 0.5 to 1.0). At least one adverse event was reported by 209 patients (64.5%) in the DAPA + SAXA group and 217 (68.0%) in the INS group. Adverse events considered by the investigator to be treatment-related were more common in the DAPA + SAXA group (11.1%) versus the INS group (4.7%).
Frias et al.[70] (2020) Dapagliflozin 10 mg (DAPA) + saxagliptin 5 mg (SAXA) vs glimepiride 1 to 6 mg (GLIM)	AC, DB, MC, RCT Patients ≥18 years of age with type 2 diabetes who were inadequately controlled (HbA_{1c} 7.5 to 10.5%) on metformin monotherapy	N=443 52 weeks	Primary: Mean change in HbA_{1c} from baseline Secondary: Change from baseline in total body weight; proportion of patients achieving a therapeutic response, defined as HbA_{1c} <7.0%; change from baseline in systolic blood pressure (SBP); and time to treatment intensification	Primary: The adjusted mean change from baseline in HbA_{1c} at 52 weeks was greater with DAPA + SAXA (−1.35%) than with GLIM (−0.98%; P<0.001 vs GLIM). Secondary: The proportion of patients who achieved HbA_{1c} <7.0% at 52 weeks was greater with DAPA + SAXA than with GLIM (P=0.044). Total body weight decreased from baseline to week 52 with DAPA + SAXA, whereas it increased with GLIM (P<0.001). Similarly, SBP decreased from baseline to week 52 with DAPA + SAXA and increased with GLIM (P=0.007). Significantly fewer patients required treatment intensification with DAPA + SAXA than with GLIM (P=0.002); however, these results were not included in sequential testing, because there were <10 patients in each treatment group.
Schernthaner et al.[71] (2015) GENERATION	DB, MC, RCT Patients with type 2 diabetes ≥65 years	N=720 52 weeks	Primary: HbA_{1c} <7.0% without	Primary: The proportions of patients achieving HbA_{1c} <7.0% at week 52 without confirmed/severe hypoglycemia were similar with saxagliptin and glimepiride: 37.9 vs 38.2% (OR, 0.99; 95% CI, 0.73 to 1.34; P=0.9415);

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Saxagliptin 5 mg/day vs glimepiride ≤6 mg/day	of age on stable metformin monotherapy at any dose for ≥8 weeks before enrolment and had an HbA_{1c} concentration of 7.0 to 9.0%		confirmed/severe hypoglycemia Secondary: Incidence of confirmed/severe hypoglycemia	however, a significant treatment-by-age interaction was detected (P=0.0389). Secondary: Fewer patients in the saxagliptin group experienced ≥1 confirmed/severe hypoglycemic event over the treatment period, compared with the glimepiride group: 1.1 vs 15.3% (OR, 0.06; 95% CI, 0.02 to 0.17; nominal P<0.0001).
Hermans et al.[72] (2012) PROMPT Fixed-dose metformin 1500 mg/day, plus either: Add-on saxagliptin 5 mg/day (SAXA-MET) vs metformin uptitration (MET-UP) to a max dose (2500 mg/day)	DB, RCT metformin-tolerant patients ≥18 years of age with type 2 diabetes and insufficient glycemic control on submaximal metformin therapy	N=286 24 weeks	Primary: Absolute change from baseline in HbA_{1c} Secondary: Proportion of patients achieving a therapeutic glycemic response, change from baseline in FPG, safety and tolerability	Primary: Compared with baseline, an adjusted mean change in HbA_{1c} at Week 24 of -0.47% was observed in the SAXA-MET group and -0.38% in the MET-UP group. The difference in adjusted mean change from baseline HbA_{1c} between treatment groups was -0.10%, which was not statistically significant (P=0.260). Secondary: The proportion of patients achieving therapeutic glycemic response (HbA_{1c} <7%) at Week 24 was 43.8% (SAXA-MET) and 35.0% (MET-UP). In comparison, the proportion of patients achieving therapeutic glycemic response (HbA_{1c} ≤6.5%) at Week 24 was 20.5% (SAXA-MET) and 16.8% (MET-UP). During the 24-week treatment period, 51.0% (75/147) of patients in the SAXA-MET group and 43.9% (61/139) in the MET-UP group experienced at least one adverse event.
DeFronzo et al.[73] (2009) Saxagliptin 2.5 to 10 mg QD and metformin (existing therapy) vs	DB, PC, RCT Type 2 diabetics 18 to 77 years of age with inadequate glycemic control (HbA_{1c} ≥7.0 to ≤10.0%), receiving stable doses of metformin (≥1,500	N=743 24 weeks	Primary: Change in baseline HbA_{1c} Secondary: Change in baseline FPG and PPG $AUC_{0\text{-}3hr}$, proportion of	Primary: Saxagliptin significantly decreased HbA_{1c} compared to placebo (-0.59, -0.69, and -0.58 vs 0.13%; P<0.0001 for all), with significance achieved after four weeks. Secondary: Saxagliptin significantly decreased FPG compared to placebo (-14.31, -22.03, and -20.50 vs 1.24 mg/dL; P<0.0001 for all). Similar results were observed with PPG $AUC_{0\text{-}3hr}$ (-8,891, -9,586, and -8,137 vs -3,291 [mg/minute]/[dL]; P<0.0001 for all).

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metformin (existing therapy) and placebo	to <2,550 mg/day) ≥8 weeks, fasting C-peptide concentration ≥1 ng/mL, and BMI ≤40 kg/m^2		patients achieving an HbA_{1c}<7.0%	A significantly greater proportion of patients achieved an HbA_{1c} <7.0% with saxagliptin compared to placebo (37.1, 43.5, and 44.4 vs 16.6%; P<0.0001 for all).
Pfutzner et al.[74] (2011) Saxagliptin 5 and 10 mg QD plus metformin 500 mg/day vs saxagliptin 10 mg QD vs metformin 500 mg/day	AC, DB, ES, MC, RCT Type 2 diabetics 18 to 77 years of age, HbA_{1c} ≥8.0 to ≤12.0%, fasting C-peptide concentration ≥1 ng/mL, and BMI ≤40 kg/m^2	N=1,306 52 weeks (76 weeks total)	Primary: Change in baseline HbA_{1c} Secondary: Change in baseline body weight, proportion of patients achieving an HbA_{1c} <7.0 and ≤6.5%	Primary: Decreases in HbA_{1c} with saxagliptin 5 mg plus metformin were -2.31% (95% CI -2.44 to -2.18) and -2.33% (95% CI -2.46 to -2.20) with saxagliptin 10 mg plus metformin compared to -1.55 (95% CI, -1.70 to -1.40) and -1.79% (95% CI, -1.93 to -1.65) with saxagliptin and metformin monotherapies, respectively; P<0.0001 for combination therapy vs monotherapy). Secondary: Decreases in body weight were -1.2 kg with saxagliptin 5 mg plus metformin, -0.7 kg with saxagliptin 10 mg plus metformin, -0.3 kg with saxagliptin, and -1.0 kg with metformin (P values not reported). A greater proportion of patients achieved an HbA_{1c} <7.0% with saxagliptin 5 mg plus metformin and saxagliptin 10 mg plus metformin compared to saxagliptin and metformin (51.5 and 50.5 vs 25.0 and 34.7%, respectively; P values not reported). Similar results were observed with HbA_{1c} <6.5% (P values not reported).
Jadzinsky et al.[75] (2009) Saxagliptin 5 mg QD plus metformin 500 to 2,000 mg daily vs saxagliptin 10 mg QD plus metformin	AC, DB, MC, RCT Type 2 diabetics 18 to 77 years of age, HbA_{1c} ≥8.0 to ≤12.0%, fasting C-peptide concentration ≥1 ng/mL, and BMI ≤40 kg/m^2	N=1,306 24 weeks	Primary: Change in baseline HbA_{1c} Secondary: Change in baseline FPG and PPG $AUC_{0\text{-}3hr}$, proportion of patients achieving an HbA_{1c} <7.0 and ≤6.5%, proportion of patients	Primary: Combination therapy significantly decreased HbA_{1c} compared to monotherapy with either saxagliptin or metformin (-2.5 and -2.5 vs -1.7 and -2.0%, respectively; P<0.0001 vs monotherapy for all). Secondary: Combination therapy significantly decreased FPG compared to monotherapy with either saxagliptin or metformin (P=0.0002 for saxagliptin 5 mg plus metformin vs saxagliptin and P<0.001 for saxagliptin 10 mg plus metformin vs saxagliptin and metformin). Similar results were observed for PPG $AUC_{0\text{-}3hr}$ (P<0.0001 for all vs monotherapy).

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500 to 2,000 mg daily vs saxagliptin 10 mg QD vs metformin 500 to 2,000 mg daily			requiring rescue for failing to achieve prespecified glycemic targets or discontinuing for lack of efficacy at 24 weeks	The proportion of patients achieving an HbA_{1c} <7.0% was significantly greater with combination therapy compared to monotherapy with either agent (60.3 and 59.7 vs 32.2 and 41.1%; P<0.0001 for all vs monotherapy). Similar results were observed for HbA_{1c} ≤6.5% (45.3 and 40.6 vs 20.3 and 29.0%; P<0.0001 for saxagliptin 5 mg plus metformin vs saxagliptin and metformin; P<0.0001 for saxagliptin 10 mg plus metformin vs saxagliptin, and P=0.0026 for saxagliptin 10 mg plus metformin vs metformin). At week 24, 7.5% of patients receiving saxagliptin 5 mg plus metformin and 21.2% of patients receiving saxagliptin 10 mg were discontinued or rescued for lack of glycemic control (P<0.0001). No significance was observed when saxagliptin 5 mg plus metformin was compared to metformin (P=0.2693). Similar results were observed with saxagliptin 10 mg plus metformin compared to either monotherapy (P<0.0001 vs saxagliptin 10 mg and P=0.0597 vs metformin).
Hollander et al.[76] (2009) Saxagliptin 2.5 mg and TZD (existing therapy) vs saxagliptin 5 mg and TZD (existing therapy) vs TZD (existing therapy) and placebo	DB, MC, RCT Type 2 diabetics 18 to 77 years of age with inadequate glycemic control (HbA_{1c} ≥7.0 to ≤10.5%) receiving stable doses of TZD (pioglitazone 30 or 45 mg/day or rosiglitazone 4 or 8 mg/day for ≥12 weeks), fasting C-peptide ≥0.3 nmol/L, and BMI ≤45 kg/m^2	N=565 24 weeks	Primary: Change in baseline HbA_{1c} Secondary: Change in baseline FPG and PPG $AUC_{0\text{-}3hr}$, proportion of patients achieving an HbA_{1c} <7.0%	Primary: Saxagliptin significantly decreased HbA_{1c} compared to placebo (saxagliptin 2.5 mg, -0.66%; treatment difference, -0.36%; P<0.0007 vs placebo and saxagliptin 5 mg, -0.94%; treatment difference, -0.63%; P<0.0001 vs placebo). Secondary: Saxagliptin significantly decreased FPG compared to placebo (saxagliptin 2.5 mg treatment difference, -0.8 mmol/L; P<0.0053 vs placebo and saxagliptin 5 mg treatment difference, -1.0 mmol/L; P=0.0005 vs placebo). A significantly greater proportion of patients receiving saxagliptin achieved an HbA_{1c} <7.0% compared to patients receiving placebo (42.2 [P=0.0010] and 41.8 [P=0.0013] vs 25.6%). Saxagliptin significantly decreased PPG $AUC_{0\text{-}3hr}$ compared to placebo (P<0.0001 for both). Similar results were observed with PPG $AUC_{0\text{-}2hr}$ (P<0.0001 for both).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Overall, saxagliptin was well tolerated. The proportion of patients experiencing any adverse effect was 68.0 vs 66.8%, with the highest frequency with saxagliptin 5 mg. The frequency of hypoglycemic events was similar between the two treatments (3.4 vs 3.8%). The most commonly reported adverse events were upper respiratory tract infection, peripheral edema, and headache.
Frederich et al.[77] (2010) Saxagliptin 2.5 to 10 mg QD vs glyburide, metformin, or placebo	SR Inadequately controlled type 2 diabetics	N=4,607 16 to 116 weeks	Primary: Composite of cardiovascular events, cardiovascular death, MI, and stroke Secondary: Not reported	Primary: There were 38 (1.1%) cardiovascular events with saxagliptin compared to 23 (1.8%) with the comparator drugs (RR, 0.59; 95% CI, 0.35 to 1.00). There were 23 (0.7%) cardiovascular deaths, MIs, and stroke events with saxagliptin compared to 18 (1.4%) with the comparator drugs (RR, 0.44; 95% CI, 0.24 to 0.82). There were seven (0.2%) cardiovascular deaths with saxagliptin compared to 10 (0.8%) with comparator drugs (RR, 0.24; 95% CI, 0.09 to 0.63). Secondary: Not reported
Scheen et al.[78] (2010) Saxagliptin 5 mg QD vs sitagliptin 100 mg QD Patients also received metformin.	AC, DB, MC, PG, RCT Type 2 diabetics ≥18 years of age, with uncontrolled HbA_{1c} (6.5 to 10.0%) despite monotherapy with a stable dose of metformin ≥1,500 mg for ≥8 weeks	N=801 18 weeks	Primary: Change in baseline HbA_{1c} Secondary: Proportion of patients achieving an HbA_{1c} ≤6.5%; proportion of patients with baseline HbA_{1c} ≥7.0% achieving an HbA_{1c} <7.0%; change in baseline FPG, insulin, C-peptide, proinsulin, and β cell function	Primary: Saxagliptin was non-inferior to sitagliptin (-0.52 vs -0.62%). The adjusted mean decrease in HbA_{1c} was 0.09% (95% CI, -0.01 to 0.20), with the upper limit for non-inferiority <0.3%. Secondary: A higher proportion of patients receiving sitagliptin achieved HbA_{1c} ≤6.5% compared to patients receiving saxagliptin (29.1 vs 26.3%; P value not reported). For patients with baseline HbA_{1c} ≥7.0%, a non-significantly higher proportion of patients receiving sitagliptin achieved an HbA_{1c} <7.0% compared to patients receiving saxagliptin (39.1 vs 33.0%; treatment difference, -6.1%; 95% CI, -13.8 to 1.6%). Sitagliptin significantly decreased FPG compared to saxagliptin (-16.2 vs -10.8 mg/dL; treatment difference, -5.42 mg/dL; 95% CI, 1.37 to 9.47). There were no apparent differences between the two treatments for the changes in fasting insulin, glucagon, proinsulin, or C-peptide. Similarly,

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				the small improvement in β cell function did not differ between the two treatments.
Göke et al.[79] (2010) Saxagliptin 5 mg/day vs glipizide 5 mg/day, titrated up to 20 mg/day	DB, NI, RCT Patients ≥18 years of age with type 2 diabetes with type 2 diabetes, HbA_{1c} >6.5 to 10.0%, and inadequate glycemic control on metformin alone	N=858 52 weeks	Primary: Change in baseline HbA_{1c} Secondary: Hypoglycemia, safety	Primary: The per protocol analysis demonstrated non-inferiority of saxagliptin vs glipizide; adulated mean changes from baseline HbA_{1c} were -0.74 vs -0.80%, respectively; the between-group difference was 0.06% (95% CI, -0.05 to 0.16). There was a significantly smaller risk in HbA_{1c} (%/week) from week 24 to 52 with saxagliptin vs glipizide (0.001 vs 0.004%; *P*=0.04) indicating a sustained glycemic effect beyond week 24. Secondary: Treatment with saxagliptin vs glipizide was associated with a significantly smaller proportion of patients with hypoglycemic events (3.0 vs 36.3%; *P*<0.0001) and a divergent impact on body weight (adjusted mean change from baseline, -1.1 vs 1.1 kg; *P*<0.0001). Excluding hypoglycemic events, the proportion of patients reporting adverse events was smaller with glipizide (60.0 vs 56.7%); however, treatment-related adverse events were less common with saxagliptin (9.8 vs 31.2%), attributable to the higher frequency of hypoglycemia with glipizide. Discontinuation rates resulting from adverse events were similar (approximately 4%).
Göke et al.[80] (2013) Saxagliptin 5 mg/day vs glipizide 5 to 20 mg/day	AC, DB, MC, RCT Adults with type 2 diabetes and inadequate glycemic control on metformin alone (HbA_{1c} > 6.5 to 10%)	N=858 52 week initial phase followed by 52 week extension phase	Primary: Non-inferiority in mean change from baseline HbA_{1c}, safety and tolerability Secondary: Not reported	Primary: Improvement in HbA_{1c} at week 104 was similar with saxagliptin + metformin and glipizide + metformin. At week 104, the adjusted mean ±SE change from baseline HbA_{1c} was -0.41±0.04% with saxagliptin + metformin and -0.35±0.04% with glipizide + metformin [a between-group difference of -0.05% (95% CI, -0.17 to 0.06%)]. Over the course of the 104-week study, 896 hypoglycemic events were reported in 165 patients (38.4%) in the glipizide + metformin group, and 24 hypoglycemic events were reported in 15 patients (3.5%) in the saxagliptin + metformin group (difference, -34.9%; 95% CI for difference, -39.8 to -30.0%). Most of these events occurred during the initial 52 weeks.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Both treatments as an add-on to metformin				Over the course of the study, mean body weight decreased in the saxagliptin + metformin group and increased in the glipizide + metformin group. Secondary: Not reported
Harashima et al.[81] (2012) Sitagliptin 100 mg QD All patients received existing sulfonylurea therapy.	PRO, SA Type 2 diabetics ≥20 years of age inadequately controlled on sulfonylureas, with or without metformin and/or α-glucosidase inhibitors, HbA_{1c} ≥6.9%, no improvement in HbA_{1c} ≥0.5% within 3 months, and a wish to diet and exercise to improve health	N=82 52 weeks	Primary: Change in baseline HbA_{1c} Secondary: Changes in BMI, BP, urinary albumin excretion, unresponsive rate, hypoglycemia	Primary: Change in HbA_{1c} was -0.80% (95% CI, -0.90 to -0.68; P<0.001). Secondary: Change in BMI, SBP, DBP, and urinary albumin excretion were -0.38 kg/m^2 (95% CI, -0.72 to -0.04; P<0.05), -6.7/-3.6 mm Hg (95% CI, -10.0 to -3.4/-4.8 to -2.4; P<0.001), and -43.2 mg/gCr (95% CI, -65.7 to -20.8; P<0.001), respectively. The unresponsive rate was 6.1%. Mild hypoglycemia was observed in three cases.
Brazg et al.[82] (2007) Sitagliptin 50 mg BID vs placebo	DB, PC, RCT, XO Type 2 diabetics 25 to 75 years of age with inadequate glycemic control receiving metformin monotherapy, and an HbA_{1c} of 6.5 to 9.6%	N=28 8 weeks	Primary: 24-hour weighted mean glucose Secondary: Change in FPG, mean daily glucose, fructosamine, and β cell function; safety	Primary: Sitagliptin (-32.8 mg/dL) significantly decreased 24-hour weighted mean glucose compared to placebo (P<0.05). Secondary: Despite a carryover effect from Period 1 to 2, the combined Period 1 and 2 results for glycemic measurements were significant with sitagliptin compared to placebo. The Period 1 results were also compared between the groups, in consideration of any carryover.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
All patients were receiving metformin ≥1,500 mg daily.				Following Period 1, there were significant decreases in FPG of -20.3 mg/dL, mean daily glucose of -28 mg/dL, and fructosamine of -33.7 mmol/L with sitagliptin compared to placebo (P<0.05). Sitagliptin significantly improved β cell function compared to placebo. There was no difference in weight gain, gastrointestinal adverse events, and hypoglycemia between the two treatments.
Charbonnel et al.[83] (2006) Sitagliptin 100 mg QD vs placebo All patients were receiving metformin ≥1,500 mg daily.	DB, MC, PC, PG, RCT Type 2 diabetics 18 to 78 years of age with inadequate glycemic control (HbA_{1c} ≥7.0 to ≤10.0%) on metformin monotherapy	N=701 24 weeks	Primary: Change in baseline HbA_{1c} Secondary: Change in baseline FPG, PPG, insulin, C-peptide concentrations, β cell function, and lipid profile; safety	Primary: Sitagliptin significantly decreased HbA_{1c} compared to placebo (treatment difference, -0.65%; P<0.001). A significantly greater proportion of patients receiving sitagliptin achieved an HbA_{1c} <7.0% (47.0 vs 18.3%; P<0.001) and <6.5% (17.2 vs 4.9%; P<0.001) compared to patients receiving placebo. Secondary: Sitagliptin significantly decreased FPG compared to placebo (treatment difference, -25.4 mg/dL; P<0.001). Similar results were observed with PPG (treatment difference, -50.6 mg/dL; P≤0.001). Sitagliptin significantly increased fasting insulin (P<0.050) and fasting C-peptide (P<0.010) compared to placebo. There was observed improvement in fasting proinsulin:insulin ratio (P<0.010) and HOMA-B (P<0.001) consistent with improved β cell function with sitagliptin. There were differences between the two treatments in changes in LDL-C. There were no differences between two treatments in the incidences of overall or serious adverse reactions, rates of hypoglycemia, or gastrointestinal adverse events. A reduction in weight of 0.6 to 0.7 kg was observed with both treatment groups (P<0.050), but there was no difference between the two treatments (P=0.835).
Derosa et al.[84] (2014) Sitagliptin 100 mg/day	DB, MC, RCT Caucasian patients with type 2 diabetes	N=205 2 years	Primary: Body weight, BMI, HbA_{1c}, FPG, PPG, lipids	Primary: In the sitagliptin group, there was a significant decrease in body weight and BMI compared with baseline and with placebo (P<0.05, for both). HbA_{1c} significantly decreased after 24 months compared with baseline

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vs placebo	aged >18 with uncontrolled type 2 diabetes mellitus (HbA_{1c} >7.0%) in therapy with different antidiabetic drugs for at least 6 months		Secondary: Not reported	(P<0.01), while HbA_{1c} increased in the placebo group (P<0.05). These results were mirrored in the FPG and PPG parameters. Total cholesterol (TC) and LDL-C significantly decreased after 18 (P<0.05) and 24 months (P<0.02) after the addition of sitagliptin, while no variations were registered with placebo. Moreover, TC and LDL-C observed with sitagliptin were significantly lower than the ones recorded with placebo after 24 months. Secondary: Not reported
Green et al.[85] (2015) TECOS Sitagliptin 100 mg/day vs placebo Open-label use of antihyperglycemic therapy was encouraged as required	DB, MC, RCT Patients with type 2 diabetes and established cardiovascular disease who were at least 50 years of age, with a HbA_{1c} of 6.5 to 8.0% when treated with stable doses of one or two oral antihyperglycemic agents (metformin, pioglitazone, or sulfonylurea) or insulin (with or without metformin)	N=14,671 Median of 3.0 years	Primary: Composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina Secondary: Composite of the first confirmed event of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke	Primary: Overall in the intention-to-treat population, the primary composite cardiovascular outcome occurred in 839 patients in the sitagliptin group (11.4%, 4.06 per 100 person-years) and 851 in the placebo group (11.6%, 4.17 per 100 person-years). There was no significant between-group difference in the primary composite cardiovascular outcome (HR in the per-protocol analysis, 0.98; 95% CI, 0.88 to 1.09; P<0.001 for noninferiority; HR in the intention-to-treat analysis, 0.98; 95% CI, 0.89 to 1.08; P=0.65 for superiority). Secondary: There was no significant between-group difference in the secondary composite cardiovascular outcome (HR in the per-protocol analysis, 0.99; 95% CI, 0.89 to 1.11; P<0.001 for noninferiority; HR in the intention-to-treat analysis, 0.99; 95% CI, 0.89 to 1.10; P=0.84 for superiority).
Raz et al.[86] (2008) Sitagliptin 100 mg daily plus metformin 1,500 to 2,550 mg	DB, MC, PC, PG, RCT Type 2 diabetics 18 to 78 years of age, HbA_{1c} 7.0 to 10.0% receiving metformin	N=190 30 weeks	Primary: Change in baseline HbA_{1c} at 18 weeks Secondary: Change in baseline FPG at 18 weeks,	Primary: Sitagliptin significantly decreased HbA_{1c} compared to placebo (treatment difference, -1.0%; 95% CI, -1.4 to -0.7; P<0.001). Numerically greater decreases in HbA_{1c} were observed in patients with a higher baseline HbA_{1c}. A greater proportion of patients receiving sitagliptin achieved an HbA_{1c} <7.0% at weeks 18 and 30 compared to patients receiving placebo (13.7 and 22.1 vs 3.3 and 3.3%; P values not reported).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
daily (existing therapy) vs metformin 1,500 to 2,550 mg daily (existing therapy) plus placebo	or other oral antihyperglycemic agents as monotherapy or being treated with metformin in combination with other oral antihyperglycemic agents		two-hour PPG at 18 weeks, and HbA_{1c} at 30 weeks; safety and tolerability	Secondary: Sitagliptin significantly decreased FPG compared to placebo (treatment difference, -1.4 mmol/L; 95% CI, -2.1 to -0.7; P<0.001). Sitagliptin significantly decreased two-hour PPG compared to placebo (treatment difference, -3.0 mmol/L; 95% CI, -4.2 to -1.9; P<0.001). Sitagliptin significantly decreased HbA_{1c} compared to placebo at week 30 (treatment difference, -1.0%; 95% CI, -1.4 to -0.6; P<0.001). The incidence of adverse events was similar with both treatments. No serious adverse events or discontinuations due to clinical adverse events were reported with sitagliptin. With placebo, there were six serious clinical adverse events that resulted in one death and two discontinuations. None of the adverse events were deemed to be drug-related. There were no differences between the two treatments in the incidences of hypoglycemia or gastrointestinal adverse events (abdominal pain, nausea, vomiting, and diarrhea). Over the 30 week period a small decrease in weight of 0.5 kg was observed with both treatments.
Derosa et al.[87] (2012) metformin + placebo vs metformin + sitagliptin All patients underwent a run-in period of 8±2 months of metformin monotherapy	DB, MC, PC, RCT Type 2 diabetic patients aged >18, drug-naïve, with poor glycemic control (HbA_{1c} level >8.0%), and overweight (body mass index [BMI] ≥25 and <30 kg/m2)	N=178 12 months	Primary: BMI, glycemic control, fasting plasma insulin (FPI), homeostasis model assessment insulin resistance index (HOMA-IR), homeostasis model assessment β-cell function index (HOMA-β), fasting plasma proinsulin (FPPr), proinsulin/fasting plasma insulin ratio (Pr/FPI	Primary: A similar decrease of body weight and BMI was observed with both treatments at 12 months (P<0.05 for both), without any difference between the two groups. HbA_{1c} and PPG improved in both groups at six (P<0.05), nine (P< 0.01), and 12 months (P<0.001) with sitagliptin + metformin, and at nine (P<0.05) and 12 months (P<0.01) with placebo + metformin, even though sitagliptin + metformin were more effective than placebo + metformin in reducing HbA_{1c}, and PPG at 12 months (P<0.05). FPG obtained with sitagliptin + metformin was significantly lower compared to the value reached with placebo + metformin at 12 months (P<0.05). Most other parameters achieved favorable change from baseline but no significant difference between treatment groups. Sitagliptin + metformin resulted better than placebo + metformin in reducing HOMA-IR and glucagon at 12 months (P<0.05).

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			ratio), C-peptide, glucagon, adiponectin (ADN), and high sensitivity-C reactive protein (Hs-CRP). Secondary: Not reported	Secondary: Not reported
Goldstein et al.[88] (2007) Sitagliptin 50 mg BID plus metformin 500 mg BID vs sitagliptin 50 mg BID plus metformin 1,000 mg BID vs sitagliptin 100 mg QD vs metformin 500 mg BID vs metformin 1,000 mg BID	DB, MC, PC, PG, RCT Type 2 diabetics 18 to 78 years of age and an HbA_{1c} of 7.5 to 11.0%	N=1,091 24 weeks	Primary: Change in baseline HbA_{1c} Secondary: Change in baseline FPG, fasting serum insulin, fasting serum proinsulin, lipid profiles, β cell function, insulin resistance; adverse events	Primary: Decreases in HbA_{1c} were significant with all active treatments as compared to placebo and for combination therapy compared to monotherapy ($P<0.001$). There was an additive effect seen in the combination treatment groups. The proportion of patients achieving an HbA_{1c} <7.0% was significantly greater with all active treatments compared to placebo ($P<0.001$). Secondary: Significant decreases in FPG were achieved between combination therapy and monotherapy, and between all active treatments compared to placebo ($P<0.001$). Data on fasting serum insulin and lipid profiles were not reported. Combination therapy demonstrated an additive effect, as compared to monotherapy, with regards to improvements in β cell function. HOMA-B increased with all active treatments compared to placebo ($P<0.001$). The combination therapy significantly increased HOMA-B compared to monotherapy (sitagliptin and low-dose metformin; $P\leq0.001$). Significant improvements in the proinsulin:insulin ratio observed with all active treatments compared to placebo ($P<0.05$). Differences between combination therapy and monotherapy were also significant ($P<0.05$).

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vs placebo				The incidence of adverse events was similar between combination therapy and metformin. Gastrointestinal adverse events including diarrhea, nausea, abdominal pain, and vomiting were most frequently observed with metformin high-dose both as monotherapy and combination therapy. A low frequency of hypoglycemia was similar among all treatments (0.6 to 2.2%). No change in weight was observed with sitagliptin compared to all other active treatments, where there was a significant decrease in body weight (-0.6 to -1.3 kg; P<0.05) and placebo (-0.9 kg; P<0.01).
Reasner et al.[89] (2011) Sitagliptin/ metformin 50/500 to 1,00 mg BID vs metformin 500 to 1,000 mg BID	DB, MC, PG, RCT Treatment-naïve type 2 diabetics 18 to 78 years of age, and an HbA_{1c} ≥7.5%	N=1,250 18 weeks	Primary: Change in baseline HbA_{1c} Secondary: Proportion of patients achieving an HbA_{1c} <7.0 and <6.5%, change in baseline FPG, proinsulin:insulin ratio, and β cell function	Primary: Combination therapy significantly decreased HbA_{1c} compared to metformin (-2.4 vs -1.8%; P<0.001). Secondary: A significantly greater proportion of patients receiving combination therapy achieved an HbA_{1c} <7.0% (49.2 vs 34.2%, respectively; P<0.001) and <6.5% (31.8 vs 16.0%, respectively; P<0.001) compared to patients receiving metformin. Combination therapy significantly decreased FPG compared to metformin (-3.8 vs -3.0 mg/dL; P<0.001). Combination therapy significantly decreased proinsulin:insulin ratio compared to metformin (-0.238 vs -0.186; P<0.05). Combination therapy significantly improved β cell function compared to metformin (P<0.05).
Rosenstock et al.[90] (2006) Sitagliptin 100 mg QD vs placebo	DB, MC, PC, PG, RCT Type 2 diabetics ≥18 years of age with inadequate glycemic control (HbA_{1c} ≥7.0 to ≤10.0%) on pioglitazone monotherapy	N=353 24 weeks	Primary: Change in baseline HbA_{1c} Secondary: Change in baseline FPG, fasting insulin, proinsulin, and lipid profiles; safety and tolerability	Primary: Combination therapy (-0.70%; 95% CI, -0.85 to -0.54) significantly decreased HbA_{1c} compared to placebo (P<0.001). A significantly greater proportion of patients receiving combination therapy achieved HbA_{1c} <7.0% compared to patients receiving placebo (45 vs 23%; P<0.001). Secondary: Combination therapy significantly decreased FPG compared to placebo (treatment difference, -17.7 mg/dL; 95% CI, -24.3 to -11.0; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
All patients were receiving pioglitazone 30 or 45 mg QD.				Combination therapy significantly decreased fasting serum proinsulin (P=0.009) and proinsulin:insulin ratio (P<0.001) compared to placebo. Combination therapy significantly decreased TG compared to placebo (treatment difference, -11.2%; 95% CI, -22.0 to -0.4; P<0.041). There were no significant changes in other lipid parameters. Combination therapy was well tolerated, with no increased risk of hypoglycemia compared to placebo. There was a significant increase in the incidence of abdominal pain with combination therapy compared to placebo. There was no difference in the change of body weight between the two treatments.
Lavalle-González et al.[91] (2013) canagliflozin 100 mg vs canagliflozin 300 mg vs sitagliptin 100 mg vs placebo	DB, PG, RCT Patients with type 2 diabetes aged ≥18 and ≤80 years who had inadequate glycemic control (HbA_{1c} ≥7.0% and ≤10.5%) on metformin therapy	N=1,284 2 week placebo run-in, 26 week placebo- and active-control treatment period (period I), followed by a 26 week active-control treatment period (period II), and a 4 week follow-up period	Primary: Change from baseline in HbA_{1c} at week 26 Secondary: Changes in HbA_{1c} (week 52) and FPG, body weight, and systolic blood pressure (BP; weeks 26 and 52), adverse events	Primary: At week 26, canagliflozin 100 mg and 300 mg significantly reduced HbA_{1c} from baseline compared with placebo (P<0.001 for both). Secondary: At week 26, a greater proportion of participants treated with canagliflozin 100 mg and 300 mg achieved HbA_{1c} <7.0% than with placebo (45.5, 57.8, and 29.8%, respectively; P=0.000 for both); 54.5% of sitagliptin-treated participants achieved HbA_{1c} <7.0%. Both canagliflozin doses significantly reduced FPG and 2-hour PPG at week 26 vs placebo (P<0.001 for all); FPG and 2-hour PPG were also reduced from baseline with sitagliptin. At 52 weeks, canagliflozin 100 mg and 300 mg demonstrated non-inferiority to sitagliptin 100 mg in HbA_{1c}-lowering effect. Canagliflozin 300 mg demonstrated statistical superiority to sitagliptin in HbA_{1c}-lowering effect. Canagliflozin 100 mg and 300 mg significantly reduced body weight compared with sitagliptin. Canagliflozin 100 mg and 300 mg significantly decreased systolic BP relative to sitagliptin at 52 weeks. The change in diastolic BP from baseline was −1.8 mmHg with both canagliflozin doses and −0.3 mmHg with sitagliptin. Overall incidences of adverse events and adverse event-related discontinuations were generally comparable across groups over 52 weeks. Canagliflozin was associated with a higher incidence of genital mycotic

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				infections in men and women. These were generally mild or moderate in intensity and led to few discontinuations.
Weinstock et al.[92] (2015) AWARD-5 Sitagliptin 100 mg vs dulaglutide (1.5 or 0.75 mg)	DB, MC, RCT Patients 18 to 75 years of age with type 2 diabetes (≥6 months' duration) and an HbA_{1c} value of >8.0% and ≤9.5% on diet and exercise alone, or ≥7.0% and ≤9.5% on monotherapy or combination therapy (metformin plus another oral antihyperglycemic medication), and a BMI of 25 to 40 kg/m^2	N=1,098 104 weeks	Primary: HbA_{1c} Secondary: Percentage of participants achieving an HbA_{1c} target of <7.0% and ≤6.5%; body weight; FPG and fasting insulin; β-cell function; lipids; safety	Primary: Changes in HbA_{1c} at 104 weeks were (least squares mean ± standard error) −0.99 ± 0.06%, −0.71 ± 0.07% and −0.32 ± 0.06% for dulaglutide 1.5 mg, dulaglutide 0.75 mg and sitagliptin, respectively (P<0.001, both dulaglutide doses vs sitagliptin). Secondary: At 104 weeks, the percentage of participants attaining the HbA_{1c} target goal of <7.0% was significantly higher in the dulaglutide 1.5 mg and dulaglutide 0.75 mg arms (54 and 45%, respectively) compared with sitagliptin (31%; P<0.001, both comparisons). Additionally, 39 and 24% of participants in the dulaglutide 1.5 mg and dulaglutide 0.75 mg arms, respectively, achieved HbA_{1c} targets of ≤6.5%, compared with 14% in the sitagliptin arm (P<0.001, both comparisons). The measurement of insulin sensitivity (HOMA2-%S) was not different between treatment groups, while β-cell function, as assessed by HOMA2-%β, increased significantly more with dulaglutide 1.5 mg and dulaglutide 0.75 mg than with sitagliptin. Weight loss was greater with dulaglutide 1.5 mg (P<0.001) and similar with 0.75 mg versus sitagliptin (2.88 ± 0.25, 2.39 ± 0.26 and 1.75 ± 0.25 kg, respectively). Gastrointestinal adverse events were more common with dulaglutide 1.5 and 0.75 mg versus sitagliptin (nausea 17 and 15% vs 7%, diarrhea 16 and 12% vs 6%, vomiting 14 and 8% vs 4% respectively). Pancreatic, thyroid, cardiovascular and hypersensitivity safety were similar across groups.
Gadde et al.[93] (2017) DURATION-NEO-2 Sitagliptin 100 mg QD vs	MC, OL, RCT Type 2 diabetics ≥18 years of age, receiving a stable metformin therapy for ≥2 months, HbA_{1c} 7.1 to 11.0%	N=365 28 weeks	Primary: Change in baseline HbA_{1c} Secondary: Proportion of patients achieving HbA_{1c} <7.0% and change in FPG and	Primary: Exenatide led to greater HbA_{1c} reduction from baseline to week 28 vs sitagliptin (least-squares mean difference, −0.38%; 95% CI, −0.70 to −0.06%; P=0.021) or placebo (−0.72%; 95% CI, −1.15 to −0.30%; P=0.001). Secondary: At week 28, a higher proportion of exenatide-treated patients (43.1%) achieved HbA_{1c} < 7.0% than did sitagliptin- (32.0%) or placebo-treated patients (24.6%).

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exenatide 2 mg once-weekly suspension for autoinjection vs placebo			body weight from baseline	Exenatide resulted in numerically greater FPG reductions than sitagliptin and greater FPG reductions than placebo (P<0.001). The difference in FPG reduction for exenatide vs sitagliptin was not statistically significant. Body weight decreased over the 28-week treatment period with exenatide QWS-AI and sitagliptin, with no difference observed between groups (nominal P=0.8625).
Bergenstal et al.[94] (2010) DURATION-2 Exenatide ER 2 mg SC once weekly vs sitagliptin 100 mg QD vs pioglitazone 45 mg QD All patients received existing metformin therapy.	DB, DD, MC, PG, RCT Type 2 diabetics ≥18 years of age, receiving a stable metformin therapy for ≥2 months, HbA_{1c} 7.1 to 11.0%, and BMI 25 to 45 kg/m^2	N=514 26 weeks	Primary: Change in baseline HbA_{1c} Secondary: Proportion of patients achieving an HbA_{1c} ≤6.5 or ≤7.0%, FPG, six-point self-monitored glucose concentrations, body weight, fasting lipid profile, fasting insulin profile, BP, cardiovascular risk markers, patient-reported quality of life, safety	Primary: Exenatide ER (-1.5%; 95% CI, -1.7 to -1.4) significantly decreased HbA_{1c} compared to sitagliptin (-0.9% [95% CI, -1.1 to -0.7]; treatment difference, -0.6% [95% CI, -0.9 to -0.4]; P<0.0001) and pioglitazone (-1.2% [95% CI, -1.4 to -1.0]; treatment difference, -0.3% [95% CI, -0.6 to -0.1]; P=0.0165). Secondary: A significantly greater proportion of patients receiving exenatide achieved HbA_{1c} targets of ≤6.5 (P<0.0001 and P=0.0120) or ≤7.0% (P<0.0001 and P=0.0015) compared to patients receiving sitagliptin or pioglitazone. Exenatide ER (-1.8 mmol/L; 95% CI, -2.2 to -1.3) achieved significantly greater decreases in FPG compared to sitagliptin (-0.9 mmol/L [95% CI, -1.3 to -0.5]; treatment difference, -0.9 mmol/L [95% CI, -0.3 to -1.4]; P=0.0038), but not pioglitazone (-1.5 mmol/L [95% CI, -1.9 to -1.1]; treatment difference, -0.2 mmol/L [95% CI, -0.8 to 0.3]; P=0.3729). A significantly greater proportion of patients receiving exenatide ER (60%) achieved the FPG goal of ≤7 mmol/L compared to patients receiving sitagliptin (35%; P<0.0001), but no difference was observed between patients receiving pioglitazone (52%; P=0.1024). In all measurements of the six-point self-monitored glucose concentrations profile, decreases at week 26 were significantly greater with exenatide ER compared to sitagliptin, but not pioglitazone (P values not reported). Weight loss with exenatide ER (-2.3 kg; 95% CI, -2.9 to -1.7) was significantly greater compared to sitagliptin (difference, -1.5 kg; 95% CI, -

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				2.4 to -0.7; P=0.0002) and pioglitazone (difference, -5.1 kg; 95% CI, -5.9 to -4.3; P<0.0001). Pioglitazone was the only treatment to achieve significant decreases in TG (-16%; 95% CI, -21 to -11) and increases in TC (0.16 mmol/L; 95% CI, 0.04 to 0.28), the former of which was significantly different compared to exenatide ER (-5%; 95% CI, -11 to 0). Fasting insulin was significantly increased after 26 weeks with exenatide ER (3.6 µIU/mL; 95% CI, 1.6 to 5.6) compared to sitagliptin (0.4 µIU/mL [95% CI, -1.6 to 2.3]; treatment difference, 3.2 µIU/mL [95% CI, 0.6 to 5.8]; P=0.0161) and pioglitazone (-3.9 µIU/mL [95% CI, -5.9 to -2.0]; treatment difference, 7.5 µIU/mL [95% CI, 4.9 to 10.1]; P<0.0001). Decreases in SBP with exenatide ER were significantly greater compared to sitagliptin (treatment difference, -4 mm Hg; 95% CI, -6 to -1), but not pioglitazone (data reported in graphical form only). All treatments achieved significant improvements in high-sensitivity CRP and adiponectin. Exenatide ER was the only treatment to achieve a significant improvement in BNP and albumin:creatinine ratio, with the changes in BNP being significantly greater compared to sitagliptin and pioglitazone (P values not reported). All five domains of weight-related quality of life and IWQOL total score were significantly improved with exenatide ER (IWQOL total score, 5.15; 95% CI, 3.11 to 7.19) and sitagliptin (4.56; 95% CI, 2.56 to 6.57), but not pioglitazone (1.20; 95% CI, -0.87 to 3.28), which improved only on self-esteem. Improvements in IWQOL with exenatide ER were significantly greater compared to sitagliptin (treatment difference, 3.94; 95% CI, 1.28 to 6.61; P=0.0038). All treatments achieved improvements in all domains of the PGWB and DTSQ total score, with greater improvement in overall satisfaction recorded with exenatide ER (3.96; 95% CI, 2.78 to 5.15) compared to sitagliptin (2.35 [95% CI, 1.19 to 3.51]; treatment difference, 1.61 [95% CI, 0.07 to 3.16]; P=0.0406).

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				The most commonly reported adverse events with exenatide ER and sitagliptin were nausea (24 vs 10%, respectively) and diarrhea (18 vs 10%, respectively). Upper respiratory tract infection (10%) and peripheral edema (8%) were the most commonly reported adverse events with pioglitazone. No episodes of major hypoglycemia were reported.
Pratley et al.[95] VERTIS FACTORIAL Ertugliflozin 15 mg QD vs ertugliflozin 5 mg QD vs sitagliptin 100 mg QD vs ertugliflozin 15 mg/sitagliptin 100 mg QD vs ertugliflozin 5 mg/sitagliptin 100 mg QD Subjects received glycemic rescue therapy with open-	DB, MC, RCT Patients ≥18 years of age with type 2 DM and HbA_{1c} ≥7.5% to ≤11.0% on ≥1,500 mg/day of metformin monotherapy for at least eight weeks	N=1,233 52 weeks (two 26 phases)	Primary: Change from baseline at week 26 in HbA_{1c} Secondary: Change from baseline in FPG, body weight and SBP at week 26	Primary: The least-squares mean HbA_{1c} reductions from baseline at week 26 were greater with ertugliflozin 5 mg/sitagliptin 100 mg (-1.5%) and ertugliflozin 15 mg/sitagliptin 100 mg (-1.5%) than with individual agents (-1.0%, -1.1% and -1.1% for ertugliflozin 5 mg, ertugliflozin 15 mg and sitagliptin 100 mg, respectively; P<0.001 for all comparisons). Secondary: FPG reductions were significantly greater with ertugliflozin 5 mg/sitagliptin 100 mg and ertugliflozin 15 mg/sitagliptin 100 mg compared with individual agents. Body weight and SBP significantly decreased with ertugliflozin 5 mg/sitagliptin 100 mg and ertugliflozin 15 mg/sitagliptin 100 mg compared to sitagliptin 100 mg alone. Glycemic control, body weight and SBP effects of ertugliflozin were maintained to week 52.

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label glimepiride (or insulin glargine) if they met certain rescue criteria				
Nauck et al.[96] (2007) Sitagliptin 100 mg QD vs glipizide 5 to 20 mg QD All patients received metformin ≥1,500 mg daily.	AC, DB, MC, NI, PG, RCT Patients 18 to 78 years of age with type 2 diabetes who were inadequately controlled (HbA_{1c} ≥6.5 and ≤10%) on metformin monotherapy	N=1,172 52 weeks	Primary: Change in baseline HbA_{1c} Secondary: FPG, fasting insulin, proinsulin, and lipid parameters, β-cell function, insulin resistance and sensitivity, safety and tolerability, change in body weight	Primary: In both treatments, the least squares mean HbA_{1c} change from baseline was -0.67% (95% CI, -0.75 to -0.59). A similar proportion of patients reached an HbA_{1c} <7.0% in each group (63 vs 59%; difference of 3.9%; 95% CI, -2.8 to 10.7). Secondary: The change in FPG was not significantly different between the two treatments. The least squares change from baseline for sitagliptin was -0.56 mmol/L (95% CI, -0.81 to -0.30) and -0.42 mmol/L for glipizide (95% CI, -0.67 to -0.17). Sitagliptin led to a decrease in fasting proinsulin compared with an increase with glipizide. Patients receiving glipizide demonstrated a higher rate of hypoglycemia as compared to patients receiving sitagliptin (32 vs 5%; P<0.001). No meaningful differences in overall serious clinical adverse events were observed between the two treatments. Body weight significantly decreased with sitagliptin; the least squares mean change from baseline was -1.5 kg (95% CI, -2 to -0.9). Body weight significantly increased with glipizide with a least squares mean change from baseline of 1.1 kg (95% CI, 0.5 to 1.6). The between-treatment difference was -2.5 kg (95% CI, -3.1 to -2.0; P<0.001).
Hermansen et al.[97] (2007) Sitagliptin 100 mg QD, glimepiride 4 to 8 mg daily, and metformin 1,500 to 3,000 mg daily	DB, DD, MC, PC, PG, RCT Type 2 diabetics 18 to 75 years of age, HbA_{1c} 6.7 to 10.6%, and inadequately controlled on	N=441 24 weeks	Primary: Change in baseline HbA_{1c} Secondary: Change in baseline FPG, plasma lipids, β cell function, and	Primary: Sitagliptin significantly decreased HbA_{1c} (P<0.001) compared to placebo (treatment difference, -0.74%; 95% CI, -0.90 to -0.57). Patients who were receiving triple therapy (-0.89%; 95% CI, -1.10 to -0.68) had a significantly greater decrease in HbA_{1c} compared to patients receiving combination therapy (-0.57%; 95% CI, -0.82 to -0.32). A significantly greater proportion of patients receiving sitagliptin achieved an HbA_{1c} <7.0% compared to patients receiving placebo (17.1 vs 4.8%;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs sitagliptin 100 mg QD plus glimepiride 4 to 8 mg daily vs glimepiride 4 to 8 mg daily, metformin 1,500 to 3,000 mg daily, and placebo vs glimepiride 4 to 8 mg daily plus placebo	glimepiride with or without metformin		insulin resistance; safety and tolerability	P<0.001). A significantly greater proportion of patients receiving triple therapy achieved an HbA_{1c} <7.0% compared to patients receiving combination therapy with glimepiride plus metformin (22.6 vs 1.0%; P<0.001). No difference was observed between combination therapy with glimepiride plus sitagliptin compared to glimepiride (10.8 vs 8.7%; P<0.638). Secondary: Sitagliptin significantly decreased FPG compared to placebo (treatment difference, -20.1 mg/dL; 95% CI, -28.4 to -11.8; P<0.001). Sitagliptin demonstrated neutral effects on plasma lipids compared to placebo (specific figures not reported). A significant increase in HOMA-B was achieved with sitagliptin compared to placebo (11.3 [95% CI, 4.4 to 18.1] vs -0.7% [95% CI, -8.2 to 6.8]; P<0.001). There were no differences in fasting proinsulin, proinsulin:insulin ratio, HOMA-IR, and QUICKI between the treatments. Sitagliptin significantly increased fasting insulin compared to placebo (1.8 vs 0.1 μIU/mL; P<0.001). Sitagliptin was well tolerated, both in combination with glimepiride and in triple therapy. There was a higher incidence of overall adverse events (difference of 8.0%; 95% CI, 2.2 to 13.9) observed with sitagliptin compared to placebo, with the majority of that difference due to rates of minor to moderate hypoglycemia. A significant increase in body weight of 0.8 kg (95% CI, 0.4 to 1.2) was noted with sitagliptin compared to a slight decrease in weight with placebo (-0.4 kg; 95% CI, -0.8 to 0.1).
Arechavaleta et al.[98] (2011) Sitagliptin 100 mg/day	DB, NI, RCT Patients with type 2 diabetes, HbA_{1c} 6.5 to 9.0%, and on a stable dose of	N=1,035 30 weeks	Primary: Change in baseline HbA_{1c} Secondary	Primary: After 30 weeks, the least squares mean change in HbA_{1c} from baseline was -0.47% with sitagliptin compared to -0.54% with glimepiride, with a between-group difference of 0.07% (95% CI, -0.03 to 0.16). This result met the prespecified criterion for declaring non-inferiority.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs glimepiride 1 mg/day, titrated up to 6 mg/day	metformin (≥1,500 mg/day) combined with diet and exercise for ≥12 weeks		Proportions of patients achieving HbA_{1c} <7.0%, change in baseline FPG, hypoglycemia, body weight	Secondary: The proportions of patients with HbA_{1c} <7.0% at week 30 were 52 and 60% with sitagliptin and glimepiride, respectively. The least squares mean change in FPG from baseline was -0.8 mmol/L (95% CI, -1.0 to -0.6) with sitagliptin compared to -1.0 mmol/L (95% CI, -1.2 to -0.8) with glimepiride, for a between-group difference of 0.2 mmol/L (95% CI, -0.1 to 0.4). The proportions of patients who reported hypoglycemia were 7 and 22% with sitagliptin and glimepiride (percentage-point difference, -15; P<0.001). Relative to baseline, sitagliptin was associated with a mean weight loss compared to a mean weight gain with glimepiride (-0.8 vs 1.2 kg), yielding a between-group difference of -2.0 kg (P<0.001).
Srivastava et al.[99] (2012) Sitagliptin 50 mg/day, titrated up to 100 mg/day vs glimepiride 1 mg/day, titrated up to 2 mg/day	PG, RCT Patients with type 2 diabetes inadequately controlled with metformin alone	N=50 18 weeks	Primary: Change in baseline HbA_{1c} Secondary: Change in baseline FPG and two-hour PPG, body weight, hypoglycemia	Primary: At 18 weeks, both treatments significantly (*P*<0.001) reduced baseline HbA_{1c} (-0.636 vs -1.172%), with 12% of patients receiving sitagliptin and 36% of patients receiving glimepiride achieving target HbA_{1c}. Secondary: Reductions were significant (*P*<0.001) for both treatments in FPG (-15.49 vs -26.84 mg, respectively) and two-hour PPG (-34.28 vs -44.83 mg, respectively). Sitagliptin showed a net decrease in body weight by 0.102 kg, whereas glimepiride showed net increase in body weight by 0.493 kg. Incidence of hypoglycemia was 4 and 8% with sitagliptin and glimepiride.
Seck et al.[100] (2011) Sitagliptin vs	DB, RCT Patients with type 2 diabetes receiving metformin	N=803 1 year	Primary: Composite endpoint of HbA_{1c} reduction, lack of hypoglycemia, and no body weight	Primary: Both treatments provided similar degrees of glycemic efficacy (least squares mean difference, -0.67%; between-group difference, -0.01; 95% CI, -0.09 to 0.08); however, significantly more patients receiving sitagliptin achieved an HbA_{1c} reduction >0.5% without hypoglycemia and without an increase in body weight (least squares mean difference, -1.5 vs 1.1 kg; P<0.001; between-group difference, -2.5 kg; 95% CI, -3.1 to -2.0).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
glimepiride			Secondary: Not reported	Patients receiving glipizide reported more than 10 times as many events of hypoglycemia compared to patients receiving sitagliptin. Secondary: Not reported
Charbonnel et al.[101] (2013) Sitagliptin starting at 100 mg/day, with glimepiride added if further glucose control needed (oral) vs liraglutide starting at 0.6 mg/day, up-titrated to 1.2 mg/day after 1 week (injectable)	AC, OL, RCT Patients with type 2 diabetes mellitus aged 18 to 79 years, on a stable dose of metformin monotherapy ≥1,500 mg/day for ≥12 weeks, with an HbA_{1c} ≥7.0% and ≤11.0% and a fasting fingerstick glucose <15 mmol/L at the randomization visit, deemed capable by the investigator of using a Victoza pen injection device	N=653 (per protocol patients were analyzed, N=522) 26 weeks	Primary: Change in HbA_{1c} (non-inferiority) Secondary: FPG, plasma lipids, safety	Primary: HbA_{1c} decreased over 26 weeks in both treatment strategy groups, with a larger initial reduction at week 12 in the injectable group. The mean change in HbA_{1c} at week 26 was -1.3% in the oral group and -1.4% in the injectable group. The primary hypothesis was met to declare that the oral treatment was non-inferior to the injectable in lowering HbA_{1c}. Secondary: Significant reductions in FPG at week 26 were observed in both groups, with a greater reduction observed in the injectable group. No meaningful between-group differences were found in any lipid variable or in the incidence of clinical adverse effects overall. The incidence of drug-related adverse events or adverse events leading to discontinuation was greater in the injectable group than in the oral group. These differences were mainly related to the significantly higher incidence of gastrointestinal adverse events, such as abdominal pain, diarrhea, nausea, and vomiting, in the injectable group.
Takihata et al.[102] (2013) Sitagliptin 50 mg/day vs pioglitazone 15 mg/day	MC, OL, RCT Japanese type 2 diabetic men and women between the ages of 20 and 75 years whose diabetes had been inadequately controlled (HbA_{1c}, 6.9 to 9.5%) with	N=130 Up to 24 weeks	Primary: Difference in the mean changes in the HbA_{1c} level from baseline at 24 weeks Secondary: Levels of FPG, fasting insulin, inflammation	Primary: Difference in HbA_{1c} in the sitagliptin group was -0.86 and in the pioglitazone group was -0.58 (P=0.024). Secondary: Difference in FPG and fasting insulin did not differ significantly between groups. Body weight decreased by 0.29 kg in the sitagliptin group and increased by 1.70 kg in the pioglitazone group (P<0.001). The levels of LDL-C and HDL-C were significantly decreased in the sitagliptin group. The triglyceride level was not altered. The Estimated glomerular filtration

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(both groups could have doses titrated up at 16 weeks if HbA_{1c} ≥6.5%)	metformin and/or sulfonylurea.		mediators, N-terminal pro-B-type natriuretic peptide, and markers of lipids, uric acid, liver function, and renal function	rate and creatinine level were significantly exacerbated in both groups, and the uric acid level was also exacerbated in the sitagliptin group. Hypoglycemia (3.4 vs 3.5%), gastrointestinal symptoms (5.2 vs 1.8%) and pedal edema (0 vs 68.4%, P<0.001) were observed for 24 weeks in the sitagliptin and pioglitazone groups, respectively. No severe cases of hypoglycemia, rash, or bone fracture were observed in either group during the trial.
Perez-Monteverde et al.[103] (2011) Sitagliptin 100 mg QD vs sitagliptin/ metformin vs pioglitazone 30 to 45 mg QD In Phase 1, patients were randomized to either sitagliptin 100 mg QD or pioglitazone 30 mg QD. In Phase 2, patients randomized to sitagliptin in Phase 1 were switched to sitagliptin/	DB, RCT Patients with type 2 diabetes and HbA_{1c} 7.5 to 12.0%	N=492 (Phase 1) 12 weeks (Phase 1) plus 28 weeks (Phase 2)	Primary: Change in baseline HbA_{1c} Secondary: Change in baseline FPG and 2-hour PPG, proportion of patients achieving HbA_{1c} <7.0%, safety, body weight	Primary: At the end of Phase 1 (12 weeks), mean changes from baseline in HbA_{1c} were -1.0 and -0.9% with sitagliptin and pioglitazone. At the end of Phase 2 (40 weeks), improvements in HbA_{1c} were greater with combination therapy compared to pioglitazone (-1.7 vs -1.4%; P=0.002). Secondary: At the end of Phase 1 (12 weeks), mean changes from baseline were -26.6 and -28.0 mg/dL for FPG and -52.8 and -50.1 mg/dL for 2-hour PPG. At the end of Phase 2 (40 weeks), improvements in FPG and 2-hour PPG were greater with combination therapy compared to pioglitazone (-45.8 vs -37.6 mg/dL; P=0.03 and -90.3 vs -69.1 mg/dL; P=0.001). Significantly more patients receiving combination therapy achieved an HbA_{1c} <7.0% (55.0 vs 40.5%; P=0.004). A numerically higher incidence of gastrointestinal adverse events and a significantly lower incidence of edema were observed with combination therapy compared to pioglitazone. The incidence of hypoglycemia was similarly low with both treatments. Body weight decreased with combination therapy and increased with pioglitazone (-1.1 vs 3.4 kg; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
metformin, and patients randomized to pioglitazone in Phase 1 were up titrated to 45 mg/day				
Wainstein et al.[104] (2012) Sitagliptin/ metformin 50/500 mg BID, titrated up to 50/1,000 mg BID vs pioglitazone 30 mg/day, titrated up to 45 mg/day	DB, RCT Treatment-naïve patients with type 2 diabetes HbA_{1c} 7.5 to 12.0%	N=517 32 weeks	Primary: Change from baseline HbA_{1c}, proportion of patients who achieved HbA_{1c} <7.0% Secondary: Change from baseline FPG	Primary: The least squares mean changes in HbA_{1c} at week 32 were -1.9 and -1.4% with combination therapy compared to pioglitazone, respectively (between-group differences, -0.5%; P<0.001). A greater proportion of patients achieved an HbA_{1c} <7.0% at week 32 with combination therapy compared to pioglitazone (57 vs 43%; P<0.001). Secondary: Compared to pioglitazone, combination therapy resulted in a greater least squares mean reductions in FPG (-56.0 vs -44.0 mg/dL; P<0.001) and 2-hour PPG (-102.2 vs -82.0 mg/dL; P<0.001) at week 32. A substantially greater reduction in FPG (-40.5 vs -13.0 mg/dL; P<0.001) was observed at week 1 with combination therapy compared to pioglitazone. A greater reduction in the fasting proinsulin:insulin and a greater increased in HOMA-B were observed with combination therapy compared to pioglitazone, while greater decreases in fasting insulin and HOMA-IR, and a greater increase in quantitative insulin sensitivity check index were observed with pioglitazone compared to combination therapy. Combination therapy resulted in a decrease in body weight (-1.4 kg) and pioglitazone resulted in an increase in body weight (3.0 kg; P<0.001). Higher incidences of diarrhea (15.3 vs 4.3%; P<0.001), nausea (4.6 vs 1.2%; P=0.02), and vomiting (1.9 vs 0.0%; P=0.026), and a lower incidence of edema (1.1 vs 7.0%; P<0.001) were observed with combination therapy compared to pioglitazone. There was no difference between the two treatments in the incidence of hypoglycemia (8.4 vs 8.3%; P=0.055).

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Scott et al.[105] (2008) Sitagliptin 100 mg QD plus metformin (existing therapy) vs rosiglitazone 8 mg QD plus metformin (existing therapy) vs metformin (existing therapy) plus placebo	AC, DB, MC, PG, RCT Type 2 diabetics 18 to 75 years of age receiving stable metformin doses (≥1,500 mg/day for ≥10 weeks) and inadequate glycemic control (HbA_{1c} ≥7.0 and ≤11.0%)	N=273 18 weeks	Primary: Change in baseline HbA_{1c} Secondary: Change in baseline FPG, fasting serum insulin, fasting serum proinsulin, β cell function, insulin resistance, and lipid profile	Primary: Sitagliptin significantly decreased HbA_{1c} compared to placebo (treatment difference, -0.50%; 95% CI, -0.87 to -0.60; P≤0.001). Similar results were observed with rosiglitazone (treatment difference, -0.57%; 95% CI, -0.76 to -0.37; P value not reported). There was no difference between sitagliptin and rosiglitazone (treatment difference, -0.06%; 95% CI, -0.25 to 0.14). The proportion of patients achieving an HbA_{1c}<7.0% was significantly greater with sitagliptin (55%; P=0.006) and rosiglitazone (63%; P value not reported) compared to placebo (38%). There was no difference between sitagliptin and rosiglitazone (treatment difference, 8%; 95% CI, -6 to 22; P value not reported). Secondary: Sitagliptin (treatment difference, -17.8 mg/dL; 95% CI, -27.6 to -8.1; P≤0.001) and rosiglitazone (treatment difference, -30.6 mg/dL; 95% CI, -40.6 to -20.7; P value not reported) significantly decreased FPG compared to placebo. Rosiglitazone significantly decreased FPG compared to sitagliptin (treatment difference, -12.8 mg/dL; 95% CI, -22.6 to -3.0; P value not reported). Sitagliptin (treatment difference, 16.3; 95% CI, 2.3 to 30.3; P≤0.05) and rosiglitazone (treatment difference, 15.3; 95% CI, 1.0 to 29.6; P value not reported, respectively) had significant increases in HOMA-B compared to placebo. The increase in HOMA-B was not significantly different between sitagliptin and rosiglitazone (P value not reported). Rosiglitazone significantly decreased HOMA-IR compared to placebo (treatment difference, -2.4; 95% CI, -3.4 to -1.4; P value not reported) and sitagliptin (treatment difference, -1.6; 95% CI, -2.6 to -0.7; P value not reported). There decrease in HOMA-IR was similar between sitagliptin and placebo (treatment difference, -0.7; 95% CI, -1.7 to 0.2; P value not reported).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Rosiglitazone significantly decreased fasting serum insulin compared to placebo (treatment difference, -3.4 µIU/mL; 95% CI, -5.5 to -1.4; P value not reported) and sitagliptin (treatment difference, -3.53 µIU/mL; 95% CI, -5.50 to -1.40; P value not reported). The proinsulin:insulin ratio was similar across all treatments. Compared to placebo, LDL-C decreased with sitagliptin (treatment difference, -5.3 mg/dL; 95% CI, -14.5 to 3.9; P value not reported) and increased with rosiglitazone (treatment difference, 9.5 mg/dL; 95% CI, 0.2 to 18.7; P value not reported). Compared to placebo, TC significantly decreased with sitagliptin (treatment difference, -6.3 mg/dL; 95% CI, -11.8 to -0.9; P≤0.05) and increased with rosiglitazone (treatment difference, 5.1 mg/dL; 95% CI, -0.3 to 10.6; P value not reported). Compared to placebo, TG significantly decreased with sitagliptin (treatment difference, -16.7 mg/dL; 95% CI, -27.9 to 5.5; P≤0.05) and increased with rosiglitazone (treatment difference, 1.2 mg/dL; 95% CI, -10.1 to 12.6; P value not reported). Compared to sitagliptin, lipid profiles measurements significantly increased with rosiglitazone (P values not reported).
Derosa et al.[106] (2010) Sitagliptin 100 mg QD vs metformin 850 mg BID All patients were receiving pioglitazone (15 or 30 mg/day).	DB, RCT Patients with type 2 diabetes, HbA_{1c} >7.5%, and receiving pioglitazone 30 mg/day	N=151 12 months	Primary: Body weight, BMI, HbA_{1c}, FPG, PPG, fasting plasma insulin, HOMA-IR, HOMA-B, fasting plasma proinsulin, proinsulin/fasting plasma insulin ratio, adiponectin, resistin, TNF-α, high sensitivity CRP Secondary: Not reported	Primary: A decrease in body weight and BMI were observed in patients receiving metformin, which was not observed in patients receiving sitagliptin. Significant decreases in HbA_{1c}, FPG, and PPG, and significant increases in HOMA-B were comparable between the two treatment groups. Fasting plasma insulin, fasting plasma proinsulin, proinsulin/fasting plasma insulin ratio, and HOMA-IR were decreased with both treatments. While values were lower with metformin, there were no significant differences observed between the two treatments. Sitagliptin achieved no significant changes in changes in adiponectin, resistin, TNF-α, compared to a significant increase in adiponectin and significant decreases in resistin and TNF-α achieved with metformin.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				High sensitivity CRP decreased significantly with both treatments, with no difference between them. Secondary: Not reported
Rigby et al.[107] (2010) Sitagliptin 100 mg QD and metformin (existing therapy) vs rosiglitazone 4 mg daily (QD or BID) and metformin (existing therapy) vs colesevelam 3.75 g daily (QD or BID) and metformin (existing therapy)	OL Patients 18 to 80 years of age with type 2 diabetes mellitus who had inadequate glycemic control (HbA_{1c} 6.5 to 10.0% on a stable regimen of metformin (1,500 to 2,550 mg daily), with LDL-C ≥60 mg/dL and TG <500 mg/dL	N=169 16 weeks	Primary: Change in HbA_{1c} from baseline to week 16 Secondary: Change in HbA_{1c} from baseline to week eight, change in FPG and fasting insulin from baseline to weeks eight and 16, change in two-hour PPG and postprandial insulin after a meal tolerance test, change in lipid parameters, percentage of participants who achieved an HbA_{1c} reduction >0.7% from baseline, percentage of participants who achieved HbA_{1c} <7.0%	Primary: At week 16, HbA_{1c} was reduced from baseline in all treatment groups (least square mean change from baseline): colesevelam -0.3% (95% CI, -0.52 to -0.02; P=0.031); rosiglitazone -0.6% (95% CI, -0.83 to -0.32; P<0.001); sitagliptin -0.4% (95% CI, -0.64 to -0.13; P=0.009). Secondary: At week eight, HbA_{1c} was reduced from baseline with colesevelam and sitagliptin (-0.3%; P=0.006 and -0.5%; P<0.001, respectively), but not with rosiglitazone (-0.2%; P=0.109). FPG was significantly reduced from baseline at week eight and week 16 in all treatment groups. The two-hour PPG levels were significantly reduced from baseline at week 16 in all treatment groups. There was no significant change in fasting insulin or two-hour postprandial insulin from baseline to week 16 in any treatment group. Insulin resistance did not change with colesevelam or sitagliptin; however, there was a significant reduction with rosiglitazone from baseline to week 16 (P=0.008). LDL-C was significantly reduced from baseline with colesevelam (-11.6%; P=0.001), but was significantly increased with both rosiglitazone (7.8%; P=0.040) and sitagliptin (7.7%; P=0.011). TC levels were unchanged from baseline with colesevelam and sitagliptin; however, they were significantly increased with rosiglitazone from baseline to week 16 (P=0.006). Non-HDL-C levels were unchanged with colesevelam; however, they were significantly increased with

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				rosiglitazone (P=0.001) and sitagliptin (P=0.029). Median triglyceride levels increased significantly from baseline with colesevelam (P<0.00l) and rosiglitazone (P<0.00l); however, sitagliptin did not significantly affect TG levels. HDL-C levels did not change significantly from baseline with any treatment. At week 16, 23.2% of patients in the colesevelam group, 48.l % of patients in the rosiglitazone group, and 34.5% of patients in the sitagliptin group achieved a reduction in HbA_{1c} 0.7% or greater from baseline. In addition, 10 patients in the colesevelam group, 19 in the rosiglitazone group, and 15 in the sitagliptin group achieved HbA_{1c} <7.0%. The percentages of patients who had an adverse event were 61.4% in the colesevelam group, 46.4% in the rosiglitazone group, and 48.2% in the sitagliptin group. Most of the adverse events were mild to moderate in severity.
Vilsbøll et al.[108] (2010) Sitagliptin 100 mg QD vs placebo All patients received insulin therapy with or without metformin.	RCT, DB, PC, PG Patients ≥21 years of age with type 2 diabetes on insulin (≥15 IU/day) alone or in combination with metformin (≥1500 mg/day) who had inadequate glycemic control (HbA_{1c} 7.5 to 11%), and BMI 20 to 43 kg/m^2	N=641 24 weeks	Primary: Change in HbA_{1c} from baseline Secondary: FPG, two-hour postmeal glucose, and the proportion of patients with an HbA_{1c} <7.0% or <6.5% at week 24	Primary: At week 24, the addition of sitagliptin to insulin therapy (± metformin) significantly reduced HbA_{1c} by 0.6% (P<0.001) compared with no change in the placebo group. Secondary: At week 24, mean change in FPG from baseline was -18.5 mg/dL in the sitagliptin group compared to -3.5 mg/dL in the placebo group (P<0.001). The two-hour post meal glucose was significantly reduced from baseline in the sitagliptin group (−30.9 mg/dL) compared to placebo (+5.2 mg/dL; P<0.001). The proportion of patients with an HbA_{1c} <7.0% at week 24 was significantly higher in the sitagliptin group compared with the placebo group (13 vs 5%, respectively). There was no difference between groups in the proportion of patients with an HbA_{1c} <6.5% at week 24.
Ahrén et al.[109] (2017) SUSTAIN 2	DB, MC, AC, PG, RCT	N=1,231 56 weeks	Primary: HbA_{1c} Secondary:	Primary: Treatment with semaglutide 0.5 mg and 1 mg once weekly resulted in a reduction in HbA_{1c} compared to sitagliptin 100 mg daily (-1.3% and 1.5% vs -0.7%; P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Sitagliptin 100 mg QD vs semaglutide 0.5 mg SC weekly vs semaglutide 1 mg SC weekly Subjects with unacceptable hyperglycemia were to be offered metformin (first choice) or other antidiabetic medications (not GLP-1, DPP-4 inhibitors or amylin analogs) as add-on to their randomized treatment (rescue medication) at the discretion of the investigator.	Patients ≥18 years with type 2 DM inadequately controlled with metformin, TZD or metformin and a TZD for ≥90 days before screening and an HbA_{1c} ≥7% to ≤10.5%		Change in body weight, FPG, SMPG, BMI, waist circumference, SBP and safety evaluations.	Secondary: The semaglutide groups had greater body weight reduction vs sitagliptin and significantly greater reductions in FPG, mean 7-point SMPG, mean prandial increment (across all meals) of the 7-point SMPG (only semaglutide 1 mg), BMI, waist circumference and systolic blood pressure. There were also significantly greater odds of achieving A_{1c} targets and categorical weight loss targets with semaglutide 0.5 mg or 1 mg vs sitagliptin. The most frequently reported adverse events in both semaglutide groups were gastrointestinal in nature: nausea was reported in 73 (18%) who received semaglutide 0.5 mg, 72 (18%) who received semaglutide 1.0 mg, and 30 (7%) who received placebo, and diarrhoea was reported in 54 (13%) who received semaglutide 0.5 mg, 53 (13%) who received semaglutide 1.0 mg, and 29 (7%) who received placebo.
Rosenstock et al.[110] (2019) PIONEER 3 Sitagliptin 100 mg QD	AC, DB, MC, PG, RCT Adults with type 2 DM insufficiently controlled with diet and exercise and	N=1,864 78 weeks	Primary: Change in HbA1c from baseline at week 26 Secondary:	Primary: Treatment with semaglutide 7 mg and 14 mg once daily for 26 weeks resulted in a statistically significant reduction in HbA1c compared to sitagliptin 100 mg once daily (-1.0% and -1.3% vs -0.8%; P<0.001 for both comparisons).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs semaglutide 3 mg orally QD vs semaglutide 7 mg orally QD vs semaglutide 14 mg orally QD All patients randomized to oral semaglutide initiated treatment with 3 mg QD with dose escalations every four weeks until the randomized maintenance dose was achieved.	HbA1c 7.0 to 10.5% and on a stable dose of metformin (with or without a SU) ≥90 days before screening		Changes in measures of glucose control, achievement of an HbA1c target of ,7% or ≤6.5% [and achievement of weight loss of at least 5% or 10%, as well as C-reactive protein, fasting lipid levels from baseline (at weeks 26, 52 and 78) and safety	At week 78, HbA1c reductions from baseline remained statistically significantly greater with semaglutide, 7 mg/day and 14mg/day compared to sitagliptin. Secondary: The mean changes in weight from baseline to week 26 were -2.2 kg and -3.1 kg in the semaglutide 7 and 14 mg groups and -0.6 kg in sitagliptin group, respectively (95% CI, -1.1 to -2.0 and -2.0 to -3.0, respectively).1 The body weight reductions at week 78 remained statistically significantly greater with all dosages of semaglutide compared with sitagliptin. For fasting plasma glucose and mean self-measured whole-blood glucose, the reductions from baseline were significantly greater in the 14 mg/day semaglutide group at weeks 26 and 78 compared with sitagliptin. In the 7 mg/day-and 14 mg/day semaglutide groups, significantly greater proportions of patients and achieved HbA1c levels lower than 7.0%, and body weight loss of 5% or greater. The most frequent adverse events by system organ class were gastrointestinal disorders in the 14 mg/day semaglutide group and infections and infestations in the 3 mg/day and 7 mg/day semaglutide and sitagliptin groups.
Pieber et al.[111] (2019) PIONEER 7 Sitagliptin 100 mg once daily vs semaglutide orally with flexible dose	MC, OL, RCT Adults with type 2 diabetes (diagnosed ≥90 days before screening), HbA_{1c} of 7.5 to 9.5%, and were inadequately controlled on stable daily doses of one or two oral glucose-lowering drugs (for	N=504 52 weeks	Primary: Achievement of HbA_{1c} < 7% and change in bodyweight from baseline to week 52 according to two efficacy-related estimands were prespecified: treatment policy (regardless of	Primary: A greater proportion of participants achieved an HbA_{1c} <7% with oral semaglutide than did with sitagliptin (treatment policy estimand: 58% vs 25%; and trial product estimand: 63% vs 28%). The odds of achieving an HbA_{1c} <7% was better with oral semaglutide than sitagliptin (treatment policy estimand: odds ratio [OR] 4.40; 95% CI, 2.89 to 6.70; P<0.0001; and trial product estimand: 5.54; 3.54 to 8.68; P<0.0001). The odds of decreasing mean bodyweight from baseline to week 52 were higher with oral semaglutide than with sitagliptin (estimated mean change in bodyweight, treatment policy estimand: -2.6 kg vs -0.7 kg, estimated treatment difference, -1.9 kg; 95% CI, -2.6 to -1.2; P<0.0001; and trial

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
adjustments to 3, 7, or 14 mg once daily	90 days or more before screening)		treatment discontinuation or use of rescue medication) and trial product (on treatment and without use of rescue medication) Secondary: Safety	product estimand: -2.9 kg vs -0.8 kg; estimated treatment difference, -2.2 kg; -2.9 to -1.5; P<0.0001). Secondary: Adverse events occurred in 197 (78%) of 253 participants in the oral semaglutide group versus 172 (69%) of 250 in the sitagliptin group, and nausea was the most common adverse event with oral semaglutide (53 [21%]). Two deaths occurred in the sitagliptin group during the trial.
Esposito et al.[112] (2011) Alogliptin 12.5 to 25 mg QD vs saxagliptin 5 mg QD vs sitagliptin 100 mg QD vs vildagliptin* 100 mg QD	MA (43 RCT) Type 2 diabetics were treatment-naïve or receiving background therapy with other agents	N=19,101 Duration not reported	Primary: Proportion of patients achieving an HbA_{1c} <7.0%, change in baseline body weight, incidence of hypoglycemia Secondary: Not reported	Primary: Proportion of patients achieving an aHbA_{1c} <7.0% Treatment with saxagliptin demonstrated a greater chance to achieve n HbA_{1c} <7.0% compared to placebo (POR, 2.81; 95% CI, 2.31 to 3.72), but not compared to comparator drugs (POR, 0.95; 95% CI, 0.8 to 1.11). Saxagliptin was associated with a greater decrease in HbA_{1c} compared to placebo (WMD, -0.69%; 95% CI, -0.1 to -0.37), but not compared to comparator drugs (WMD, 0.15%; 95% CI, -0.14 to 1.7). Sitagliptin was associated with a greater chance to achieve an HbA_{1c} <7.0% compared to placebo (POR, 3.15; 95% CI, 2.47 to 3.72), but not compared to comparator drugs (POR, 0.70; 95%CI, 0.35 to 1.12). Sitagliptin was also associated with a greater decrease in HbA_{1c} compared to placebo (WMD, -0.78%; 95% CI, -0.93 to -0.63), but not compared to comparator drugs (WMD, 0.19%; 95% CI, -0.13 to 0.52). Change in baseline body weight Saxagliptin was associated with small and no significant changes in body weight compared to baseline or other comparator drugs (WMD, -0.56 kg; 95% CI, -2.8 to 1.7), but with a significant difference compared to placebo (0.63 kg; 95% CI, 0.03 to 1.17). The absolute change in weight was small and not significantly different from baseline with sitagliptin (0.08 kg); however, the difference compared to placebo was significant (WMD, 0.48 kg; 95% CI, 0.19 to 0.77). The

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				overall change in weight with sitagliptin was not different from that of comparator drugs. Incidence of hypoglycemia Saxagliptin was associated with similar risk of hypoglycemia compared to placebo (RR, 1.1; 95% CI, 0.81 to 1.42) and comparator drugs (RR, 0.55; 95% CI, 0.4 to 1.9). Sitagliptin was associated with a significantly lower risk of hypoglycemia compared to placebo (RR, 1.8; 95% CI, 0.61 to 2.5) and comparator drugs (RR, 0.87; 95% CI, 0.30 to 2.80). Secondary: Not reported
Park et al.[113] (2012) Sitagliptin vs saxagliptin vs vildagliptin* vs linagliptin	MA Patients ≥ 18 years of age with type 2 diabetes	N=30,563 (62 RCTs) 12 or more weeks	Primary: Mean changes in HbA_{1c} and body weight, safety Secondary: Not reported	Primary: DPP-4 inhibitors lowered HbA_{1c} significantly more than placebo (weighted mean difference [WMD] –0.76%; 95% CI, –0.83 to –0.68); however, heterogeneity was substantial (I^2=82%). Exclusion of Japanese trials (N=7) resulted in a reduction of heterogeneity (I^2=59%). In the non-Japanese RCTs (N=55), DPP-4 inhibitors were associated with a reduction in HbA_{1c} (WMD –0.65%; 95% CI, –0.71 to –0.60) but higher risk of hypoglycemia (OR, 1.30; 95% CI, 1.00 to 1.68) compared to placebo. The seven Japanese-specific RCTs showed a greater reduction in HbA_{1c} (WMD –1.67%; 95% CI, –1.89 to –1.44) and a nonsignificant increase in risk of hypoglycemia (OR, 1.41; 95% CI, 0.51 to 3.88) with DPP-4 inhibitors vs placebo. When comparing DPP-4 inhibitors to active comparators, the I^2 was still high after deleting Japanese studies. In these 17 active comparator trials, there was no significant difference in HbA_{1c} reduction (WMD 0.04%; 95% CI, –0.09 to 0.16) or risk of hypoglycemia (OR, 0.60; 95% CI, 0.22 to 1.61) for DPP-4 inhibitors compared to other antihyperglycemics. There were similar odds of any or serious adverse events with DPP-4 inhibitors compared to placebo, but a decreased risk compared to other antihyperglycemics. Secondary: Not reported
Kim et al.[114]	DB, MC, RCT	N=292	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2017) Sitagliptin-metformin 50-1000 mg fixed-dose combination BID vs glimepiride starting at 1 mg and titrated as needed	Patients ≥18 years of age with type 2 diabetes with HbA_{1c} levels ranging from ≥7.0 to ≤9.5% for patients not on antihyperglycemic agents for at least 12 weeks or from ≥6.5 to ≤9.0% for patients taking antihyperglycemic agents	30 weeks	Change from baseline in HbA_{1c} Secondary: Proportion of patients achieving target goal (HbA_{1c} <7.0%) and change from baseline in FPG; safety	At Week 30, the mean HbA_{1c} fell from 8% at baseline to 6.5% in the sitagliptin-metformin group, and from 8.1% to 7.3% in the glimepiride group. The least squares mean change in HbA_{1c} from baseline was −1.49% and −0.71% in the sitagliptin-metformin and glimepiride groups, respectively. The between-group difference was −0.78% (95% CI, −0.96 to −0.59; P<0.001). Secondary: At 30 weeks, a higher proportion of patients in the sitagliptin-metformin group met the target HbA_{1c} goal compared with the glimepiride group (81.2% vs 40.1%; P<0.001; RR, 2.02). Treatment with sitagliptin-metformin provided a greater reduction (from baseline) in FPG compared with glimepiride (LS mean difference, − 23.5 mg/dL; P<0.001). Both drugs were generally well tolerated. Hypoglycemia events and weight gain were lower in patients with sitagliptin-metformin than with glimepiride (5.5% vs 20.1% and -0.83 vs +0.90 kg, respectively; both P<0.001). No serious drug-related adverse events or deaths were reported.
GRADE Study Research Group[115] (2022) Insulin glargine U-100 administered daily at an initial dose of up to 20 U and adjusted according to glucose levels vs glimepiride, increased from 1 to 2 mg to a maximum of 8 mg per day, administered in	MC, PG, RCT Participants with type 2 diabetes of less than 10 years' duration who were receiving metformin and had glycated hemoglobin levels of 6.8 to 8.5%	N=5,047 5 years	Primary: Cumulative incidence of a glycated hemoglobin level of 7.0% or higher Secondary: Cumulative incidence of a glycated hemoglobin level of 7.5% or higher	Primary: Over the mean 5-year follow-up, 71% of the cohort had a primary metabolic outcome event, with the highest frequency in the sitagliptin group (77%), intermediate frequency in the glimepiride group (72%), and the lowest frequency in the liraglutide (68%) and glargine (67%) groups. The between-group differences in the Kaplan–Meier estimates of the cumulative incidence of a primary-outcome event were significant (P<0.001 by the log-rank test). Secondary: The differences among the groups with respect to a glycated hemoglobin level greater than 7.5% (the secondary outcome) paralleled those of the primary outcome. A secondary-outcome event occurred in 55% of the participants in the sitagliptin group over a mean follow-up of 5 years, followed by glimepiride (in 50%), liraglutide (in 46%), and glargine (in 39%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
divided doses and adjusted according to glucose levels vs liraglutide initiated at a dose of 0.6 mg, with escalation to a maximum dose of 1.8 mg daily, depending on gastrointestinal side effects vs sitagliptin at a dose of 100 mg, with the dose adjusted according to kidney function Metformin was supplied to all the participants				
GRADE Study Research Group[116] (2022) Insulin glargine U-100 administered daily at an initial dose of up to 20 U and adjusted according to glucose levels	MC, PG, RCT Participants with type 2 diabetes of less than 10 years' duration who were receiving metformin and had glycated hemoglobin levels of 6.8 to 8.5%	N=5,047 5 years	Primary: Hypertension and dyslipidemia, confirmed moderately or severely increased albuminuria or an estimated glomerular filtration rate of less than 60	Primary: There were no material differences among the interventions with respect to the development of hypertension or dyslipidemia or with respect to microvascular outcomes; the mean overall rate (i.e., events per 100 participant-years) of moderately increased albuminuria levels was 2.6, of severely increased albuminuria levels 1.1, of renal impairment 2.9, and of diabetic peripheral neuropathy 16.7. The treatment groups did not differ with respect to MACE (overall rate, 1.0), hospitalization for heart failure (0.4), death from cardiovascular causes (0.3), or all deaths (0.6). There were small differences with respect to rates of any cardiovascular disease, with 1.9, 1.9, 1.4, and 2.0 in the glargine, glimepiride, liraglutide, and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs glimepiride, increased from 1 to 2 mg to a maximum of 8 mg per day, administered in divided doses and adjusted according to glucose levels vs liraglutide initiated at a dose of 0.6 mg, with escalation to a maximum dose of 1.8 mg daily, depending on gastrointestinal side effects vs sitagliptin at a dose of 100 mg, with the dose adjusted according to kidney function Metformin was supplied to all the participants			ml/min/1.73 m^2, diabetic peripheral neuropathy, cardiovascular events (major adverse cardiovascular events [MACE], hospitalization for heart failure, or an aggregate outcome of any cardiovascular event), and death Secondary: Not reported	sitagliptin groups, respectively. When one treatment was compared with the combined results of the other three treatments, the hazard ratios for any cardiovascular disease were 1.1 (95% confidence interval [CI], 0.9 to 1.3) in the glargine group, 1.1 (95% CI, 0.9 to 1.4) in the glimepiride group, 0.7 (95% CI, 0.6 to 0.9) in the liraglutide group, and 1.2 (95% CI, 1.0 to 1.5) in the sitagliptin group. Secondary: Not reported
Mearns et al.[117] (2015)	Network MA (62 RCTs)	N=32,185 3 to 12 months	Primary: Changes in HbA_{1c}, body weight, and	Primary: All agents significantly reduced HbA_{1c} vs placebo; although, not to the same extent (range, 0.43% for miglitol to 1.29% for glibenclamide).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Hypoglycemic medications (Alpha-glucosidase inhibitors, DPP-4 inhibitors, colesevelam, meglitinides, GLP-1 analogs, long-acting, once-daily basal insulin, SGLT2 inhibitors, sulfonylureas, TZDs, and combinations of the above agents)	Patients with inadequately controlled type 2 diabetes on metformin alone		SBP; risk of developing hypoglycemia and urinary and genital tract infection Secondary: Not reported	Glargine, sulfonylureas, and nateglinide were associated with increased hypoglycemia risk vs placebo. SGLT2 inhibitors, GLP-1 analogs, miglitol, and empagliflozin/linagliptin significantly reduced body weight (range, 1.15 to 2.26 kg) whereas sulfonylureas, TZDs, glargine, and alogliptin/pioglitazone caused weight gain (range, 1.19 to 2.44 kg). SGLT2 inhibitors, empagliflozin/linagliptin, liraglutide, and sitagliptin decreased SBP (range, 1.88 to 5.43 mmHg). No therapy increased UTI risk vs placebo; however, SGLT2 inhibitors were associated with an increased risk of genital tract infection (RR range, 2.16 to 8.03). Secondary: Not reported
Kheirbek et al.[118] (2013) Hypoglycemic medications (metformin, glyburide, glipizide, rosiglitazone, acarbose, chlorpropamide, glimepiride, pioglitazone, tolazamide, repaglinide, troglitazone, insulin, and DPP-4 inhibitors) *Defined as any use of the medication independent of dose or days of use	OS, RETRO Veterans with diabetes cared for at a Veterans Administration Capital area medical center	N=17,773 Variable duration	Primary: All-cause mortality Secondary: Not reported	Primary: After adjustments were made for severity of illness and patient demographics, the remaining variance in mortality was explained by exposure to five medications, listed in order of impact on risk-adjusted mortality: glipizide (OR=1.566), glyburide (OR=1.804), rosiglitazone (OR=1.805), insulin (OR=2.382), and chlorpropamide (OR=3.026). None of the other medications (metformin, acarbose, glimepiride, pioglitazone, tolazamide, repaglinide, troglitazone, and DPP-4 inhibitors) were associated with excess mortality beyond what could be expected from the patients' severity of illness or demographic characteristics. Insulin, glyburide, glipizide, and rosiglitazone continued to be associated with statistically significant increased mortality after controlling for possible drug interactions. Secondary: Not reported

*Agent not available in the United States.
Drug regimen abbreviations: BID=twice daily, ER=extended-release, QD=once daily, SC=subcutaneous
Study abbreviations: AC=active-comparator, DB=double-blind, DD=double-dummy, ES=extension study, MA=meta-analysis, MC=multicenter, NI=noninferiority, OL=open-label, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized-controlled trial, SA=single-arm, SR=systematic review, XO=cross-over
Miscellaneous: AUC=area under the curve, BMI=body mass index, BNP=brain natriuretic peptide, BP=blood pressure, CI=confidence interval, CRP=C-reactive protein, DBP=diastolic blood pressure, DPP-4 inhibitor=dipeptidyl peptidase-4 inhibitor, DTSQ=Diabetes Treatment Satisfaction Questionnaire, EQ-5D=EuroQol Quality of Life, FPG=fasting plasma glucose, GLP-1=glucagon-like peptide-1, HbA_{1c}=glycosylated hemoglobin, HDL-C=high density lipoprotein-cholesterol, HOMA-B=homeostasis model assessment-beta, HOMA-IR=homeostasis model assessment-insulin resistance, IWQOL=Impact of Weight on Quality of life Questionnaire, LDL-C=low density lipoprotein-cholesterol, MI=myocardial infarction, OR=odds ratio, PGWB=Psychological General Well-being index, PPG=post-prandial glucose, POR=pooled odds ratio, QOL=quality of life, QUICKI=Quantitative insulin sensitivity check index, RR=relative risk, SBP=systolic blood pressure, TC=total cholesterol, TG=triglycerides, TNF-α=tumor necrosis factor-α, TZD=thiazolidinedione, ULN=upper limit of normal, 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 brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

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

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

Rx=prescription

Table 10. Relative Cost of the Dipeptidyl Peptidase-4 (DPP-4) Inhibitors

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Single Entity Agents				
Alogliptin	tablet	Nesina®*	$$$$$	$$$$
Linagliptin	tablet	Tradjenta®	$$$$$	N/A
Saxagliptin	tablet	Onglyza®	$$$$$	N/A
Sitagliptin	tablet	Januvia®	$$$$$	N/A
Combination Products				
Alogliptin and metformin	tablet	Kazano®*	$$$$	$$$
Alogliptin and pioglitazone	tablet	Oseni®*	$$$$$	$$$$
Linagliptin and metformin	extended-release tablet, tablet	Jentadueto®, Jentadueto XR®	$$$$$	N/A
Saxagliptin and metformin	extended-release tablet	Kombiglyze XR®	$$$$$	N/A
Sitagliptin and metformin	extended-release, tablet, tablet	Janumet®, Janumet XR®	$$$$$	N/A

N/A=Not available

X. Conclusions

The dipeptidyl peptidase-4 (DPP-4) inhibitors are approved for use as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Available DPP-4 inhibitor combination products with metformin and pioglitazone are available for use when treatment with both drug components is appropriate.[1-11] Alogliptin and alogliptin combination products are available in a generic formulation; metformin and pioglitazone are also available generically in a separate formulation.

The goal of treatment for type 2 diabetes is to control hyperglycemia and reduce the risk of long-term complications. A notable new theme in diabetes treatment guidelines is an emphasis on a complication-centric approach, beyond glucose levels, to frame decisions regarding first-line pharmacologic choices for the treatment of persons with diabetes. Pharmacologic therapy should be guided by person-centered treatment factors, including comorbidities and treatment goals. In adults with type 2 diabetes and established/high risk of atherosclerotic cardiovascular disease, heart failure, and/or chronic kidney disease, the treatment regimen should include agents that reduce cardiorenal risk. Pharmacologic approaches that provide adequate efficacy to achieve and maintain treatment goals should be considered, such as metformin or other agents, including combination therapy.[12-15] The DPP-4 inhibitors are recommended as an alternative treatment option to be added to or used in combination with metformin in patients not achieving glycemic goals.[12-15]

A variety of clinical trials have been conducted with the DPP-4 inhibitors. The majority of the clinical trials have compared active treatment to placebo in patients not adequately controlled on other antidiabetic medications. In these trials, the more aggressive treatment regimens improved glycemic parameters to a greater extent than the less-intensive treatment regimens.[20-118] In treatment naïve patients, sitagliptin was shown to be non-inferior to metformin when used as monotherapy; however, monotherapy with exenatide was more beneficial with regards to glycemic parameters compared to monotherapy with sitagliptin.[32-33] Sitagliptin was also shown to be as effective as rosiglitazone or glipizide when these agents were added to existing metformin monotherapy.[96,105] The addition of exenatide to metformin led to a greater reduction in two-hour postprandial glucose concentrations compared to the addition of sitagliptin to metformin.[31] Limited head-to-head clinical trials comparing DPP-4 inhibitors have been conducted. In one trial, saxagliptin demonstrated non-inferiority to sitagliptin when both agents were added to existing metformin therapy.[78] There have been minimal clinical efficacy or safety trials conducted with any of the DPP-4 inhibitor fixed-dose combination products; bioequivalence of these products with co-administration of the individual drug components has been demonstrated for all tablet strengths.[5-11] Available trials evaluating the fixed-dose combination of sitagliptin and metformin support its efficacy and safety in the management of type 2 diabetes. Specifically, combination therapy was associated with significantly improved glycemic control compared to metformin monotherapy.[89] Alogliptin and pioglitazone combination therapy has also demonstrated significant improvements in HbA_{1c} when compared to monotherapy with either agent.[46-48]

The DPP-4 inhibitors are generally well tolerated. There have been postmarketing reports of serious hypersensitivity reactions in patients taking a DPP-4 inhibitor. These reactions include anaphylaxis, angioedema and exfoliative skin conditions including Stevens-Johnson syndrome. There have also been reports in the postmarketing setting and in randomized clinical trials of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, in patients taking a DPP-4 inhibitor. Additional warnings and precautions include heart failure, hepatic effects, severe arthralgia, and bullous pemphigoid. In the EXAMINE trial which enrolled patients with type 2 diabetes and recent acute coronary syndrome, 106 (3.9%) of patients treated with alogliptin and 89 (3.3%) of patients treated with placebo were hospitalized for congestive heart failure. Consider the risks and benefits of alogliptin prior to initiating treatment in patients at risk for heart failure, such as those with a prior history of heart failure and a history of renal impairment, and observe these patients for signs and symptoms of heart failure during therapy.[2-4,43] Combination DPP-4 inhibitor products containing metformin are associated with a risk of lactic acidosis.[1-11]

There is insufficient evidence to support that one brand DPP-4 inhibitor is safer or more efficacious than another within its given indication. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand products 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 DPP-4 inhibitor is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

XII. References

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Incretin Mimetics
AHFS Class 682006
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I. Overview

Diabetes mellitus is a chronic condition which results in hyperglycemia. It is differentiated into four main classes: 1) type 1 diabetes; 2) type 2 diabetes; 3) gestational diabetes; and 4) other types (drug- or chemical-induced, genetic defects in β-cell function or insulin action, and diseases of the exocrine pancreas). Type 2 diabetes is the most prevalent form of the disease in the United States. Inadequate glycemic control may lead to both acute and long-term complications, including microvascular and macrovascular events. There are a variety of oral and injectable antidiabetic agents currently available to treat diabetes. The antidiabetic agents are categorized into 12 different American Hospital Formulary Service (AHFS) classes, which differ with regards to their mechanism of action, efficacy, safety profiles, tolerability, and ease of use.

The incretin mimetics are approved for use as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus.[1-9] The incretin mimetics are glucagon-like peptide-1 (GLP-1) receptor agonists. GLP-1 is a human incretin hormone that is secreted from the small intestine in response to food intake, which has multiple effects on the stomach, liver, pancreas, and brain to control glucose concentrations. Human GLP-1 is inactivated by the dipeptidyl peptidase-4 (DPP4) enzyme within minutes. Endogenous GLP-1 levels have been shown to be reduced in patients with type 2 diabetes. Exenatide is a synthetic peptide with approximately 50% homology to human GLP-1, but is more resistant to inactivation by DPP-4. Liraglutide is an acylated human GLP-1 with 97% homology to the endogenous form and also has increased stability against metabolic degradation. Dulaglutide is 90% homologous to native human GLP-1 and is dosed weekly. Semaglutide is a GLP-1 analogue with 94% sequence homology to human GLP-1. The principal mechanism of protraction resulting in the long half-life of semaglutide is albumin binding, which results in decreased renal clearance and protection from metabolic degradation. Furthermore, semaglutide is stabilized against degradation by the DPP-4 enzyme. Semaglutide has an elimination half-life of approximately one week and is dosed weekly. The incretin mimetics enhance glucose-dependent insulin secretion by pancreatic beta cells, suppress glucagon secretion, slow gastric emptying, and reduce food intake.[1-9]

Victoza® (liraglutide) and Ozempic® (semaglutide) are approved to reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus and established cardiovascular disease.[3,5] Trulicity® (dulaglutide) is also approved to reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus who have established cardiovascular disease or multiple cardiovascular risk factors. Rybelsus® (semaglutide) is the first orally available GLP-1 agonist. As peptides have low oral bioavailability, oral semaglutide is coformulated with salcaprozate sodium, which facilitates semaglutide absorption across the gastric mucosa.[6] Mounjaro® (tirzepatide) is a first in class combination glucose-dependent insulinotropic polypeptide (GIP) receptor GLP-1 receptor agonist that selectively binds to and activates the GIP and GLP-1 receptors, the targets for native GIP and GLP-1. GIP and GLP-1 are incretins that have multiple actions on glucose (stimulates insulin secretion and lowers glucagon secretion).[7,10]

The incretin mimetics 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 November 2021.

Table 1. Incretin Mimetics Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Dulaglutide	injection	Trulicity®	Trulicity®
Exenatide	injection	Byetta®, Bydureon®	Byetta®
Liraglutide	injection	Victoza®	Victoza®
Semaglutide	injection, tablet	Ozempic®, Rybelsus®	none
Tirzepatide	injection	Mounjaro®	none

PDL=Preferred Drug List

II. Evidence-Based Medicine and Current Treatment Guidelines

Current clinical guidelines are summarized in Table 2. Please note that guidelines addressing the treatment of type 2 diabetes are presented globally, addressing the role of various medication classes.

Table 2. Treatment Guidelines Using the Incretin Mimetics

Clinical Guideline	Recommendation(s)
American Diabetes Association: **Standards of Care in Diabetes (2023)**[11]	Current criteria for the diagnosis of diabetes • The following are the criteria for a diagnosis of diabetes: glycosylated hemoglobin (HbA_{1c}) ≥6.5%, or a fasting plasma glucose (FPG) ≥126 mg/dL, or a two-hour plasma glucose ≥200 mg/dL during an oral glucose tolerance test or patients with classic symptoms of hyperglycemia, or classic symptoms of hyperglycemia or hyperglycemic crisis (random plasma glucose ≥200 mg/dL). Prevention or delay of type 2 diabetes • Refer adults with overweight/obesity at high risk of type 2 diabetes, as typified by the Diabetes Prevention Program (DPP), to an intensive lifestyle behavior change program to achieve and maintain a weight reduction of at least 7% of initial body weight through healthy reduced-calorie diet and ≥150 minutes/week of moderate-intensity physical activity. • A variety of eating patterns can be considered to prevent diabetes in individuals with prediabetes. • Metformin therapy for prevention of type 2 diabetes should be considered in adults at high risk of type 2 diabetes, as typified by the DPP, especially those aged 25 to 59 years with BMI ≥35 kg/m^2, higher FPG) (e.g., ≥110 mg/dL), and higher A1C (e.g., ≥6.0%), and in individuals with prior gestational diabetes mellitus (GDM). • Long-term use of metformin may be associated with biochemical vitamin B12 deficiency; consider periodic measurement of vitamin B12 levels in metformin-treated individuals, especially in those with anemia or peripheral neuropathy. Glycemic goals in adults • An A1C goal for many nonpregnant adults of <7% (53 mmol/mol) without significant hypoglycemia is appropriate. • If using ambulatory glucose profile (AGP)/glucose management indicator (GMI) to assess glycemia, a parallel goal for many nonpregnant adults is time in range (TIR) of >70% with time below range (TBR) <4% and time <54 mg/dL <1%. For those with frailty or at high risk of hypoglycemia, a target of >50% TIR with <1% TBR is recommended. • On the basis of health care provider judgment and patient preference, achievement of lower A1C levels than the goal of 7% may be acceptable and even beneficial if it can be achieved safely without significant hypoglycemia or other adverse effects of treatment. • Less stringent A1C goals (such as <8% [64 mmol/mol]) may be appropriate for patients with limited life expectancy or where the harms of treatment are greater than the benefits. HCPs should consider deintensification of therapy if appropriate to reduce the risk of hypoglycemia in patients with inappropriate stringent A1C targets. Pharmacologic therapy for type 1 diabetes • Most individuals with type 1 diabetes should be treated with multiple dose insulin injections (three to four injections per day of basal and pre-prandial insulin) or continuous subcutaneous (SC) insulin infusion therapy. • Most patients should use rapid-acting insulin analogs to reduce hypoglycemia risk.

Clinical Guideline	Recommendation(s)
	• Patients with type 1 diabetes should receive education on how to match prandial insulin doses to carbohydrate intake, premeal blood glucose, and anticipated physical activity. <u>Pharmacologic therapy for type 2 diabetes</u> • Healthy lifestyle behaviors, diabetes self-management education and support, avoidance of clinical inertia, and social determinants of health should be considered in the glucose-lowering management of type 2 diabetes. Pharmacologic therapy should be guided by person-centered treatment factors, including comorbidities and treatment goals. • In adults with type 2 diabetes and established/high risk of atherosclerotic cardiovascular disease, heart failure, and/or chronic kidney disease, the treatment regimen should include agents that reduce cardiorenal risk. • Pharmacologic approaches that provide adequate efficacy to achieve and maintain treatment goals should be considered, such as metformin or other agents, including combination therapy. • Weight management is an impactful component of glucose-lowering management in type 2 diabetes. The glucose-lowering treatment regimen should consider approaches that support weight management goals. • Metformin should be continued upon initiation of insulin therapy (unless contraindicated or not tolerated) for ongoing glycemic and metabolic benefits. • Early combination therapy can be considered in some individuals at treatment initiation to extend the time to treatment failure. • The early introduction of insulin should be considered if there is evidence of ongoing catabolism (weight loss), if symptoms of hyperglycemia are present, or when A1C levels (>10% [86 mmol/mol]) or blood glucose levels (≥300 mg/dL [16.7 mmol/L]) are very high. • A person-centered approach should guide the choice of pharmacologic agents. Consider the effects on cardiovascular and renal comorbidities, efficacy, hypoglycemia risk, impact on weight, cost and access, risk for side effects, and individual preferences. • Among individuals with type 2 diabetes who have established atherosclerotic cardiovascular disease or indicators of high cardiovascular risk, established kidney disease, or heart failure, a sodium–glucose cotransporter 2 inhibitor and/or glucagon-like peptide 1 receptor agonist with demonstrated cardiovascular disease benefit is recommended as part of the glucose-lowering regimen and comprehensive cardiovascular risk reduction, independent of A1C and in consideration of person-specific factors. • In adults with type 2 diabetes, a glucagon-like peptide 1 receptor agonist is preferred to insulin when possible. • If insulin is used, combination therapy with a glucagon-like peptide 1 receptor agonist is recommended for greater efficacy, durability of treatment effect, and weight and hypoglycemia benefit. • Recommendation for treatment intensification for individuals not meeting treatment goals should not be delayed. • Medication regimen and medication-taking behavior should be reevaluated at regular intervals (every three to six months) and adjusted as needed to incorporate specific factors that impact choice of treatment. • Clinicians should be aware of the potential for over-basalization with insulin therapy. Clinical signals that may prompt evaluation of over-basalization include basal dose more than ~0.5 units/kg/day, high bedtime–morning or post-preprandial glucose differential, hypoglycemia (aware or unaware), and high glycemic variability. Indication of over-basalization should prompt reevaluation to further individualize therapy.

Clinical Guideline	Recommendation(s)
American Diabetes Association/ European Association for the Study of Diabetes: **Management of Hyperglycemia in Type 2 Diabetes. A consensus report by the American Diabetes Association and the European Association for the Study of Diabetes (2022)**[12]	Consensus recommendations • All people with type 2 diabetes should be offered access to ongoing diabetes self-management education and support programs. • Providers and health care systems should prioritize the delivery of person-centered care. • Optimizing medication adherence should be specifically considered when selecting glucose-lowering medications. • Medical nutrition therapy focused on identifying healthy dietary habits that are feasible and sustainable is recommended in support of reaching metabolic and weight goals. • Physical activity improves glycemic control and should be an essential component of type 2 diabetes management. • Adults with type 2 diabetes should engage in physical activity regularly (>150 min/week of moderate- to vigorous-intensity aerobic activity) and be encouraged to reduce sedentary time and break up sitting time with frequent activity breaks. • Aerobic activity should be supplemented with two to three resistance, flexibility, and/or balance training sessions/week. Balance training sessions are particularly encouraged for older individuals or those with limited mobility/poor physical function. • Metabolic surgery should be considered as a treatment option in adults with type 2 diabetes who are appropriate surgical candidates with a BMI ≥40.0 kg/m^2 (BMI ≥37.5 kg/m^2 in people of Asian ancestry) or a BMI of 35.0 to 39.9 kg/m^2 (32.5 to 37.4 kg/m^2 in people of Asian ancestry) who do not achieve durable weight loss and improvement in comorbidities (including hyperglycemia) with nonsurgical methods. • In people with established CVD, a GLP-1 RA with proven benefit should be used to reduce MACE, or an SGLT2i with proven benefit should be used to reduce MACE and HF and improve kidney outcomes. • In people with CKD and an eGFR ≥20 ml/min per 1.73 m^2 and a urinary albumin/creatinine ratio >3.0 mg/mmol (>30 mg/g), an SGLT2i with proven benefit should be initiated to reduce MACE and HF and improve kidney outcomes. Indications and eGFR thresholds may vary by region. If such treatment is not tolerated or is contraindicated, a GLP-1 RA with proven cardiovascular outcome benefit could be considered to reduce MACE and should be continued until kidney replacement therapy is indicated. • In people with HF, SGLT2i should be used because they improve HF and kidney outcomes. • In individuals without established CVD but with multiple cardiovascular risk factors (such as age ≥55 years, obesity, hypertension, smoking, dyslipidemia, or albuminuria), a GLP-1 RA with proven benefit could be used to reduce MACE, or an SGLT2i with proven benefit could be used to reduce MACE and HF and improve kidney outcomes. • In people with HF, CKD, established CVD, or multiple risk factors for CVD, the decision to use a GLP-1 RA or SGLT2i with proven benefit should be independent of background use of metformin. • SGLT2i and GLP-1 RA reduce MACE, which is likely to be independent of baseline HbA1c. In people with HF, CKD, established CVD, or multiple risk factors for CVD, the decision to use a GLP-1 RA or an SGLT2i with proven benefit should be independent of baseline HbA1c. • In general, selection of medications to improve cardiovascular and kidney outcomes should not differ for older people. • In younger people with diabetes (<40 years), consider early combination therapy. • In women with reproductive potential, counseling regarding contraception and taking care to avoid exposure to medications that may adversely affect a fetus are important.

Clinical Guideline	Recommendation(s)
American Association of Clinical Endocrinologists/ American College of Endocrinology: **Clinical Practice Guidelines for Developing a Diabetes Mellitus Comprehensive Care Plan (2022)**[13]	Antihyperglycemic Pharmacotherapy for Persons with Type 2 Diabetes • Individualized pharmacotherapy for persons with T2D should be prescribed based on evidence for benefit that includes glucose lowering, avoidance of hypoglycemia and weight gain, and reduction of cardio-renal risk. • Persons with T2D and their health care professionals should use patient-centered shared decision-making to agree on therapy targets and treatments as well as a regimen for glucose monitoring (i.e., BGM, structured BGM, or CGM). • Glycemic targets include A1C, BGM, and, for those using CGM, achievement of CGM targets such as time in range (TIR), percentage in low and very low range, time above range, and glycemic variability. Nonglycemic targets include avoidance of hypoglycemia, control of BP, lipids, other CVD risk factors, and achieving and maintaining a healthy body weight. • Independent of glycemic control, targets, or treatment, if there is established or high risk for ASCVD, HF, and/or CKD, clinicians should prescribe a GLP-1 RA or an SGLT2i with proven efficacy for the specific condition(s) of the person with T2D being treated. • DM therapy should be individualized based on level of glycemia and the presence of comorbidities, complications, and access. Metformin is often the preferred initial therapy. Other agents may be appropriate as first line or in addition to metformin to reduce BG and/or to address specific comorbidities (such as ASCVD, HF, CKD, obesity, NAFLD), independent of glucose-lowering effects. • For some recently diagnosed individuals with T2D and more severe hyperglycemia (A1C ≥7.5%), unlikely to attain the A1C target with a single agent, early combination pharmacotherapy should be considered, usually to include metformin plus another agent that does not cause hypoglycemia, especially a GLP-1 RA, SGLT2i, or dipeptidyl peptidase 4 (DPP-4) inhibitor. • For newly diagnosed persons with T2D and an entry A1C >9.0% and/or ≥1.5% above target, one should initiate, along with lifestyle modifications, dual- or possibly triple-combination pharmacotherapy usually including metformin. Basal insulin along with noninsulin therapy is recommended if there are significant signs or symptoms of hyperglycemia, especially including catabolism (e.g., weight loss) or a very high A1C >10% (86 mmol/mol) or BG levels (≥300 mg/dL [16.7 mmol/L]). • Clinicians should discuss with persons with T2D the likelihood that most persons with T2D ultimately require a combination of multiple complementary antihyperglycemic agents, in addition to lifestyle interventions, to attain and maintain optimal glycemic control. • The DM care team should assess medication adherence and safety and glycemic control in persons with T2D quarterly or more frequently as needed. Subsequent visits will depend upon the metabolic targets achieved and the stability of metabolic control. • Persons with T2D who start on metformin should continue it unless intolerance or contraindications occur. When intensification of antihyperglycemic treatment is needed, other agents should be added to metformin. • Most persons with T2D who require intensification of antihyperglycemic therapy with a GLP-1 RA or insulin should initially be prescribed a GLP-1 RA. If further intensification is required, one should prescribe a basal insulin or a switch to a fixed-ratio combination of a basal insulin and a GLP-1 RA (insulin glargine U100 + lixisenatide [GlarLixi] or insulin degludec + liraglutide [IdegLira]). • Insulin should be prescribed for persons with T2D when noninsulin antihyperglycemic therapy fails to achieve target glycemic control or when a person has symptomatic hyperglycemia.

Clinical Guideline	Recommendation(s)
	• Long-acting basal insulin analogs are the recommended initial choice of insulin therapy for persons with T2D. The insulin analogs glargine (U100 or U300), degludec (U100 or U200), or detemir are preferred over intermediate-acting Neutral Protamine Hagedorn (NPH) insulin because analog insulins have demonstrated less hypoglycemia in some studies. Glargine U300 and degludec can be associated with less hypoglycemia than glargine U100 or detemir. • Many persons with T2D receiving basal insulin and not at goal A1C can have significantly improved glycemia by the addition of a GLP-1 RA or being switched to a fixed-ratio combination basal insulin–GLP-1 RA (GlarLixi or IdegLira). One of these changes should be considered before adding a meal-time insulin for postprandial glycemic control. • When control of postprandial hyperglycemia is needed and a basal insulin and a GLP-1 RA are already being used, preference should be given to rapid-acting insulins (the analogs lispro, aspart, and glulisine or the rapid-acting inhaled human insulin powder) over regular human insulin. The former have a more consistent and a more rapid onset and offset of action with less risk of hypoglycemia. • Ultra-rapid-acting insulins (faster-acting insulin aspart, lispro aabc, and [human insulin] inhalation powder) may allow a decrease in the time between insulin administration and food intake and reduce the postprandial peak of PG as compared with rapid-acting insulins. The significance of this on long-term complications is unknown. • Basal-bolus insulin regimens or continuous subcutaneous insulin infusion (CSII) (i.e., insulin pump) allow for adjustment of insulin doses according to carbohydrate intake and activity levels and are recommended for intensive insulin therapy in persons with T2D. • Premixed insulin formulations (fixed combinations of shorter- and longer-acting components) of human or analog insulin may be considered for persons with T2D who have consistent dietary and exercise patterns and in whom adherence to more intensive insulin regimens is problematic. However, these preparations have reduced dosage flexibility and may increase the risk of hypoglycemia compared with basal insulin or basal-bolus regimens. • In persons with T2D who are treated with basal-bolus insulin therapy, adding a GLP-1 RA, or switching to a fixed-ratio combination of a GLP-1 RA and a basal insulin, or adding an SGLT2i or pramlintide (less commonly used) may be able to reduce postprandial hyperglycemia, A1C, and weight. GLP-1 RAs may also allow reduction or discontinuation of bolus insulin in some individuals. <u>How should insulin therapy be used for management of persons with type 1 diabetes?</u> • Insulin must be used to treat all persons with T1D. • Physiologic insulin replacement regimens, which provide both basal and prandial (meal-related or bolus) insulin, are recommended for most persons with T1D. • Achievement of glucose targets using either MDI of insulin or CSII, is needed to prevent development of life-threatening crises, such as acute hyperglycemic crises (DKA and hyperglycemic hyperosmolar state) and catabolic state. • A multi-component self-management DM education program is recommended for persons with T1D. Ideally, this is provided by a professional with expertise (i.e., certified diabetes care and education specialist) in the topics of healthy lifestyle, insulin technique including prandial insulin dosing guided by carbohydrate counting and diet adjustments for special situations, such as physical activity and prolonged fasting. Instruction is also needed in how to deal with sick days and prevention of DKA and hypoglycemia, and other relevant issues. Due to changes in DM self-management practices and each individual's medical history, personal and cultural background, and educational needs, specific education topics may need to be repeated at regular intervals.

Clinical Guideline	Recommendation(s)
	• The ideal insulin regimen should be personalized to an individual's needs and glycemic targets, attempting to better emulate physiological insulin replacement to maintain near normoglycemia, to prevent the development and progression of DM complications, while minimizing hypoglycemia and providing flexibility for specific daily life situations/scenarios such as: exercise, sleep, acute illness, psychological stress, etc. • Insulin regimens usually should involve the use of insulin analogs for most persons with T1D and include the following approaches: o MDI, which usually involve 1 to 2 subcutaneous injections daily of basal insulin to suppress ketogenesis and gluconeogenesis and to control glycemia between meals and overnight, and subcutaneous injections of prandial insulin or use of inhaled insulin before each meal to control meal-related glycemic excursions. CGM is the preferred method of glucose monitoring for all individuals with T1D. o Insulin pump therapy (CSII) provides constant/continuous infusion of fast-acting insulin driven by mechanical force and delivered via a cannula inserted under the skin. CSII can improve (or enhance) glycemic control and should be an option for insulin delivery for appropriate persons with DM. Ideally, these individuals should also use CGM as stated in R13.6.a. o Automated insulin delivery systems (AIDs), which include an insulin pump, an integrated CGM, and computer software algorithm, aim to better emulate physiological insulin replacement and achieve glycemic targets. This technology is recommended for many persons with T1D since its use has been shown to increase TIR while often reducing hypoglycemia or at least without causing increased hypoglycemia. o Open-loop (use of a pump and sensor which do not communicate) and sensor-augmented pump (SAP) systems: (CGM communicates with pump facilitating needed adjustments to basal rate; temporary interruption of insulin delivery when glucose levels are low or forecast to be low within 30 min). Insulin pump with a CGM or an SAP is recommended to manage persons with DM treated with intensive insulin management who prefer not to use AIDs or have no access to them. <u>How should diabetes mellitus in pregnancy be managed?</u> • For women with GDM, the following treatment goals are recommended: preprandial glucose concentration ≤95 mg/dL and either a 1-h post-meal glucose ≤140 mg/dL or a 2-h post-meal glucose ≤120 mg/dL to decrease adverse fetal outcomes. • All women with preexisting DM (T1D, T2D, or previous GDM) need access to preconception care and counseling to ensure adequate nutrition, healthy weight, and glucose control before conception, during pregnancy, and in the postpartum period. • Rapid-acting insulin analogs (insulin-lispro, insulin-aspart) should be used to treat postprandial hyperglycemia in pregnant women. • Options for basal insulin include long-acting insulin (e.g., NPH, detemir, or glargine) or rapid-acting insulin via a CSII. Regular insulin, although not recommended as first-line therapy, is acceptable to use in managing pregnant women with DM when rapid-acting insulin analogs are not available. • Insulin is the preferred therapeutic choice for pregnant women with GDM or T2D, but metformin has been given a category B for pregnancy with accumulating clinical evidence of metformin's safety during the first trimester and beyond. Metformin has been shown to improve pregnancy and fetal outcomes except for increased rates of infants with SGA and later onset of obesity. The prescriber should discuss the potential risks and benefits of oral agent therapy during pregnancy as well as the need for longer-term outcome studies.

Clinical Guideline	Recommendation(s)
American Association of Clinical Endocrinologists/ American College of Endocrinology: **Consensus Statement on the Comprehensive Type 2 Diabetes Management Algorithm (2023)**[14]	Principles underlying the algorithm • Lifestyle modification underlies all therapy. • Maintain or achieve optimal weight. • Choice of antihyperglycemic therapy reflects glycemic targets, atherosclerotic cardiovascular disease (ASCVD), congestive heart failure (CHF), chronic kidney disease (CKD), overweight/obesity, and nonalcoholic fatty liver disease (NAFLD). • Choice of therapy includes ease of use and access. • Optimal hemoglobin A1c (A1C) is ≤6.5% or as close to normal as is safe and achievable for most patients. • Individualize all glycemic targets (A1C, glucose management indicator [GMI], time in range [TIR], fasting blood glucose [FBG], and PPG). • Get to goal as soon as possible (adjust ≤3 months). • Avoid hypoglycemia. Hypoglycemia, defined as blood glucose (BG) <70 mg/dL, is associated with an increased risk for adverse outcomes including mortality. • CGM is highly recommended to assist persons with diabetes in reaching goals safely. • Comorbidities must be managed for comprehensive care. Algorithm summative information • The algorithm is intended as a more concise document than the guideline, providing easily accessible, visual guidance for decision-making in the clinic setting. • In this 2023 algorithm, there continues to be an emphasis on lifestyle modification and treatment of overweight/obesity as key pillars of the management of prediabetes and DM. • The importance of appropriate management of the atherosclerotic risk factors of dyslipidemia and hypertension is highlighted. • One notable new theme is an obvious emphasis on a complication-centric approach, beyond glucose levels, to frame decisions regarding first-line pharmacologic choices for the treatment of persons with diabetes. • The algorithm is divided into discrete graphic sections that outline the principles for management of T2D and guide management of adiposity-based chronic disease (ABCD), prediabetes, and atherosclerotic risk factors of dyslipidemia and hypertension. In addition, the algorithms for antihyperglycemic agents include both complication-centric and glucose-centric approaches, and there is direction for insulin initiation and titration. Tables summarizing the benefits and risks of antihyperglycemic medications (updated) and weight-loss pharmacotherapy (new) are provided.

American Academy of Pediatrics: **Management of Newly Diagnosed Type 2 Diabetes Mellitus (T2DM) in Children and Adolescents (2013)**[15]	• Clinicians must ensure that insulin therapy is initiated for children and adolescents with T2DM who are ketotic or in diabetic ketoacidosis and in whom the distinction between types 1 and 2 diabetes mellitus is unclear and, in usual cases, should initiate insulin therapy for patients.
	  ○ Who have random venous or plasma blood glucose (BG) concentrations ≥250 mg/dL.
	  ○ Whose HbA_{1c} is >9%.
	• In all other instances, clinicians should initiate a lifestyle modification program, including nutrition and physical activity, and start metformin as first-line therapy for children and adolescents at the time of diagnosis of T2DM.
	• Monitoring of HbA_{1c} concentrations is recommended every three months and intensifying treatment is recommended if treatment goals for finger-stick BG and HbA_{1c} concentrations are not being met.
	• Advise patients to monitor finger-stick BG concentrations in patients who:

Clinical Guideline	Recommendation(s)
	○ Are taking insulin or other medications with a risk of hypoglycemia; or ○ Are initiating or changing their diabetes treatment regimen; or ○ Have not met treatment goals; or ○ Have intercurrent illnesses. • Incorporate the Academy of Nutrition and Dietetics' *Pediatric Weight Management Evidence-Based Nutrition Practice Guidelines* in dietary or nutrition counseling of patients with T2DM at the time of diagnosis and as part of ongoing management. • Encourage children and adolescents with T2DM to engage in moderate-to-vigorous exercise for at least 60 minutes daily and to limit nonacademic "screen time" to less than two hours a day.
American Diabetes Association: **Type 1 Diabetes in Children and Adolescents: A Position Statement by the American Diabetes Association (2018)[16]**	<u>Blood Glucose Management: Monitoring and Treatment</u> • Most children with type 1 diabetes should be treated with intensive insulin regimens via either multiple daily injections of prandial insulin and basal insulin or continuous subcutaneous insulin infusion. • An HbA_{1c} target of <7.5% should be considered in most children and adolescents but should be individualized based on the needs and situation of the patient and family. • Children and adolescents with type 1 diabetes should have blood glucose levels monitored up to six to ten times/day including premeal, pre-bedtime, and as needed for safety (e.g., exercise, driving, illness, or the presence of symptoms of hypoglycemia). • Continuous blood glucose monitoring should be considered in all children and adolescents whether using insulin injections or an insulin pump. • In pediatric patients with type 1 diabetes automated insulin delivery systems can improve glycemic control and reduce hypoglycemia. <u>Lifestyle Management</u> • Individualized medical nutrition therapy is recommended for children and adolescents with type 1 diabetes. • Monitoring carbohydrate intake, whether by carbohydrate counting or experience-based estimation, is key to achieving optimal glycemic control. • Exercise if recommended for all children and adolescents with type 1 diabetes. The suggested goal is 60 minutes of moderate to vigorous aerobic activity daily with muscle-strengthening and bone-strengthening activities three times a week. • Children and adolescents with type 1 diabetes should be educated about prevention and management of potential hypoglycemia during and after exercise. • Strategies to prevent hypoglycemia during exercise, after exercise, and overnight following exercise include reducing prandial insulin dosing for the meal/snack preceding exercise, increasing carbohydrate intake, eating bedtime snacks, using continuous blood glucose monitoring, and/or reducing basal insulin doses. <u>Behavioral Aspects of Self-Management</u> • Children and adolescents with diabetes should be assessed for psychosocial issues and family stresses that could impact diabetes management at diagnosis and routine follow-up. • Consider including children in consent processes as early as cognitive development indicates understanding of health consequences of behavior. • Offer adolescents time by themselves with their care provider(s) starting at age 12 years, or when developmentally appropriate. <u>Complications and Comorbidities</u> • Diabetic Ketoacidosis

Clinical Guideline	Recommendation(s)
	○ All individuals with type 1 diabetes should have access to an uninterrupted supply of insulin. Lack of access and insulin omissions are major causes of diabetic ketoacidosis. ○ Patients with type 1 diabetes should have continuous access to medical support for sick-day management. • Hypoglycemia ○ The recommended treatment of hypoglycemia (blood glucose <70 mg/dL) in conscious patients is 15 g of glucose, although any form of carbohydrate can be used. If hypoglycemia continues after 15 minutes, treatment should be repeated. Once blood glucose has returned to normal patients should consider consuming a meal/snack and/or reduce insulin. ○ All individuals with type 1 diabetes should be prescribed glucagon and families/caregivers should be educated on administration. ○ Treatment regimens should be reevaluated in those with hypoglycemia unawareness or one or more episodes of severe hypoglycemia. • Diabetic Kidney Disease ○ Annual screening for albuminuria with a random spot urine sample for albumin-to-creatinine ratio should be considered at puberty or at age >10 years, whichever is earlier, once the child has had diabetes for 5 years. ○ An angiotensin-converting-enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB), titrated to normalization of albumin excretion, may be considered when elevated urinary albumin-to-creatinine ratio is documented. • Retinopathy ○ An initial dilated and comprehensive eye examination is recommended at age 10 years or after puberty has started, whichever is earlier, once the patient has had diabetes for three to five years. ○ Annual routine follow-up is recommended but may be given every two years based on the advice of an eye care professional. • Neuropathy ○ Consider an annual comprehensive foot exam for adolescents at the start of puberty or at age 10 years, whichever is earlier, once the patient has had type 1 diabetes for 5 years. • Hypertension ○ Children and adolescents with type 1 diabetes should have blood pressure monitored at each visit. Elevated blood pressure should be confirmed on three separate days. ○ Initial treatment of high-normal blood pressure should include dietary modification and increased exercise. Pharmacologic treatment should be considered if blood pressure is not controlled after three to six months. ○ In patients with conformed hypertension pharmacologic treatment should be added to lifestyle modification at diagnosis. ○ ACE inhibitors and ARBs should be considered for initial treatment. • Dyslipidemia ○ A fasting lipid profile should be taken in children ≥10 years of age or older after the diagnosis of diabetes. Obtain a fasting lipid profile in children 10 years of age or older as soon as convenient after the diagnosis of diabetes ○ If lipids are abnormal, initial therapy should consist of optimizing glucose control and medical nutrition therapy using a Step 2 American Heart Association diet that restricts saturated fat to 7% of total calories and dietary cholesterol to 200 mg/day. ○ If lipids remain abnormal after six months of lifestyle intervention, consider adding a statin in children at least 10 years of age.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the incretin mimetics 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.

It is important to note that the incretin mimetics are not a substitute for insulin, and these agents should not be used in type 1 diabetics or for the treatment of diabetic ketoacidosis. The incretin mimetics would not be effective in these situations.[1-7]

According to FDA-approved package labeling, due to the uncertain relevance of the rat thyroid C-cell tumor findings to humans, exenatide (Bydureon®) is not recommended as first-line therapy for patients who have inadequate glycemic control on diet and exercise.[1-7] Liraglutide, dulaglutide, semaglutide, and tirzepatide also have the warning for the risk of thyroid C-cell tumors, but may be used as first-line therapy in patients with compelling indications.[1-7]

Table 3. FDA-Approved Indications for the Incretin Mimetics[1-7]

Indications	Dulaglutide	Exenatide	Liraglutide	Semaglutide	Tirzepatide
Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus		✔ (SubQ)		✔	✔
Adjunct to diet and exercise to improve glycemic control in adults and pediatric patients aged 10 years and older with type 2 diabetes mellitus	✔	✔ (SubQ ER)	✔		
Reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus and established cardiovascular disease			✔	✔ (SubQ only)	
Reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus who have established cardiovascular disease or multiple cardiovascular risk factors	✔				

IV. Pharmacokinetics

The pharmacokinetic parameters of the incretin mimetics are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Incretin Mimetics[8]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life
Dulaglutide	47 to 65	Not reported	Protein catabolism (% not reported)	Not reported	5 days
Exenatide	65 to 76†	Not reported	Plasma/tissues (% not reported)	Renal (% not reported)	2.4 hours
Liraglutide	55	>98	Not significant (% not reported)	Renal (0 unchanged; 6 changed), Feces (0 unchanged; 5 unchanged)	13 hours

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life
Semaglutide	Oral: 0.4 to 1 subQ: 89	>99	Proteolysis and beta-oxidation (% not reported)	Renal & Feces (% not reported)	1 week
Tirzepatide	80	99	Proteolysis and beta-oxidation (% not reported)	Renal & Feces (% not reported)	5 days

†Information derived from animal data.

V. Drug Interactions

Concurrent use of tirzepatide and oral hormonal contraceptives may result in decreased absorption of oral contraceptives.[7,8] There are no other significant drug interactions reported with the incretin mimetics.[8] However, these agents slow gastric emptying and thereby have the potential to impact the absorption of concomitantly administered oral medications. Caution should be exercised when oral medications are concomitantly administered with the incretin mimetics.[1-7]

VI. Adverse Drug Events

The most common adverse drug events reported with the incretin mimetics are listed in Table 5. The boxed warnings for the incretin mimetics are listed in Tables 6 through 11. Based on postmarketing data, the incretin mimetics have been associated with acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis. There have been postmarketing reports of altered renal function, including increased serum creatinine, renal impairment, worsened chronic renal failure and acute renal failure, sometimes requiring hemodialysis or kidney transplantation. Patients may develop antibodies to exenatide consistent with the potentially immunogenic properties of protein and peptide pharmaceuticals. In a small percentage of patients, the formation of antibodies to exenatide at high titers could result in failure to achieve adequate improvement in glycemic control.[1-7]

Table 5. Adverse Drug Events (%) Reported with the Incretin Mimetics[9]

Adverse Event	Dulaglutide	Exenatide/ Exenatide ER	Liraglutide	Semaglutide	Tirzepatide
Abdominal distention	2 to 3	-	-	2 to 3 (oral)	3
Abdominal pain	7 to 9	-	-	6 to 11	5 to 6
Anorexia	-	-	9	-	-
Antibody development (non-neutralizing)	2	-	-	1	-
Asthenia	-	4	-	-	-
Atrioventricular block	2	-	-	-	-
Back pain	-	-	5	-	-
Cholelithiasis	-	-	-	≤2	-
Constipation	4	-/6.3 to 10.1	5.1 to 9.9	3 to 6	6 to 7
Cough	-	-	-	6 to 9 (oral)	-
Decreased appetite	5 to 9	1 to 2/5	9.3	-	5 to 11
Diarrhea	9 to 13	1 to 13/9.3 to 20.0	7.2 to 17.1	9	12 to 17
Dizziness	-	1 to 9	5.2	-	-
Dyspepsia	4 to 6	3 to 7/5.0 to 7.4	5.2 to 6.5	3 to 4	5 to 8
Eructation	1 to 2	-	-	1 to 3	3
Fatigue	4 to 6	-/5.6 to 6.1	5.1	-	-
Feeling jittery	-	9	-	-	-
Flatulence	3	-	-	2	1 to 3
Gastroenteritis viral	-	-/8.8	-	-	-
Gastroesophageal reflux disease	2	3/7.4	-	2	2 to 3
Gastritis	-	-	-	2 (oral)	-

Adverse Event	Dulaglutide	Exenatide/ Exenatide ER	Liraglutide	Semaglutide	Tirzepatide
Headache	-	9/6.1 to 9.9	8.2 to 9.6	-	-
Hyperhidrosis	-	3	-	-	-
Hypertension	-	-	3	-	-
Hypoglycemia	3 to 6	3.8 to 35.7/0 to 20	0.1 to 27.4	2 to 4	-
Hypersensitivity reaction	-	-	-	-	3
Increased amylase	-	-	-	13	33 to 38
Increased serum lipase	-	-	-	22	31 to 42
Influenza	-	-	7.4	-	-
Injection site erythema	-	-/5.4 to 7.4	-	-	-
Injection site hematoma	-	-/5.4	-	-	-
Injection site nodule	-	-/6.0 to 10.5	-	-	-
Injection site pruritus	-	-/5.0 to 18.2	-	-	-
Injection site reaction	-	-	-	-	3
Nasopharyngitis	-	-	5.2	-	-
Nausea	12 to 21	8 to 44/11.3 to 27.0	7.5 to 34.6	11 to 20	12 to 18
P-R prolongation	3	-	-	-	-
Sinus tachycardia	3 to 6	-	-	-	5 to 10
Sinusitis	-	-	5.6	-	-
Upper respiratory tract infection	-	-	9.5	-	-
Urinary tract infection	-	-	6	-	-
Vomiting	6 to 13	4 to 13/10.8 to 11.3	6.5 to 12.4	5 to 9	5 to 9

*Corresponds to monotherapy or combination therapy with other antidiabetic therapies.
-Event not reported.

Table 6. Boxed Warning for Trulicity® (dulaglutide)[4]

WARNING
WARNING: RISK OF THYROID C-CELL TUMORS • In male and female rats, dulaglutide causes a dose-related and treatment-duration-dependent increase in the incidence of thyroid C-cell tumors (adenomas and carcinomas) after lifetime exposure. It is unknown whether Trulicity causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans as human relevance of dulaglutide-induced rodent thyroid C-cell tumors has not been determined. • Trulicity is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Counsel patients regarding the potential risk of MTC with use of Trulicity and inform them of symptoms of thyroid tumors (e.g., mass in the neck, dysphagia, dyspnea, persistent hoarseness). Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with Trulicity.

Table 7. Boxed Warning for Bydureon® (exenatide extended-release)[2]

WARNING
WARNING: RISK OF THYROID C-CELL TUMORS • Exenatide extended-release causes an increased incidence in thyroid C-cell tumors at clinically relevant exposures in rats compared to controls. It is unknown whether Bydureon causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as the human relevance of exenatide extended-release-induced rodent thyroid C-cell tumors has not been determined. • Bydureon is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Counsel patients regarding the potential risk for MTC with the use of Bydureon and inform them of symptoms of thyroid tumors (e.g., mass in the neck, dysphagia, dyspnea, persistent hoarseness). Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for detection of MTC in patients treated with Bydureon.

Table 8. Boxed Warning for Victoza® (liraglutide)[3]

WARNING
WARNING: RISK OF THYROID C-CELL TUMORS • Liraglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures in both genders of rats and mice. It is unknown whether Victoza causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as the human relevance of liraglutide-induced rodent thyroid C-cell tumors has not been determined. • Victoza is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Counsel patients regarding the potential risk for MTC with the use of Victoza and inform them of symptoms of thyroid tumors (e.g., a mass in the neck, dysphagia, dyspnea, persistent hoarseness). Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with Victoza.

Table 9. Boxed Warning for Ozempic® and Rybelsus® (semaglutide)[5,6]

WARNING
WARNING: RISK OF THYROID C-CELL TUMORS • In rodents, semaglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures. It is unknown whether semaglutide causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans as human relevance of semaglutide-induced rodent thyroid C-cell tumors has not been determined. • Semaglutide is contraindicated in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Counsel patients regarding the potential risk for MTC with the use of semaglutide and inform them of symptoms of thyroid tumors (e.g., a mass in the neck, dysphagia, dyspnea, persistent hoarseness). Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with semaglutide.

Table 10. Boxed Warning for Mounjaro® (tirzepatide)[7]

WARNING
WARNING: RISK OF THYROID C-CELL TUMORS • In both male and female rats, tirzepatide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures. It is unknown whether Mounjaro causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans as human relevance of tirzepatide-induced rodent thyroid C-cell tumors has not been determined. • Mounjaro is contraindicated in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Counsel patients regarding the potential risk for MTC with the use of Mounjaro and inform them of symptoms of thyroid tumors (e.g., a mass in the neck, dysphagia, dyspnea, persistent hoarseness). Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with Mounjaro.

VII. Dosing and Administration

The usual dosing regimens for the incretin mimetics are listed in Table 11. The incretin mimetics are administered by subcutaneous injection. There are currently two formulations of exenatide available. The immediate-release formulation (Byetta®) is administered twice daily and should be given within 60 minutes prior to a meal, while the extended-release (ER) formulation (Bydureon®) is administered once weekly and can be administered without regard to meals.[1,2] The extended effect of exenatide ER results from the addition of a biodegradable polymer poly D, L-lactic-co-glycolic acid to the active component, exenatide, which forms microspheres. After exenatide ER is administered, continued infiltration of water into the microspheres causes them to swell and release the medication in a slow predictable fashion. Of note, patients who administer exenatide ER will have a palpable SC nodule at the injection site that dissipates as the medication is released.[20] Oral semaglutide (Rybelsus®) should be taken at least 30 minutes before the first food, beverage, or other oral medications of the day with no more than 4 ounces of plain water only. Waiting less than 30 minutes, or taking with food, beverages (other than plain water)

or other oral medications will lessen the effect of Rybelsus®. Waiting more than 30 minutes to eat may increase the absorption of Rybelsus®.[7]

Table 11. Usual Dosing Regimens for the Incretin Mimetics[1-7]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Dulaglutide	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus, reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus who have established cardiovascular disease or multiple cardiovascular risk factors: Injection: initial, 0.75 mg once weekly, may be increased to 1.5 mg once weekly, may be increased to 3 mg once weekly and 4.5 mg once weekly after at least 4 weeks on the previous dose	Adjunct to diet and exercise to improve glycemic control in patients ≥10 years of age with type 2 diabetes mellitus: Injection initial, 0.75 mg once weekly, may be increased to 1.5 mg once weekly after at least 4 weeks on the previous dose	Injection: 0.75 mg/0.5 mL 1.5 mg/0.5 mL 3 mg/0.5 mL 4.5 mg/0.5 mL
Exenatide	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus: Injection (Bydureon®): 2 mg SC once weekly Injection (Byetta®): initial, 5 µg SC BID; maintenance, 10 µg SC BID after one month of therapy	Adjunct to diet and exercise to improve glycemic control in patients ≥10 years of age with type 2 diabetes mellitus: Injection (Bydureon®): 2 mg SC once weekly	Injection: 5 µg/0.02 mL (Byetta®)* 10 µg /0.04 mL (Byetta®)† 2 mg/vial (Bydureon®)‡ 2 mg/pen (Bydureon®)^
Liraglutide	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus, reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus and established cardiovascular disease: Injection: initial, 0.6 mg SC QD for one week; maintenance, 1.2 to 1.8 mg SC QD	Adjunct to diet and exercise to improve glycemic control in patients ≥10 years of age with type 2 diabetes mellitus: initial, 0.6 mg SC QD for one week; maintenance, 1.2 to 1.8 mg SC QD	Injection: 6 mg/mL§
Semaglutide	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus, reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus and established cardiovascular disease: Injection: initial, 0.25 mg SC once weekly for four weeks; maintenance, 0.5 to 2 mg SC once weekly Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus: Tablet: initial, 3 mg once daily for 30 days; maintenance, 7 mg once daily; dose may be increased to 14 mg once daily if additional glycemic control is needed after at least 30 days on the 7 mg dose	Safety and efficacy have not been established in pediatric patients.	Injection: 0.25 or 0.5 mg dose (2 mg/1.5 mL or 2 mg/3 mL) 1 mg/0.75 mL (4 mg/3 mL) 2 mg/0.75 mL (8 mg/3 mL) Tablet: 3 mg 7 mg 14 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Tirzepatide	adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus: Injection: initial, 2.5 mg SC once weekly; after four weeks, increase the dosage to 5 mg SC once weekly; If additional glycemic control is needed, increase the dosage in 2.5 mg increments after at least four weeks on the current dose; maximum dosage is 15 mg SC once weekly	Safety and efficacy have not been established in pediatric patients.	Injection: 2.5 mg/0.5 mL 5 mg/0.5 mL 7.5 mg/0.5 mL 10 mg/0.5 mL 12.5 mg/0.5 mL 15 mg/0.5 mL

BID=twice daily, QD=once daily, SC=subcutaneous
*Supplied as a pre-filled syringe (1.2 mL, 60 doses).
†Supplied as a pre-filled syringe (2.4 mL, 60 doses).
‡Supplied in cartons of four single-dose trays (one vial containing 2 mg exenatide, one pre-filled syringe, one vial connector, and two custom needles).
^Supplied in cartons of four single-dose pens containing 2 mg of exenatide and diluent and including one needle. Each carton contains one spare needle.
§Supplied as 0.6 (30 doses), 1.2 (15 doses), and 1.8 mg (10 doses) pre-filled, multi-dose pens (3 mL) available in a package of two or three pens.

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the incretin mimetics are summarized in Table 12.

Table 12. Comparative Clinical Trials with the Incretin Mimetics

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Type 2 Diabetes – Monotherapy				
Nauck et al.[18] (2016) HARMONY 2 Albiglutide 30 mg or 50 mg once weekly vs placebo	PC, RCT Patients ≥18 years of age with type 2 diabetes uncontrolled by diet and exercise (HbA_{1c} ≥7.0 and ≤10.0%)	N=309 3 years	Primary: Change in HbA_{1c} from baseline to week 52 Secondary: FPG, proportions of patients achieving HbA_{1c} values ≤6.5 and ≤7.0%, weight; safety	Primary: Over 52 weeks of treatment, HbA_{1c} decreased from baseline in both albiglutide groups and increased in the placebo group. The treatment difference (albiglutide minus placebo) of the model-adjusted least-squares mean change in HbA_{1c} from baseline to week 52 was statistically significant for both albiglutide groups (albiglutide 30 mg: −0.84%; 95% CI, −1.11 to −0.58%; P<0.0001; albiglutide 50 mg: −1.04%; 95% CI, −1.31 to −0.77%; P<0.0001). Secondary: Changes in FPG at week 52 were consistent with HbA_{1c} results. The treatment difference was statistically significant for both albiglutide groups (albiglutide 30 mg vs placebo: −1.89 mmol/l; 95% CI, −2.55 to −1.22; P<0.0001; albiglutide 50 mg vs placebo: −2.38 mmol/l; 95% CI, −3.05 to −1.71; P<0.0001). At week 52, the HbA_{1c} treatment goal of <7.0% was met by 49.0, 40.2, and 21.4% of patients treated with albiglutide 30 mg, albiglutide 50 mg and placebo, respectively (both P≤0.0002) and the goal of HbA_{1c} <6.5% was met by 25.0, 24.7, and 10.2% of patients treated with albiglutide 30 mg, albiglutide 50 mg and placebo, respectively (both P<0.005). The difference in the time to hyperglycemia rescue was statistically significant in favor of each albiglutide group (albiglutide 30 mg or 50 mg; P<0.0001). Weight loss was not statistically significantly different when comparing the placebo and albiglutide groups at week 52 (least-squares mean change from baseline −0.39 kg with albiglutide 30 mg, −0.86 kg with albiglutide 50 mg and −0.66 kg with placebo). For the safety profile at week 52, the proportion of patients experiencing adverse events was higher with albiglutide 30 mg and albiglutide 50 mg than with placebo.
Miyagawa et al.[19] (2015)	DB, PC, OL, RCT (blinded to treatment	N=492 52 weeks	Primary: Comparison of change in HbA_{1c}	Primary: At 26 weeks, once-weekly dulaglutide was superior to placebo for HbA_{1c} change from baseline (P<0.001).

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Dulaglutide subcutaneous 0.75 mg once-weekly vs Liraglutide subcutaneous injections uptitrated from 0.3 mg/day during week 1 to 0.6 mg/day during week 2 and 0.9 mg/day starting at week 3 vs placebo	assignment for dulaglutide and placebo but not for liraglutide) Patients with type 2 diabetes ≥20 years of age who were oral antidiabetic medication-naïve (diet and exercise only) or had discontinued oral antidiabetic medication monotherapy (excluding thiazolidinedione).		from baseline at 26 weeks in dulaglutide vs placebo superiority Secondary: Comparison of change in HbA_{1c} from baseline at 26 weeks in dulaglutide vs liraglutide non-inferiority	Secondary: Dulaglutide was non-inferior, but not superior, to once-daily liraglutide ($P_{non\text{-}inferiority}$ <0.001). The LS mean (standard error) changes in HbA_{1c} from baseline to 26 weeks were −1.43% (0.05) for dulaglutide, −1.33% (0.07) for liraglutide, and 0.14% (0.10) for placebo. The LS mean difference between dulaglutide and placebo was −1.57% (95% CI, −1.79 to −1.35) and between dulaglutide and liraglutide was −0.10% (95% CI, −0.27 to 0.07). For each timepoint from baseline to primary endpoint, dulaglutide significantly reduced HbA_{1c} compared with placebo (P<0.001 all timepoints).
Moretto et al.[20] (2008) Exenatide 5 µg BID vs exenatide 10 µg BID vs placebo	DB, PG, RCT Patients ≥18 years of age with type 2 diabetes who were drug naïve and whose diabetes was inadequately controlled on diet and exercise alone	N=232 24 weeks	Primary: HbA_{1c}, fasting serum glucose, six-point self-monitored blood glucose, proportions of patients achieving HbA_{1c} values ≤6.5 and ≤7.0%, weight; HOMA-B, safety Secondary: Not reported	Primary: Mean changes in HbA_{1c} from baseline (LSM) were significantly greater with exenatide 5 and 10 µg compared to placebo (-0.7 and -0.9 vs -0.2%, respectively; P=0.003 and P<0.001 vs placebo). Mean changes in fasting serum glucose from baseline were significantly greater with exenatide 5 and 10 µg compared to placebo (-17.5 and -18.7 vs -5.2 mg/dL, respectively; P=0.029 and P=0.016 vs placebo). Changes in daily mean PPG excursions from baseline to end point were significantly greater with exenatide 5 and 10 µg compared to placebo (-21.3 and -24.7 vs -8.3 mg/dL, respectively; P<0.001 vs placebo for both). With exenatide 5 and 10 µg, 31 and 35% of patients achieved HbA_{1c} ≤6.5% at end point vs 19% of patients receiving placebo (P value not significant and P=0.026, respectively), while 48 and 46 vs 29% of patients achieved HbA_{1c} ≤7.0% (P=0.024 and P=0.036, respectively).

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				Changes in weight at 24 weeks were greater with exenatide 5 and 10 µg compared to placebo (-2.8 and -3.1 vs -1.4 kg, respectively; P=0.004 and P<0.001). HOMA-B values increased from baseline to end point by 32 and 28% with exenatide 5 and 10 µg, respectively, compared to 6% with placebo. Improvements from baseline to end point in HOMA-B were significantly greater with exenatide 5 and 10 µg compared to placebo (P=0.002 and P=0.010, respectively). Significant improvements in mean SBP and DBP from baseline to end point were also observed with exenatide (SBP: exenatide 5 and 10 µg, -3.7 mm Hg; P=0.037, DBP: exenatide 10 µg, -2.3 mm Hg; P=0.046) compared to placebo (SBP: -0.3 mm Hg and DBP: -0.3 mm Hg). Overall, 25% of patients reported at least one treatment-emergent adverse event. Nausea was reported with the greatest incidence (exenatide 5 µg, 3%; exenatide 10 µg, 13%; placebo, 0%; P=0.010 for the combined exenatide group vs placebo). Most (88%) treatment-emergent adverse events were mild or moderate in intensity. Hypoglycemia was reported in five, four, and one percent of patients receiving exenatide 5 and 10 µg and placebo groups, respectively (P value not significant), with no incidents of severe hypoglycemia reported.
DeFronzo et al.[21] (2008) Exenatide 5 µg BID for 1 week, then 10 µg BID for 1 week vs sitagliptin 100 mg QD for 2 weeks	DB, MC, RCT, XO Patients 18 to 70 years of age with type 2 diabetes who were treated with a stable regimen of metformin, HbA_{1c} 7.0 to 11.0%, FPG <280 mg/dL, and BMI 25 to 45 kg/m^2	N=95 4 weeks	Primary: 2-hour PPG Secondary: Postprandial insulin, glucagon, active GLP-1 and TG concentrations, and safety	Primary: The 2-hour PPG concentration (LSM) was lower for exenatide compared to sitagliptin (133 vs 208 mg/dL; P<0.0001). In the ITT population, the 2-hour PPG concentration was lower with exenatide compared to sitagliptin (166 vs 210 mg/dL, respectively; P<0.0001). The change in 2-hour PPG concentration (least square mean) from baseline was -112 mg/dL for exenatide compared to -37 mg/dL for sitagliptin (P<0.0001). FPG was similar following treatment with exenatide (-15 mg/dL) and sitagliptin (-19 mg/dL; P=0.3234).

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All patients were receiving existing metformin regimens.				Following crossover to the alternate therapy, patients switched from exenatide to sitagliptin experienced an increase in mean 2-hour PPG +73 mg/dL. Patients switched from sitagliptin to exenatide treatment experienced a reduction in the mean 2-hour PPG concentration -76 mg/dL. Secondary: The acute insulin response was greater for exenatide compared to sitagliptin (P=0.0017). Both exenatide and sitagliptin reduced the mean postprandial plasma glucagon concentration compared to baseline; however, the reduction was greater with exenatide compared to sitagliptin (P=0.0011). Both exenatide and sitagliptin both reduced mean postprandial TG concentrations compared to baseline; however, the decrease was greater with exenatide compared to sitagliptin (P=0.0118). Exenatide reduced the rate of gastric emptying compared to baseline and to sitagliptin (P<0.0001). Sitagliptin had no effect on gastric emptying). Adverse events with exenatide and sitagliptin were mild-to-moderate. The most common adverse events were gastrointestinal with both treatments. Nausea was experienced by 34% of patients treated with exenatide and 12% of patients treated with sitagliptin. Vomiting was experienced by 24% of patients treated with exenatide and 3% of patients treated with sitagliptin. No serious treatment-emergent adverse events were reported during the study.
Bergenstal et al.[22] (2009) Exenatide 5 µg BID for 4 weeks, then 10 µg BID vs insulin aspart 12 units QD before	OL, PG, RCT Patients 18 to 80 years of age with type 2 diabetes mellitus and HbA_{1c} ≥8%, insulin-naïve, and receiving treatment with metformin and a sulfonylurea for at least 3 months prior	N=372 24 Weeks	Primary: Change in HbA_{1c} from baseline Secondary: FPG, eight-point plasma glucose profiles, changes in body weight	Primary: At 24 weeks, HbA_{1c} values were 7.61, 7.75, 8.46% for BIAsp 30 BID, BIAsp 30 QD, and exenatide, respectively (both P<0.0001 compared to exenatide). At the end of the study, 37% of patients in the BIAsp 30 BID group achieved an HbA_{1c} <7.0% compared to 20% of patients in the exenatide group (P=0.0060). Additionally, 25% of patients in the BIAsp 30 BID group achieved an HbA_{1c} ≤6.5% compared with 8% in the exenatide group (P=0.0004). At the end of the study, 26% of patients in the BIAsp 30 QD group achieved an HbA_{1c} <7.0% compared to 20% of patients in the exenatide group

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dinner (BIAsp 30 QD) vs insulin aspart 12 units divided equally before breakfast and dinner (BIAsp 30 BID) All patients were receiving metformin with or without a sulfonylurea. Insulin dose was titrated as necessary.	to enrolling in the study			(P=0.3488). Additionally, 12% of patients in the BIAsp 30 QD group achieved an HbA_{1c} ≤6.5% compared with 8% in the exenatide group (P=0.3802). The percentage of patients who achieved HbA_{1c} ≤6.5% was higher with BIAsp 30 BID compared to BIAsp 30 QD (25 vs 12%; P=0.0122). Secondary: There were significant changes in FPG with BIAsp 30 BID (-62.7 mg/dL; P<0.0001 vs exenatide) and BIAsp 30 QD (-52.4 mg/dl; P=0.0002 vs exenatide) compared to exenatide (-21.4 mg/dL). At the end of the study, the eight-point plasma glucose profiles were significantly lower with BIAsp 30 BID and BIAsp 30 QD than exenatide. At 24 weeks, hypoglycemia was reported in 56% of patients in the BIAsp 30 QD group, 61% of patients in the BIAsp 30 BID group, and 29% in the exenatide group. Weight loss was reported in the exenatide group (-1.9 kg) compared with weight gain in the BIAsp 30 QD (+2.8 kg) and BIAsp 30 BID (4.1 kg). There were more reports of nausea and vomiting with exenatide than in the insulin groups.
Xu et al.[23] (2015) CONFIDENCE Exenatide twice daily vs insulin (75% insulin lispro protamine suspension and 25% insulin lispro	MC, PG, RCT Treatment-naïve patients 30 to 70 years of age with newly diagnosed type 2 diabetes	N=416 48 weeks	Primary: Change in baseline HbA_{1c} Secondary: Effects on weight, blood pressure, lipid profiles and β-cell function	Primary: At week 48, mean HbA_{1c} changes from baseline were −1.8% (95% CI, −1.55 to −2.05%) with exenatide, −1.7% (95% CI, −1.52 to −1.96%) with insulin and −1.5% (95% CI, −1.23 to −1.71%) with pioglitazone. Treatment differences were −0.20% (95% CI, −0.46 to 0.06%) for exenatide vs insulin (P=0.185), and −0.37% (95% CI, −0.63 to −0.12%) for exenatide vs pioglitazone (P=0.002). Secondary: Mean weight change was significantly different between the exenatide group and the insulin and pioglitazone groups from weeks four and eight until the end of the study, with weight decreasing in the exenatide group. Decreases in mean systolic and diastolic blood pressures at 48 weeks were not statistically different between groups, although significant decreases in systolic and

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injection) twice daily vs pioglitazone once daily				diastolic blood pressures were observed with exenatide (P<0.05 vs baseline), and a significant decrease in diastolic blood pressure alone was found with pioglitazone (P<0.001). Exenatide treatment resulted in improvements in overall lipid profiles, with significant decreases in TG, total cholesterol and LDL cholesterol levels, and an increase in HDL cholesterol (P<0.05 vs baseline for all variables). HDL cholesterol increased with pioglitazone (P<0.001), and LDL cholesterol decreased with insulin (P<0.05). At week 48, HOMA-B (which, together with fasting proinsulin-to-insulin ratio (PI/I), provides an indication of β-cell function during the fasting state) increased in patients treated with insulin (P<0.001 vs baseline). Improvements from baseline were similar in all treatment groups with regard to PI/I, as well as acute insulin response (AIR, which represents β-cell function during the stimulated state after intravenous glucose injection). Disposition index (DI), which provides a measure of β-cell function during the stimulated state under near-physiological conditions of food intake via the gastrointestinal system, increased significantly in all treatment groups (P<0.001 vs baseline for exenatide; P<0.05 vs baseline for insulin and pioglitazone). The greatest mean improvements from baseline in DI and AIR were observed in the exenatide treatment group.
Russell-Jones et al.[24] (2012) DURATION-4 Exenatide ER 2 mg SC once weekly vs metformin 2,000 mg/day vs pioglitazone 45 mg/day vs	DB, DD, MC, PG, RCT Drug-naïve (patients excluded if treated with any antihyperglycemic drug for >7 days within 3 months of screening) adult type 2 diabetics with HbA_{1c} 7.1 to 11.0%, BMI 23 to 45 kg/m^2, and stable weight	N=820 26 weeks	Primary: Change in baseline HbA_{1c} Secondary: Proportion of patients achieving HbA_{1c} <7.0 and ≤6.5%, fasting serum glucose, seven-point self-monitored glucose concentrations, weight, lipid profile, insulin profile, safety and tolerability,	Primary: Decreases in HbA_{1c} were -1.53±0.07, -1.48±0.07, -1.63±0.08, and -1.15±0.08% with exenatide ER, metformin (P=0.620 vs exenatide ER), pioglitazone (P=0.328 vs exenatide ER), and sitagliptin (P<0.001 vs exenatide ER). The HbA_{1c} at trial end was 6.94±0.07, 6.99±0.07, 6.84±0.08, and 7.32±0.08% with exenatide ER, metformin, pioglitazone, and sitagliptin, respectively. Secondary: Similar proportions of patients receiving exenatide ER and metformin achieved HbA_{1c} <7.0% (63 vs 55%; P value not reported). A significantly greater proportion of patients receiving exenatide ER achieved HbA_{1c} <7.0% compared to patients receiving sitagliptin (63 vs 43%; P<0.001), and ≤6.5% compared to patients receiving metformin (49 vs 36%; P=0.004) and sitagliptin, respectively (49 vs 26%; P<0.001). Decreases in fasting serum glucose at weeks 16 and 26 were significantly greater with exenatide ER compared to sitagliptin (P<0.001 for both). There

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sitagliptin 100 mg/day			patient-reported QOL	were no differences observed with exenatide ER compared to metformin (P=0.155 at week 26) and pioglitazone (P=0.153 at week 26). Seven-point self-monitored glucose concentrations demonstrated similar decreases with exenatide ER, metformin, and pioglitazone. Exenatide ER demonstrated greater decreases at all time points compared to sitagliptin. Mean decreases in post-meal excursions after 26 weeks were similar among all treatments. Decreases in weight were significantly greater with exenatide ER compared to pioglitazone and sitagliptin by weeks four and eight, and the effect was sustained through 26 weeks (P≤0.003 for all). There was no difference between exenatide ER and metformin after 26 weeks (-2.0 vs -2.0 kg; P=0.892). No clinically significant changes in serum lipids were observed with any treatment. Mean HOMA-B was significantly improved with exenatide ER compared to metformin, pioglitazone, and sitagliptin (P<0.001 for all). HOMA-S significantly improved with metformin and pioglitazone compared to exenatide ER (P<0.001 for both), and the change with exenatide ER was similar to sitagliptin (P=0.329). Serious adverse events were reported in 1.6, 5.3, 5.5, and 1.8% of patients receiving exenatide ER, metformin, pioglitazone, and sitagliptin, respectively. No serious adverse event was reported by more than one patient. Treatment-emergent adverse events reported by at least five percent of patients in any group included headache (highest with metformin), diarrhea (highest with metformin), injection site nodule (highest with exenatide ER), nasopharyngitis (highest with sitagliptin), nausea (highest with exenatide ER), dyspepsia (highest with exenatide ER), constipation (highest with exenatide ER), back pain (highest with metformin), arthralgia (highest with exenatide ER), hypertension (highest with pioglitazone), and peripheral edema (highest with pioglitazone). No major hypoglycemia was reported. One patient receiving sitagliptin with elevated lipase at screening experienced moderate chronic pancreatitis after eight days and discontinued from study treatment.

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				All treatments resulted in improvements in perceived treatment satisfaction, weight-related QOL, and binge eating behavior. All treatments, except pioglitazone, resulted in significant improvements in health status. Significant improvements in weight-related QOL, binge eating behavior, and health status were reported with exenatide ER compared to pioglitazone (P values not reported).
Fonseca et al.[25] (2012) GETGOAL-MONO Lixisenatide 10 µg QD for week, 15 µg QD for one week and then 20 µg QD thereafter vs lixisenatide 10 µg QD for two weeks, then 20 µg QD thereafter vs placebo	DB, MC, PC, PG, RCT Patients 20 to 85 years of age with type 2 DM not receiving glucose-lowering therapy and a HbA_{1c} ≥7% to ≤10%	N=361 12 weeks	Primary: HbA_{1c} Secondary: FPG, changes in body weight and safety evaluations	Primary: The one-step protocol arm resulted in greater decreases from baseline compared to placebo (-0.83% vs -0.18%, 95% CI, -0.903 to -0.399; P<0.0001) Secondary: While the FPG similarly decreased greater than placebo, there was no significant change in weight from baseline between the two groups (-1.94 kg vs -2.03 kg in the one-step protocol). The most common adverse events were gastrointestinal-nausea was the most frequent (lixisenatide 23% overall, placebo: 4.1%). Symptomatic hypoglycemia occurred in 1.7% of lixisenatide and 1.6% of placebo patients, with no severe episodes.
Sorli et al.[26] (2017) SUSTAIN 1 Semaglutide 0.5 mg SC weekly vs semaglutide 1 mg SC weekly	DB, MC, PC, PG, RCT Patients ≥18 years with type 2 DM inadequately controlled with diet and exercise and an HbA_{1c} ≥7% to ≤10%	N=388 30 weeks	Primary: HbA_{1c} Secondary: Change in body weight, FPG, SMPG, BMI, waist circumference and safety evaluations.	Primary: Monotherapy with semaglutide 0.5 mg and 1 mg once weekly resulted in a statistically significant reduction in HbA_{1c} compared with placebo (-1.4% and -1.6% vs -0.1%; P<0.001 for both comparisons). Secondary: The mean changes in body weight from baseline to week 30 were -1.2 kg, -3.8 kg and -4.7 kg in the placebo, semaglutide 0.5 mg, and 1 mg arms, respectively. The difference from placebo (95% CI) for semaglutide 0.5 mg was -2.6 kg (-3.8, -1.5; P<0.0001), and for 1 mg was -3.5 kg (95% CI, -4.8 to -2.2; P<0.0001).

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vs placebo Subjects with unacceptable hyperglycemia were to be offered metformin (first choice) or other antidiabetic medications (not GLP-1, DPP-4 inhibitors or amylin analogs) as add-on to their randomized treatment (rescue medication) at the discretion of the investigator.				The semaglutide groups had significantly greater reductions in FPG, mean 7-point SMPG, mean prandial increment (across all meals) of the 7-point SMPG (only semaglutide 1 mg), BMI and waist circumference. There were also significantly greater odds of achieving A_{1c} targets and categorical weight loss targets with semaglutide 0.5 mg or 1 mg compared with placebo. The most frequently reported adverse events in both semaglutide groups were gastrointestinal in nature: nausea was reported in 26 (20%) who received 0.5 mg semaglutide, 31 (24%) who received 1.0 mg semaglutide, and 10 (8%) who received placebo, and diarrhoea was reported in 16 (13%) who received 0.5 mg semaglutide, 14 (11%) who received 1.0 mg semaglutide, and three (2%) who received placebo.
Aroda et al.[27] (2019) PIONEER 1 Semaglutide 3 mg orally QD vs semaglutide 7 mg orally QD vs semaglutide 14 mg orally QD	DB, MC, PC, PG, RCT Adults with type 2 DM insufficiently controlled with diet and exercise and HbA_{1c} 7.0 to 9.5%	N=703 26 weeks	Primary: Change in HbA1c from baseline Secondary: Changes in measures of glucose control, achievement of an HbA1c target of ,7% or ≤6.5% and achievement of weight loss of at least 5% or 10%,	Primary: Monotherapy with 7 mg and 14 mg once daily for 26 weeks resulted in a statistically significant reduction in HbA_{1c} compared with placebo (-1.2% and -1.4% vs -0.3%, respectively; P<0.001 for both comparisons). Secondary: Both strengths were also associated with decreased in body weight (-2.3 kg and -3.7 kg vs -1.4 kg, respectively; P<0.001 for both comparisons). Other secondary endpoints involving measures of glycemic control, weight loss and lipid levels favored semaglutide over placebo. Mild-to-moderate transient GI events were the most common adverse events with oral semaglutide.

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vs placebo All patients randomized to oral semaglutide initiated treatment with 3 mg QD with dose escalations every four weeks until the randomized maintenance dose was achieved.			as well as C-reactive protein, fasting lipid levels from baseline	
Fakhoury et al.[28] (2010) Incretin-based therapies (exenatide, liraglutide, vildagliptin,* and sitagliptin) vs placebo	MA (38 RCTs: 8, exenatide; 7, liraglutide; 12, sitagliptin; 11, vildagliptin) Type 2 diabetics ≥18 years of age	N=Not reported Duration varied (4 to 52 weeks	Primary: Change in baseline HbA_{1c} and weight, hypoglycemia Secondary: Not reported	Primary: Sitagliptin (WMD, -0.79; 95% CI, -0.93 to -0.65; P<0.001) significantly decrease HbA_{1c} compared to placebo. Exenatide (WMD, -0.75; 95% CI, -0.83 to -0.67; P<0.001) and liraglutide (WMD, -1.03; 95% CI, -1.16 to -0.90; P<0.0010) significantly decreased baseline HbA_{1c}. In the adjusted analyses for exenatide, controlling for whether exenatide was given as monotherapy or in combination with another treatment provided the most variability, but even this estimate fell within the boundaries of the unadjusted model CI (WMD, -0.84; 95% CI, -0.95 to -0.73; P<0.001). In the adjusted analyses for liraglutide, no covariates were found to be significant. There was significant weight gain with sitagliptin (WMD, 0.60; 95% CI, 0.33 to 0.87; P<0.001) compared to placebo. Exenatide (WMD, -1.10; 95% CI, -1.32 to -0.88; P<0.001) and liraglutide (WMD, -0.82; 95% CI, -1.92 to -0.27; P=0.142) both exhibited reduction in weight. The most remarkable result is the average weight reduction of 1.10 kg observed with exenatide. Sitagliptin-treated patients were 156% more likely to experience some hypoglycemia compared to placebo treated patients (RR, 2.56; 95% CI, 1.23 to 5.33; P=0.01). When adjusted for covariates, age was the only variable found to be significant (RR, 1.84; 95% CI, 1.02 to 3.34; P=0.044). Exenatide-

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				treated patients were 140% more likely to experience some hypoglycemia compared to placebo treated patients (RR, 2.40; 95% CI, 1.39 to 4.11; P=0.002). Liraglutide-treated patients were 69% more likely to experience some hypoglycemia compared to placebo treated patients (RR, 1.69; 95% CI, 1.00 to 2.86; P=0.050). Secondary: Not reported
Monami et al.[29] (2011) GLP-1 receptor agonist based therapies (albiglutide, exenatide, liraglutide, lixisenatide*, semaglutide*, and taspoglutide*) vs other classes of antidiabetic medications or placebo	MA Type 2 diabetics	N=10,485 Up to 52 weeks	Primary: Major cardiovascular events Secondary: Not reported	Primary: GLP-1 receptor agonists are not associated with an increased risk of cardiovascular events (OR, 0.74; 95% CI, 0.50 to 1.08; P=0.12). Exenatide is not associated with an increased risk of cardiovascular events (OR, 0.85; 95% CI, 0.50 to 1.45; P=0.55). Liraglutide is not associated with an increased risk of cardiovascular events (OR, 0.69; 95% CI, 0.40 to 1.22; P=0.20). In PC trials, GLP-1 receptor agonists reduced the risk of cardiovascular events (OR, 0.46; 95% CI, 0.25 to 0.83; P=0.009). In AC trials, there was no difference between treatments in the risk of cardiovascular events (OR, 1.05; 95% CI 0.63 to 1.76; P=0.84). Secondary: Not reported
Shyangdan et al.[30] (2011) GLP-1 receptor agonist based therapies (albiglutide, exenatide ER, liraglutide, lixisenatide*,	MA (RCTs) Type 2 diabetics ≥18 years of age	N=not reported 8 to 26 weeks	Primary: Change in baseline HbA_{1c}, incidence of hypoglycemia, weight change Secondary: Health-related QOL, safety, mortality, morbidity, BP,	Primary: Change in baseline HbA_{1c} Exenatide ER significantly decreased HbA_{1c} compared to TZDs (-1.5 vs -1.2%; P=0.02), DPP-4 inhibitors (-1.5 vs -0.9%; P<0.0001), and insulin glargine (-1.5 vs -1.3%; treatment difference, -0.2%; 95% CI, -0.35 to -0.05; P=0.03). There was no difference in the proportion of patients achieving an HbA_{1c} <7.0% between exenatide ER and TZDs (60 vs 52%; P=0.15). A significantly greater proportion of patients receiving exenatide ER achieved an HbA_{1c} <7.0% compared to patients receiving DPP-4 inhibitors (60 vs 35%; P<0.0001) and patients receiving insulin glargine (60 vs 48%; P=0.03).

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semaglutide*, and taspoglutide*) vs non-GLP-1 receptor based therapies (placebo, TZDs, DPP-4 inhibitors, insulin glargine, and sulfonylureas)			FPG, PPG, lipid profile, β cell function	Compared to placebo, treatment with liraglutide 1.2 mg significantly decreased HbA_{1c} (-1.15%; 95% CI, -1.33 to -0.96; P<0.00001). Patients receiving liraglutide 1.2 mg were more likely to achieve an HbA_{1c} <7.0% compared to patients receiving placebo (OR, 2.91; 95% CI, 1.74 to 4.87; P<0.05). Liraglutide 1.2 mg decreased HbA_{1c} to a greater extent compared to TZDs (-0.64%; 95% CI -0.83 to -0.45; P value not reported). The likelihood of achieving an HbA_{1c} <7.0% was greater with liraglutide 1.2 mg compared to TZDs (OR, 1.60; 95% CI, 1.18 to 2.15; P value not reported). Liraglutide 1.2 mg decreased HbA_{1c} to a greater extent compared to DPP-4 inhibitors (-0.34%; 95% CI -0.53 to -0.15; P value not reported). The likelihood of achieving an HbA_{1c} <7.0% was greater with liraglutide 1.2 mg compared to DPP-4 inhibitors (OR, 2.56; 95% CI, 1.94 to 3.37; P value not reported). Liraglutide 1.2 mg was not associated with a decrease in HbA_{1c} compared to sulfonylureas (-0.01%; 95% CI, -0.27 to 0.29; P value not reported). The likelihood of achieving an HbA_{1c} <7.0% was not greater with liraglutide 1.2 mg compared to sulfonylureas (OR, 0.98; 95% CI, 0.84 to 1.14; P=0.78). Compared to placebo, liraglutide 1.8 mg significantly decreased an HbA_{1c} (-1.15%; 95% CI, -1.31 to -0.99; P<0.05). Patients receiving liraglutide 1.8 mg were more likely to achieve HbA_{1c} <7.0% compared to patients receiving placebo (OR, 3.25; 95% CI, 1.97 to 5.36; P<0.05). Liraglutide 1.8 mg decreased HbA_{1c} to a greater extent compared to TZDs (-0.69%; 95% CI -0.88 to -0.50%; P value not reported). The likelihood of achieving an HbA_{1c} <7.0% was greater with liraglutide 1.8 mg compared to TZDs (OR, 1.91; 95% CI, 1.43 to 2.53; P value not reported). Liraglutide 1.8 mg decreased HbA_{1c} to a greater extent compared to DPP-4 inhibitors (-0.60%; 95% CI -0.78 to -0.42; P value not reported). The likelihood of achieving HbA_{1c} <7.0% was greater with liraglutide 1.8 compared to DPP-4 inhibitors (OR, 1.99; 95% CI, 1.48 to 2.66; P value not reported). Liraglutide 1.8 mg was not associated with a reduction in HbA_{1c} compared to sulfonylureas (-0.02%; 95% CI -0.30 to 0.26; P value not reported). The likelihood of achieving an HbA_{1c} <7.0% was not greater with liraglutide 1.8 mg compared to sulfonylureas (OR, 1.09; 95% CI, 0.94 to 1.26; P=0.27). Liraglutide decreased HbA_{1c} to a greater extent compared to insulin glargine (-0.24%; 95% CI, -0.49 to 0.01; P value not reported). The likelihood of achieving an HbA_{1c} <7.0% was not different between insulin glargine and liraglutide (OR, 1.16; 95% CI, 0.96 to 1.40; P value not reported).

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				Liraglutide 1.2 mg was associated with a non-significant increase in HbA_{1c} compared to 1.8 mg (0.10%; 95% CI, -0.03 to 0.23; P=0.13). Patients receiving liraglutide 1.2 mg were not more likely to achieve an HbA_{1c} <7.0% compared to the 1.8 mg dose (P=0.92). Incidence of hypoglycemia The incidence of minor hypoglycemia was similar between exenatide ER and TZDs. The incidence of minor hypoglycemia was higher with DPP-4 inhibitors (five vs two patients) and insulin glargine (26 vs 8%) compared to exenatide ER. The incidence of major hypoglycemia was higher with insulin glargine compared to exenatide ER (two vs one patients). Overall, there was no difference in the incidence of minor hypoglycemia between liraglutide 1.2 mg and placebo (P=0.42), and there was significantly more hypoglycemia with liraglutide 1.8 mg (OR, 1.66; 95% CI, 1.15 to 2.40; P=0.007). The incidence of minor hypoglycemia was higher with insulin glargine compared to liraglutide (29 vs 27%). Liraglutide was associated with a significantly higher rate of minor hypoglycemia compared to TZDs (P=0.048), and similar rates compared to DPP-4 inhibitors (P values not reported). Liraglutide was associated with a significantly lower incidence of hypoglycemia compared to sulfonylureas (P<0.00001). Weight loss Exenatide ER significantly decreased weight compared to TZDs (-2.3 vs 2.8 kg; P<0.00001), DPP-4 inhibitors (-2.3 vs -0.8 kg; P=0.0009), and insulin glargine (-2.6 vs 1.4 kg; P<0.00001). Patients receiving liraglutide 1.2 mg experienced an average weight loss of -0.75 kg (95% CI, -1.95 to 0.45; P=0.22). Liraglutide 1.2 mg was associated with a greater decrease in weight compared to insulin glargine (-3.40 kg; 95% CI, -4.31 to -2.49; P value not reported), TZDs (-3.40 kg; 95% CI, -4.31 to -2.49; P value not reported), DPP-4 inhibitors (-1.90 kg; 95% CI, -2.65 to -1.15; P value not reported), and sulfonylureas (-3.60 kg; 95% CI, -4.15 to -3.05; P value not reported). Patients receiving liraglutide 1.8 mg experienced a significant weight loss compared to placebo (-1.33 kg; 95% CI, -2.38 to 0.27; P=0.0014). Liraglutide

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				1.8 mg was associated with a greater decrease in weight compared to TZDs (-2.30 kg; 95% CI, -2.85 to -1.75; P value not reported), DPP-4 inhibitors (-2.42 kg; 95% CI, -3.17 to -1.67; P value not reported), and (-3.80 kg; 95% CI, -4.35 to -3.25; P value not reported). Patients were more likely to experience weight gain with liraglutide 1.2 mg compared to 1.8 mg (0.48 kg; 95% CI, 0.16 to 0.80; P value not reported). Secondary: Data on mortality and morbidity were not reported for any treatment. QOL Exenatide ER significantly improved weight-related QOL and IWQOL total scores compared to TZDs (IWQOL treatment difference, 3.94; 95% CI, 1.28 to 6.61; P=0.0038). Both exenatide ER (IWQOL total score, 5.15; 95% CI, 3.11 to 7.19) and DPP-4 inhibitors (4.56; 95% CI, 2.56 to 6.57) resulted in significant improvements in weight-related QOL and IWQOL total scores. Treatment satisfaction was significantly greater with exenatide ER compared to DPP-4 inhibitors (treatment difference, 1.61; 95% CI, 0.07 to 3.16; P=0.0406). Exenatide ER significantly improved the self-esteem IWQOL domain and one EQ-5D dimensions compared to insulin glargine. Data for liraglutide were not reported. Safety Withdrawals due to adverse events were greater with exenatide ER compared to TZDs (6.9 vs 3.6%), DPP-4 inhibitors (6.9 vs 3.0%), and insulin glargine (4.7 vs 0.9%). More serious adverse events occurred with TZDs (6 vs 3%) compared to exenatide ER. The incidence of serious adverse events was similar between exenatide ER and DPP-4 inhibitors (3 vs 3%) and insulin glargine (5 vs 4%). Compared to placebo, withdrawals due to adverse events were between 5 and 10% with liraglutide 1.2 mg and between 4 and 15% with liraglutide 1.8 mg. Withdrawals were also higher with liraglutide compared to sulfonylureas (9.4 to 12.9 vs 1.3 to 3.0%). Liraglutide was associated with more gastrointestinal adverse events (nausea, vomiting, and diarrhea) compared to insulin glargine, TZDs, DPP-4 inhibitors, and sulfonylureas.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				BP There was no difference in the decreases in SBP and DBP between exenatide ER and TZDs. Exenatide ER significantly decreased SBP compared to DPP-4 inhibitors (treatment difference, -4 mm Hg; 95% CI, -6 to -1; P=0.0055). There was no difference in the decrease in DBP between treatments. Data comparing exenatide ER and insulin glargine were not reported. Liraglutide 1.2 mg did not significantly decrease SBP (P=0.15) compared to placebo (P=0.15) and DPP-4 inhibitors (P=0.76). Liraglutide 1.8 mg significantly decreased SBP (P=0.05) compared to placebo, but not DPP-4 inhibitors (P=0.86). Liraglutide also significantly decreased SBP compared to insulin glargine (P=0.0001) and sulfonylureas (P value not reported). No difference in SBP was observed between liraglutide and DPP-4 inhibitors. There was no difference between liraglutide in the decrease in DBP compared to placebo, insulin glargine, or sulfonylureas. DPP-4 inhibitors significantly decreased DBP compared to liraglutide 1.8 mg (P value not reported). Data comparing liraglutide and TZDs were not reported. FPG There was no difference in the decrease in FPG between exenatide ER and TZDs (-1.8 vs -1.5 mmol/L; P=0.33). Exenatide ER significantly decreased FPG compared to DPP-4 inhibitors (-0.90 mmol/L; 95% CI, -1.50 to -0.30; P=0.0038), and insulin glargine significantly decreased FPG compared to exenatide ER (-0.70 mmol/L; 95% CI, 0.14 to 1.26; P=0.01). Liraglutide significantly decreased FPG compared to placebo (1.2 mg; P<0.0001 and 1.8 mg; P<0.00001), TZDs (P≤0.006), and DPP-4 inhibitors (P<0.00001). There was no difference between liraglutide and insulin glargine or sulfonylureas in decreases in FPG (P value not reported). PPG There was no difference in the decrease in PPG between exenatide ER and TZDs. Exenatide ER significantly decreased PPG at all measurements on a 6-point self-monitored glucose concentrations profile compared to DPP-4 inhibitors (P<0.05). Both exenatide ER and insulin glargine decreased PPG at all eight time points, with significant difference in favor of exenatide ER after

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				dinner (P=0.004) and insulin glargine at 03000 hour (P=0.022) and before breakfast (P<0.0001). Liraglutide significantly decreased PPG compared to placebo (P value not reported), TZDs (P<0.05), and sulfonylureas (liraglutide 1.8 mg; P<0.0001). There was no difference between liraglutide and insulin glargine in decreases in PPG (P value not reported). It was reported that PPG recorded in trials comparing liraglutide and DPP-4 inhibitors was highly variable. Lipid profile TZDs significantly decreased TG compared to exenatide ER. Exenatide ER decreased TC and LDL-C, while TZDs and DPP-4 inhibitors increased these measures. All treatments increased HDL-C. Data comparing exenatide ER and insulin glargine were not reported. Compared to placebo, liraglutide 1.2 decreased TG (P<0.05) and LDL-C (P<0.05), and no difference was observed with liraglutide 1.8 mg. Data comparing liraglutide to insulin glargine, TZDs, DPP-4 inhibitors, and sulfonylureas were not reported. β cell function Data for exenatide ER are not reported. Liraglutide significantly improved HOMA-B compared to placebo (P value not reported), TZDs (P<0.05), and DPP-4 inhibitors (P value not reported); and proinsulin:insulin ratio compared to placebo (P value not reported), insulin glargine (P=0.0019), and TZDs (P≤0.02). There was no difference between liraglutide and sulfonylureas in the improvements in HOMA-B and proinsulin:insulin ratio.
Pinelli et al.[31] (2011) GLP-1 receptor agonist, long-acting formulations at maximum doses (liraglutide, exenatide ER, albiglutide*, and lixisenatide*)	MA, SR (5 RCTs) Adult type 2 diabetics	N=not reported Duration varied (not reported)	Primary: Change in baseline HbA_{1c}, FPG, PPG, weight, BP, and lipid profile; safety Secondary: Not reported	Primary: Pooled analysis demonstrates modest decreases in HbA_{1c} favoring long-acting GLP-1 receptor agonists over exenatide (WMD, -0.47%; 95% CI, -0.69 to -0.25) and sitagliptin (WMD, -0.60%; 95% CI, -0.75 to -0.45). Long-acting GLP-1 receptor agonists were significantly more likely to achieve HbA_{1c} <7.0% compared to exenatide (OR, 2.14; 95% CI, 1.38 to 3.34) and sitagliptin (OR, 3.84; 95% CI, 2.78 to 5.31). Pooled analysis demonstrates significant decreases in FPG favored long-acting GLP-1 receptor agonists compared to exenatide (WMD, -18.39 mg/dL;

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vs exenatide and sitagliptin				95% CI, -24.67 to -12.10) and sitagliptin (WMD, -20.96; 95% CI, -27.88 to -14.04). In one trial, exenatide achieved significantly greater decreases in PPG compared to exenatide ER (-124 vs -95 mg/dL; P=0.01). In another trial, exenatide achieved significantly greater decreases in PPG after breakfast (treatment difference, -24 mg/dL; P<0.0001) and dinner (-18 mg/dL; P=0.0005) compared to liraglutide. There was no difference between treatments after lunch. In a third trial, exenatide ER significantly decreased PPG after each meal compared to sitagliptin (P<0.05). Pooled analysis demonstrates significant decreases in weight with long-acting GLP-1 receptor agonists compared to sitagliptin (WMD, -1.99 kg; 95% CI, -2.69 to -1.09), but not exenatide (WMD, -0.48 kg; 95% CI, -1.11 to 0.44). In one trial, exenatide ER significantly decreased SBP compared to sitagliptin (treatment difference, -4 mm Hg; P=0.006), but results were not significant in the three other trials (P values not reported). One trial demonstrated sitagliptin significantly decreased DBP compared to liraglutide (-1.78 vs 0.07 mm Hg; P=0.02). Between-group differences were not significant in the other three trials (P values not reported). Long-acting GLP-1 receptor agonists significantly improved TC compared to other incretin-based therapy in two of four trials. Exenatide ER significantly decreased TC (-12.0 vs -3.9 mg/dL; P value not reported) and LDL-C (-5.0 vs 1.2 mg/dL) compared to exenatide. Liraglutide significantly decreased TC compared to sitagliptin (-6.60 vs -0.77 mg/dL; P=0.03). In one trial, long-acting GLP-1 receptor agonists significantly improved TG compared to incretin-based therapy (-36 with liraglutide vs -20 mg/dL with exenatide ER; P=0.05). No episodes of severe hypoglycemia were reported in four of the trials. In another trial, two patients receiving exenatide experienced severe hypoglycemia. Non-severe hypoglycemia occurred infrequently and in similar amounts among the treatments. The most commonly reported adverse events with long-acting GLP-1 receptor agonists were gastrointestinal-related. Compared to exenatide, the incidence of vomiting was significantly decreased with long-acting GLP-1 receptor agonists (OR, 0.55; 95% CI, 0.34

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				to 0.89), there was a trend towards decreased nausea (OR, 0.58; 95% CI, 0.32 to 1.06), and no difference in diarrhea (OR, 1.03; 95% CI, 0.67 to 1.58). Nausea (OR, 4.70; 95% CI, 1.81 to 12.24), vomiting (OR, 3.22; 95% CI, 1.63 to 6.36), and diarrhea (OR, 2.32; 95% CI, 1.42 to 3.81) with long-acting GLP-1 receptor agonists were increased compared to sitagliptin. Compared to exenatide, exenatide ER caused more injection site pruritus in two trials (17.6 vs 1.4%), in another trial exenatide had a similar rate of injection site reactions compared to placebo injection (10 vs 7%). Acute pancreatitis was not reported in any trial. One patient receiving liraglutide experienced mild pancreatitis after 88 days of treatment. Secondary: Not reported
Monami et al.[32] (2008) Metformin vs sulfonylureas, α-glucosidase inhibitors, TZDs, glinides, GLP-1 agonists	MA Patients with type 2 diabetes mellitus	N=7,890 (27 RCT) Variable duration	Primary: Reduction in HbA_{1c} at 16 to 36 months Secondary: Not reported	Primary: Combining the results of different placebo-controlled trials, sulfonylurea, α-glucosidase inhibitors, and TZDs led to a reduction in HbA_{1c} by -0.85% (95% CI, 0.78 to 0.94], -0.61% (95% CI, 0.55 to 0.67), and -0.42% (95% CI, 0.40 to 0.44), respectively when combined with metformin. In direct comparisons, sulfonylureas led to a greater reduction in HbA_{1c} (0.17%; 95% CI, 0.16 to 0.18; P<0.05) than TZDs. Differences between sulfonylureas and α-glucosidase inhibitors, and between α-glucosidase inhibitors and TZDs, were not statistically significant. Secondary: Not reported
Type 2 Diabetes – Combination Therapy (or monotherapy and combination therapy combined results)				
Pratley et al.[33] (2014) HARMONY-7 Albiglutide 30 mg SC weekly; with titration to 50 mg SC weekly starting at week 6 vs	IN, MC, PG, OL, RCT Patients ≥18 years with type 2 diabetes (i.e., HbA_{1c} ≥7.0 and ≤10.0%) uncontrolled on metformin, thiazolidinediones, sulfonylureas, or	N=841 32 weeks	Primary: Change in HbA_{1c} from baseline at week 32 for albiglutide vs liraglutide Secondary: HbA_{1c} change from baseline over time, change in FPG	Primary: At week 32, HbA_{1c} had decreased significantly from baseline in both groups. The mean HbA_{1c} level (SD) among the albiglutide-treated group decreased from 8.18% (0.89) at baseline to 7.39% (1.11) at week 32; corresponding to a treatment difference of -0.79%. The mean HbA_{1c} level (SD) among the liraglutide-treated group decreased from 8.15% (0.84) at baseline to 7.18% (1.08) at week 32; corresponding to a treatment difference of -0.98%. The treatment difference for albiglutide vs liraglutide was 0.21% (95% CI, 0.08 to 0.34; P=0.0846). Since the upper bound of the 95% CI for the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
liraglutide SC QD dosed as 0.6 mg in week one, 1.2 mg in week 2, and 1.8 mg thereafter Note: The study was comprised of four phases: screening, 4 weeks of run-in and stabilization, 32 weeks of treatment, and 8 weeks of post-treatment follow-up.	any combination of these therapies, and a BMI ≥20 kg/m² and <45 kg/m²		from baseline over time, the proportion of patients meeting HbA_{1c} treatment goals <7.0% and <6.5%, time to hyperglycemia rescue, and change in bodyweight from baseline	treatment difference exceeded the prespecified non-inferiority margin of 0.3%, the criteria for non-inferiority of albiglutide were not met. Subgroup analyses on the primary efficacy endpoint (i.e., baseline HbA_{1c}, sex, race, ethnicity, age, diabetes duration, and background oral antidiabetic drugs) were consistent with the primary endpoint for the overall population. Secondary: At week 32, HbA_{1c} had decreased significantly from baseline in both groups. The mean HbA_{1c} level (SD) among the albiglutide-treated group decreased from 8.18% (0.89) at baseline to 7.39% (1.11) at week 32; corresponding to a treatment difference of -0.79%. The mean percent change in HbA_{1c} level (SD) among the liraglutide-treated group decreased from 8.15% (0.84) at baseline to 7.18% (1.08) at week 32; corresponding to a treatment difference of -0.98%. Decreases in HbA_{1c} from baseline over time were recorded through week 32 in each treatment group, beginning at week four and stabilizing by week 12. Changes from baseline over time in FPG were consistent with changes in HbA_{1c}. At 32 weeks, the LSM change in FPG was -1.22 mmol/L (95% CI, -1.45 to -1.00) in the albiglutide group and -1.68 mmol/L (95% CI, -1.91 to -1.46) in the liraglutide group; corresponding to a treatment difference of 0.46 (95% CI, 0.14 to 0.78; P=0.0048). The HbA_{1c} treatment goal of <7.0% was achieved by 42% of albiglutide-treated patients and 52% of liraglutide-treated patients (P=0.0023); while the goal of HbA_{1c} lower than 6.5% was achieved by 20% of albiglutide-treated patients and 28% of liraglutide-treated patients (P=0.0009). Hyperglycemia rescue criteria occurred in 15% of albiglutide-treated patients and 8% of liraglutide-treated patients by week 32. The difference in time to hyperglycemia rescue favored liraglutide (P=0.005) and the probability of hyperglycemia rescue was higher in albiglutide-treated patients from week 12 to week 32 (albiglutide vs liraglutide: 0.0286 vs 0.0027 at week 12; 0.1333 vs 0.0783 at week 26; and 0.1929 vs 0.1247 at week 32).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				A significantly greater weight loss was observed in patients treated with liraglutide (-2.19 kg; 95% CI, -2.55 to -1.83) compared to albiglutide (-0.64 kg; -1.00 to -0.28); corresponding to a treatment difference at week 32 of 1.55 kg (95% CI, 1.05 to 2.06; P<0.0001). At week 32, the LSM change (SD) in weight from baseline was -2.2 kg (4.15) in patients treated with liraglutide compared to -0.6 kg (3.12) with albiglutide. The most common adverse events were injection-site reactions, GI events, and upper respiratory tract infections. GI events were common in both groups occurring at a frequency of 35.9% in albiglutide-treated patients and 49.0% in liraglutide-treated patients; corresponding to a treatment difference of -13.1% (95% CI, -19.9 to -6.4). Diarrhea was the most common GI event in the albiglutide group and occurred more frequently than the liraglutide group, although the difference was not significant. Investigator-assessed cardiovascular adverse events occurred at a similar rate in the albiglutide group (8.2%) and the liraglutide group (10.5%); corresponding to a treatment difference of -2.4% (95% CI, -6·4 to 1.6).
Hernandez et al.[34] (2018) HARMONY Albiglutide (30 to 50 mg once a week) vs placebo Treatment given in addition to standard care	DB, MC, PC, RCT Patients ≥40 years of age with type 2 diabetes and cardiovascular disease	N=9,463 Median duration of 1.6 years	Primary: First occurrence of any component of the composite outcome, which included death from cardiovascular causes, MI, and stroke Secondary: Four-component composite (the primary composite, with the addition of urgent revascularization for unstable angina), the	Primary: The primary composite endpoint occurred in 7% of patients at an event rate of 4.57 events per 100 person-years in the albiglutide group and in 9% of patients at an event rate of 5.87 events per 100 person-years in the placebo group (HR, 0.78; 95% CI, 0.68 to 0.90), indicating that albiglutide was both non-inferior to placebo for cardiovascular safety (P<0.0001 for non-inferiority) and superior to placebo for efficacy (P=0.0006 for superiority). Secondary: The HRs for each of the components of the primary composite were 0.93 (95% CI, 0.73 to 1.19; P=0.578) for death from cardiovascular causes, 0.75 (95% CI, 0.61 to 0.90; P=0.003) for myocardial infarction, and 0.86 (95% CI, 0.66 to 1.14; P=0.300) for stroke. The effects of albiglutide on the other secondary cardiovascular outcomes were consistent with its effect on the primary outcome (P=0.0005 for the four-component composite outcome). The HR for death from any cause was 0.95 (95% CI, 0.79 to 1.16; P=0.644). The composite of death from cardiovascular causes or hospital admission for heart failure was 4% in the albiglutide group and 5% in the placebo group (P=0.113).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			individual components of the primary endpoint, and the composite of cardiovascular death or hospital admission because of heart failure	
Reusch et al.[35] (2014) HARMONY 1 Albiglutide (30 mg once a week) vs placebo	DB, PC, RCT Patients ≥18 years of age with a BMI of 20 to 45 kg/m^2, diagnosed with type 2 diabetes, HbA_{1c} 7.0 to 10.0% on stable doses of pioglitazone (≥30 mg pioglitazone daily or the patient's maximum tolerated dose) with or without a stable dose of metformin (≥1500 mg or maximum tolerated dose) for at least 2 months before randomization	N=310 3 years	Primary: Change in HbA_{1c} from baseline to 52 weeks Secondary: Changes in HbA_{1c} over time, FPG (change from baseline at week 52 and over time), time to hyperglycemia rescue, percent of patients attaining HbA_{1c} of <6.5 and <7.0%, and change from baseline in body weight	Primary: The model-adjusted change from baseline in HbA_{1c} at week 52 was significantly improved with albiglutide than with placebo (−0.8%; 95% CI, −1.0 to −0.6; P<0.0001). Secondary: Change from baseline FPG was −1.3 mmol/l in the albiglutide group and 0.4 mmol/l in the placebo group (P<0.0001); a significantly higher percentage of patients reached the HbA_{1c} goals with albiglutide (P<0.0001), and the rate of hyperglycemia rescue up to week 52 for albiglutide was 24.4 versus 47.7% for placebo (P<0.0001). Albiglutide plus pioglitazone had no impact on weight, and severe hypoglycemia was observed rarely (n = 2). With few exceptions, the results of safety assessments were similar between the groups, and most adverse events were mild or moderate. The 52-week incidence rates for gastrointestinal adverse events for albiglutide and placebo were: 31.3 and 29.8%, respectively (diarrhea: 11.3 and 8.6%; nausea: 10.7 and 11.3%; vomiting: 4.0 and 4.0%).
Weissman et al.[36] (2014) HARMONY 4 Albiglutide (30 mg once a week) vs	MC, OL, NI, RCT Patients ≥18 years of age with type 2 diabetes treated with metformin (±sulfonylurea) for at least 3 months	N=779 52 weeks	Primary: Change in HbA_{1c} from baseline to 52 weeks Secondary: Change from baseline in FPG at week 52, changes	Primary: In the albiglutide group, HbA_{1c} declined from 8.28 ± 0.90% (mean ± SD) at baseline to 7.62 ± 1.12% at week 52. A similar reduction occurred in the insulin glargine group (8.36 ± 0.95% to 7.55 ± 1.04%). The model-adjusted treatment difference of 0.11% (95% CI, −0.04% to 0.27%) indicated non-inferiority of albiglutide to insulin glargine based on the pre-specified non-inferiority margin of 0.3% (P=0.0086). Secondary:

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insulin glargine (10 U once a day)	with a baseline HbA_{1c} 7.0 to 10.0%		from baseline in HbA_{1c} and FPG over time, time to hyperglycemic rescue, proportion of patients achieving HbA_{1c} goals, body weight	At week 52, FPG had declined by a mean 0.87 mmol/l in the albiglutide group and by 2.06 mmol/l in the insulin glargine group; the treatment difference was significant in favor of insulin glargine (P<0.0001). Body weight increased in the insulin glargine group and decreased in the albiglutide group, with a mean treatment difference of −2.61 kg (95% CI, −3.20 to −2.02; P<0.0001). Documented symptomatic hypoglycemia occurred in a higher proportion of patients in the insulin glargine group than in the albiglutide group (27.4 vs 17.5%, P=0.0377).
Home et al.[37] (2015) HARMONY 5 Albiglutide (30 mg/week) vs pioglitazone (30 mg/day) vs placebo current dose of metformin (>1500 mg/day) was maintained throughout and blinded uptitration of study drug was allowed	DB, MC, PG, RCT Patients ≥18 years of age with a historical diagnosis of type 2 diabetes and inadequate glycemic control on their current regimen of metformin and a sulfonylurea	N=685 156 weeks	Primary: Change in HbA_{1c} from baseline to 52 weeks Secondary: HbA_{1c} change over time, FPG, HbA_{1c} responders, body weight change, adverse events	Primary: The week 52 model-adjusted difference in change in HbA_{1c} for albiglutide versus placebo was -0.87 (95% CI, –1.07 to –0.68)%-units (P<0.001), and for albiglutide versus pioglitazone it was 0.25 (95% CI, 0.10 to 0.40)%-units; therefore, not non-inferior. Secondary: In the albiglutide group only, fasting plasma glucose reduced rapidly in the first two weeks. Confirmed hypoglycemia occurred in 14% of participants on albiglutide, 25% on pioglitazone and 14% on placebo. The mean (± standard error) weight change was −0.42 (±0.2) kg with albiglutide, 4.4 (±0.2) kg (P<0.001) with pioglitazone, and −0.40 (±0.4) kg with placebo and serious adverse events occurred in 6.3, 9.0 and 6.1% of participants in the respective groups. Injection site reactions occurred in 13% of participants on albiglutide and resulted in treatment discontinuation for four participants (1.4%).
Leiter et al.[38] (2014) Albiglutide 30 mg once weekly	DB, MC, RCT Renally impaired patients with type 2 diabetes	N=507 52 weeks	Primary: Change in HbA_{1c} from baseline to 26 weeks Secondary:	Primary: The model-adjusted LS mean for the primary end point of change from baseline in HbA_{1c} at week 26 was −0.83% in the albiglutide group and −0.52% in the sitagliptin group, with similar results across all three baseline eGFR groups. The treatment difference (albiglutide vs sitagliptin) was −0.32% (95% CI, −0.49 to −0.15). The upper bound of the CI was below the

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(uptitrated if needed) vs sitagliptin (dosed based on the eGFR value) Patients continued to receive their prescribed oral antihyperglycemic medication regimen (metformin, thiazolidinedione, sulfonylurea, or any combination of these oral antihyperglycemic medications).			FPG, weight, achievement of treatment targets, hyperglycemic rescue, and safety.	prespecified noninferiority margin of 0.4%, indicating noninferiority of albiglutide to sitagliptin. A superiority test conducted in accordance with a prespecified, step-wise procedure indicated that albiglutide was statistically superior to sitagliptin (P=0.0003). The treatment effect of albiglutide seen at week 26 was maintained through week 52. Secondary: The change in FPG from baseline at week 26 was −1.42 mmol/L in the albiglutide group and −0.22 mmol/L in the sitagliptin group. At week 26, the difference in LS means (albiglutide vs sitagliptin) was −1.20 mmol/L (P<0.0001). A higher percentage of patients in the albiglutide treatment group achieved the treatment targets of HbA_{1c} <6.5% and <7.0% at week 26 (albiglutide 15.3% and 42.6%, respectively, compared with sitagliptin 12.3% and 30.5%, respectively). The treatment difference between albiglutide and sitagliptin was statistically significant (P=0.0077) for the treatment target of HbA_{1c} <7.0% at week 26. There was a statistically significant difference between albiglutide and sitagliptin (P=0.0017) in the mean time to hyperglycemia rescue through week 52. The proportion of patients who had required hyperglycemia rescue was lower in the albiglutide group than in the sitagliptin group at week 26 (6.1% [15 patients] vs 12.1% [29 patients]) and at week 52 (17.9% [44 patients] vs 28.3% [68 patients]). Patients in both treatment groups showed a modest mean loss in body weight through week 26, with a model-adjusted LS mean weight change from baseline of −0.79 kg for albiglutide and −0.19 kg for sitagliptin (P<0.05). The incidence of any adverse event and the event rates of on-therapy adverse events over the course of the study were similar between the two treatment groups (83.5% and 347 AEs/100 person-years with albiglutide and 83.3% and 331 Aes/100 person-years with sitagliptin).

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Home et al.[39] (2017) HARMONY 1 to 5 Albiglutide weekly vs glimepiride, pioglitazone, sitagliptin, insulin glargine, or placebo Background medications allowed varied by study and ranged from none to metformin, to metformin with one additional agent	Analysis of five phase-3 HARMONY trials Patients from five of the eight HARMONY phase 3 trials, comparing albiglutide with other therapies or placebo across a spectrum of clinical care, lasted for a pre-planned three years	N=2,986 3 years	Primary: Use or lack of use of hyperglycemia rescue medication Secondary: Glycemic measures, body weight	Primary: A greater proportion of participants who received albiglutide remained rescue-free (55 to 71%) compared with placebo (35 to 51%; P<0.001 to P=0.002). The proportion of rescue-free participants with albiglutide did not differ from glimepiride or insulin glargine, was higher than with sitagliptin (P=0.013), and lower than with pioglitazone (P=0.045). Secondary: At three years, albiglutide was associated with reductions in hyperglycemia (e.g., rescue-free participants: HbA_{1c} -0.52% to -0.98%; and all participants: HbA_{1c} -0.29% to -0.92%). Albiglutide was also associated with modest reductions in body weight vs pioglitazone, glimepiride, and insulin glargine, which were associated with weight gain.
Giorgino et al.[40] (2015) AWARD-2 Dulaglutide 1.5 mg once-weekly vs dulaglutide 0.75 mg once-weekly vs once-daily glargine	OL, MC, RCT Adults with an HbA_{1c} of ≥7.0% and ≤11.0%, BMI ≥23 and ≤45 kg/m^2, and stable weight for ≥3 months, who were not optimally controlled with one, two, or three oral antihyperglycemic medications (of which one had to be metformin or a sulfonylurea) for at least three months	N=810 78 weeks	Primary: Change in HbA_{1c} from baseline to 52 weeks Secondary: Changes in HbA_{1c} from baseline to 26 and 78 weeks, the percentage of patients achieving HbA_{1c} <7.0% and ≤6.5%, and changes in FPG, 8-point self-monitored plasma glucose profiles, adverse events	Primary: The mean HbA_{1c} change from baseline to the 52-week primary end point was −1.08 ± 0.06%, −0.76 ± 0.06%, and −0.63 ± 0.06% for dulaglutide 1.5 mg, dulaglutide 0.75 mg, and glargine, respectively. Statistical criteria for superiority was met with dulaglutide 1.5 mg, LS mean difference of −0.45% (95% CI, −0.60 to −0.29; adjusted one-sided P<0.001). Statistical criteria for noninferiority were met for dulaglutide 0.75 mg, −0.13% (95% CI, −0.29 to 0.02; adjusted one-sided P<0.001). Secondary: There was no significant difference in percentages of patients who achieved the HbA_{1c} target of <7.0% for dulaglutide 0.75 mg (37.1%) compared with glargine. Greater percentages of patients on dulaglutide 1.5 mg (27.0%) and dulaglutide 0.75 mg (22.5%) achieved an HbA_{1c} target ≤6.5% than with glargine (13.5%) (P<0.001 and P=0.004, respectively). At 78 weeks, percentages of patients attaining HbA_{1c} targets were generally maintained, except for the percentage of patients with an HbA_{1c} of ≤6.5%, which was similar for dulaglutide 0.75 mg and glargine. At 52 weeks, the FPG from 8-

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				point SMPG profiles decreased more with glargine than with dulaglutide 1.5 mg and dulaglutide 0.75 mg. More patients on dulaglutide 1.5 mg achieved HbA_{1c} targets <7.0% versus glargine (P<0.001). Body weight decreased with dulaglutide and increased with glargine. Total hypoglycemia rates were lower with dulaglutide; severe hypoglycemia was minimal. Increases in pancreatic enzymes were observed for dulaglutide. Incidence of nausea (15.4, 7.7, and 1.5%) and diarrhea (10.6, 9.2, and 5.7%) were more common with dulaglutide 1.5 mg and 0.75 mg than with glargine.
Blonde et al.[41] (2015) AWARD-4 Dulaglutide 1.5 mg once-weekly vs dulaglutide 0.75 mg once-weekly vs daily bedtime glargine All groups also used a lispro dosing algorithm, and metformin was allowed	NI, OL, RCT Patients (≥18 years of age) with type 2 diabetes inadequately controlled with conventional insulin treatment	N=884 52 weeks	Primary: Change in HbA_{1c} from baseline to 26 weeks Secondary: The proportion of patients achieving HbA_{1c} of < 7.0% or of ≤6.5%, change in FPG, self-monitored plasma glucose, bodyweight, BMI, insulin doses, and patient-reported outcomes	Primary: At 26 weeks, the adjusted mean change in HbA_{1c} was greater in patients receiving dulaglutide 1.5 mg (−1.64%; 95% CI, −1.78 to −1.50) and dulaglutide 0.75 mg (−1.59%; 95% CI, −1.73 to −1.45) than in those receiving glargine (−1.41%; 95% CI, −1.55 to −1.27). The adjusted mean difference versus glargine was −0.22% (95% CI, −0.38 to −0.07; P=0.005) for dulaglutide 1.5 mg and −0.17% (95% CI, –0.33 to −0.02; P=0.015) for dulaglutide 0.75 mg. Secondary: At 26 weeks, the proportion of patients achieving an HbA_{1c} target of <7.0% was significantly greater in both the dulaglutide 1.5 mg and 0.75 mg groups versus glargine (P=0.014 and P=0.010, respectively). Compared with glargine, a significantly greater proportion of patients in the dulaglutide 1.5 mg group (P=0.027) also achieved an HbA_{1c} target of 6.5% or less at 26 weeks. At 52 weeks, a significantly greater proportion of patients in the dulaglutide 1.5 mg group achieved HbA_{1c} <7.0% versus glargine (P=0.0499). The proportion of patients achieving HbA_{1c} of 6.5% or less at week 52 did not differ significantly between the dulaglutide 1.5 mg and 0.75 mg groups and the glargine group (P=0.27 and P=0.62). For the composite endpoints assessing the proportion of patients achieving HbA_{1c} <7.0% without documented symptomatic hypoglycemia and, separately, without nocturnal or severe hypoglycemia, alone or in combination with no weight gain, significantly more patients met the criteria in the dulaglutide 1.5 mg group than the glargine group at both weeks 26 and 52 (all P<0.05). The reductions in adjusted mean FPG from baseline to week 26 were significantly greater with glargine (−1.58 mmol/L; 95% CI, −1.97 to −1.19)

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				than with dulaglutide 1.5 mg (–0.27 mmol/L; 95% CI, –0.66 to 0.12; P<0.0001) or dulaglutide 0.75 mg (0.22 mmol/L; 95% CI, –0.17 to 0.61; P<0.0001); results were similar at week 52 (both P<0.0001). The self-monitored plasma glucose values (8-point daily profile) at 26 weeks decreased at each timepoint compared with baseline in all groups. The adjusted mean changes in bodyweight at 26 weeks were −0.87 kg (95% CI, −1.40 to −0.34) in the dulaglutide 1.5 mg group, 0.18 kg (95% CI, –0.35 to 0.71) in the dulaglutide 0.75 mg group, and 2.33 kg (1.80 to 2.86) in the glargine group. The differences between the dulaglutide and glargine groups were significant (all P<0.0001) and similar differences were noted at 52 weeks. Between-group differences for change in BMI were consistent with weight findings.
Dungan et al.[42] (2014) AWARD-6 Dulaglutide 1.5 mg once-weekly vs liraglutide 1.8 mg once-daily	MC, NI, OL, RCT Metformin-treated patients with uncontrolled type 2 diabetes	N=599 26 weeks	Primary: Change in baseline HbA_{1c} Secondary: proportion of patients achieving HbA_{1c} targets, change in FPG, self-monitored plasma glucose, BMI, safety	Primary: Both dulaglutide and liraglutide significantly reduced HbA_{1c} from baseline. The HbA_{1c} reduction with dulaglutide was non-inferior, but not superior, to that achieved by liraglutide, with a between-group difference in HbA_{1c} reduction from baseline of −0.06% (95% CI, −0.19 to 0.07; $P_{non\text{-}inferiority}$<0.0001). Decreases in HbA_{1c} over time were similar between groups. Secondary: At 26 weeks, 200 of 293 (68%) patients in the dulaglutide group achieved HbA_{1c} targets of less than 7.0% compared with 199 of 293 (68%) in the liraglutide group; 160 (55%) patients achieved HbA_{1c} targets of 6.5% or less in the dulaglutide group compared with 149 (51%) in the liraglutide group. Both dulaglutide and liraglutide significantly reduced FPG concentrations between baseline and 26 weeks, with no significant difference between groups. Seven-point self-monitored plasma glucose profiles measured at baseline and 26 weeks did not differ significantly between treatments at any time point measured. The mean change from baseline in bodyweight was −2.90 kg for dulaglutide and −3.61 kg for liraglutide; between-group differences for change from baseline in BMI were consistent with weight findings. The most frequent treatment emergent adverse events were generally gastrointestinal, with nausea, diarrhoea, vomiting, and dyspepsia being the most common; there were no differences between groups.
Dungan et al.[43] (2016) AWARD-8	DB, PC, RCT	N=300 24 weeks	Primary:	Primary: Dulaglutide reduced HbA_{1c} by −1.4% from baseline compared with −0.1% for placebo, with a between-group difference of −1.3% (95% CI, −1.6 to

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Dulaglutide 1.5 mg once-weekly vs placebo	Sulphonylurea-treated (≥half-maximal dose, stable ≥3 months) patients with type 2 diabetes and inadequate glycemic control (HbA_{1c} ≥7.5 and ≤9.5%)		HbA_{1c} change from baseline at 24 weeks Secondary: proportion of patients achieving HbA_{1c} targets, change in FPG, self-monitored plasma glucose, body weight, safety	−1.0; P<0.001). This significant difference met the primary endpoint of superiority versus placebo for this study. Dulaglutide significantly improved HbA_{1c} versus placebo at all post-baseline time points, beginning at four weeks. Secondary: At 24 weeks, 55.3% (dulaglutide) and 18.9% (placebo) of participants achieved an HbA_{1c} target of <7.0% (P<0.001 dulaglutide vs placebo), while 40% (dulaglutide) and 9.4% (placebo) of participants achieved an HbA_{1c} target of ≤6.5% (P<0.001 dulaglutide vs placebo). Dulaglutide reduced FPG from baseline to 24 weeks (dulaglutide −1.70 and placebo 0.16 mmol/l); the between-group least-squares (LS) mean difference of −1.86 mmol/l (95% CI, −2.58 to −1.14) was statistically significant (−33.54 mg/dl; 95% CI, −46.55 to −20.53; P<0.001). At all time points, the LS mean values for seven-point self-monitored plasma glucose were significantly reduced in the dulaglutide-treated group (all P<0.001). The LSM change in weight from baseline was −0.91 kg for dulaglutide (P<0.001) and −0.24 kg for placebo (P=0.553). The between-group difference was not significant with an LS mean of −0.68 kg (95% CI, −1.53 to 0.18; P=0.120). A similar proportion of participants experienced treatment-emergent adverse events in the dulaglutide group (n = 111, 46.4%) compared with the placebo group (n = 23, 38.3%; P=0.259).
Ludvik et al.[44] (2018) AWARD-10 Dulaglutide 0.75 mg or 1.5 mg once-weekly vs placebo	DB, MC, PC, RCT Patients ≥18 years of age with inadequately controlled type 2 diabetes (HbA_{1c} ≥7.0% and ≤9.5%), a BMI of 45 kg/m^2 or less, and taking stable doses (>3 months) of an SGLT2 inhibitor (with or without metformin)	N=424 24 weeks	Primary: Change in HbA_{1c} concentration from baseline Secondary: Percentage of patients achieving an HbA_{1c} target concentration of <7.0%, change from baseline in bodyweight, and change from baseline in FPG	Primary: The reduction in HbA_{1c} concentration at 24 weeks was larger in patients receiving dulaglutide (least squares mean for dulaglutide 1.5 mg, -1.34%; dulaglutide 0.75 mg, -1.21%) than in patients receiving placebo (-0.54%; P<0.0001 for both groups vs placebo). Secondary: The proportions of patients who achieved the HbA_{1c} target concentrations of <7.0% at 24 weeks was larger in the dulaglutide groups than in the placebo group (P<0.0001). Reduction in bodyweight from baseline to 24 weeks was greater with dulaglutide 1.5 mg than with placebo (P=0.028), but the mean bodyweight reduction in the dulaglutide 0.75 mg group at 24 weeks did not significantly differ from that in the placebo group. The reduction in FPG by 24 weeks was larger with dulaglutide 1.5 mg than with placebo (P<0.0001).
Pozzilli et al.[45] (2017)	DB, MC, RCT	N=300	Primary: Change in HbA_{1c}	Primary:

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AWARD-9 Dulaglutide 1.5 mg weekly vs placebo All patients received titrated daily insulin glargine with or without metformin	Adults with type 2 diabetes with a body mass index ≤45 kg/m^2 and were on a stable dose of glargine (with or without metformin, ≥1500 mg/day) for ≥3 months prior to first visit	28 weeks	Secondary: Change from baseline in body weight, percentage of patients achieving HbA_{1c} <7.0% and FPG	Least squares mean HbA_{1c} changes from baseline were -1.44 ± 0.09% with dulaglutide/glargine and -0.67 ± 0.09% with placebo/glargine at 28 weeks (least squares mean difference, -0.77%; 95% CI, -0.97 to -0.56; P<0.001). Secondary: A greater percentage of patients in the dulaglutide/glargine group (66.7%) vs the placebo/glargine group (33.3%) achieved HbA_{1c} <7.0%, and a greater percentage of dulaglutide/glargine patients (50.0%) achieved HbA_{1c} ≤6.5 vs placebo/glargine (16.7%) at 28 weeks (P<0.001, both comparisons). Body weight decreased with dulaglutide/glargine and increased with placebo/glargine (least squares mean difference, -2.41 ± 0.39 kg; P<0.001). Decreases from baseline in FPG were observed with both dulaglutide 1.5 mg and placebo at 28 weeks (P<0.001, both treatment arms).
Arslanian et al.[46] (2022) AWARD-PEDS Dulaglutide 0.75 mg weekly vs dulaglutide 1.5 mg weekly vs placebo	DB, MC, PC, PG, RCT Youths (10 to <18 years of age; BMI, >85th percentile) with type 2 diabetes being treated with lifestyle modifications alone or with metformin, with or without basal insulin	N=154 26 weeks	Primary: HbA_{1c} Secondary: Percentage of participants achieving an HbA_{1c} target of <7.0%; BMI; FPG	Primary: At 26 weeks, the HbA_{1c} level had increased in the placebo group (0.6 percentage points) and had decreased in the dulaglutide groups (-0.6 percentage points in the 0.75-mg group and -0.9 percentage points in the 1.5-mg group, P<0.001 for both comparisons vs. placebo). Secondary: At 26 weeks, a higher percentage of participants in the pooled dulaglutide groups than in the placebo group had a HbA_{1c} of less than 7.0% (51% vs 14%, P<0.001). The fasting glucose concentration increased in the placebo group (17.1 mg per deciliter) and decreased in the pooled dulaglutide groups (-18.9 mg per deciliter, P<0.001), and there were no between-group differences in the change in BMI.
Weinstock et al.[47] (2015) AWARD-5 Dulaglutide (1.5 or 0.75 mg) vs sitagliptin 100 mg	DB, MC, RCT Patients 18 to 75 years of age with type 2 diabetes (≥6 months' duration) and an HbA_{1c} value of >8.0% and ≤9.5% on diet and exercise	N=1,098 104 weeks	Primary: HbA_{1c} Secondary: Percentage of participants achieving an HbA_{1c} target of <7.0% and ≤6.5%; body weight; FPG	Primary: Changes in HbA_{1c} at 104 weeks were (least squares mean ± standard error) −0.99 ± 0.06%, −0.71 ± 0.07% and −0.32 ± 0.06% for dulaglutide 1.5 mg, dulaglutide 0.75 mg and sitagliptin, respectively (P<0.001, both dulaglutide doses vs sitagliptin). Secondary: At 104 weeks, the percentage of participants attaining the HbA_{1c} target goal of <7.0% was significantly higher in the dulaglutide 1.5 mg and dulaglutide 0.75 mg arms (54 and 45%, respectively) compared with sitagliptin (31%;

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	alone, or ≥7.0% and ≤9.5% on monotherapy or combination therapy (metformin plus another oral antihyperglycemic medication), and a BMI of 25 to 40 kg/m^2		and fasting insulin; β-cell function; lipids; safety	P<0.001, both comparisons). Additionally, 39 and 24% of participants in the dulaglutide 1.5 mg and dulaglutide 0.75 mg arms, respectively, achieved HbA_{1c} targets of ≤6.5%, compared with 14% in the sitagliptin arm (P<0.001, both comparisons). The measurement of insulin sensitivity (HOMA2-%S) was not different between treatment groups, while β-cell function, as assessed by HOMA2-%β, increased significantly more with dulaglutide 1.5 mg and dulaglutide 0.75 mg than with sitagliptin. Weight loss was greater with dulaglutide 1.5 mg (P<0.001) and similar with 0.75 mg versus sitagliptin (2.88 ± 0.25, 2.39 ± 0.26 and 1.75 ± 0.25 kg, respectively). Gastrointestinal adverse events were more common with dulaglutide 1.5 and 0.75 mg versus sitagliptin (nausea 17 and 15% vs 7%, diarrhoea 16 and 12% vs 6%, vomiting 14 and 8% vs 4% respectively). Pancreatic, thyroid, cardiovascular and hypersensitivity safety were similar across groups.
Gerstein et al.[48] (2019) REWIND Dulaglutide vs placebo	DB, MC, RCT Men and women (aged ≥50 years) with established or newly detected type 2 diabetes whose HbA_{1c} was 9.5% or less (with no lower limit) on stable doses of up to two oral glucose-lowering drugs with or without basal insulin therapy were eligible if their BMI was at least 23 kg/m^2	N=9,901 Median follow-up of 5.4 years	Primary: First occurrence of the composite endpoint of non-fatal myocardial infarction, non-fatal stroke, or death from cardiovascular causes (including unknown causes) Secondary: Composite clinical microvascular outcome comprising diabetic retinopathy (defined as photocoagulation, anti-vascular endothelial growth	Primary: The primary composite outcome occurred in 594 (12.0%) participants (2.4 per 100 person-years) assigned to dulaglutide and 663 (13.4%) participants (2.7 per 100 person-years) assigned to placebo (HR, 0.88; 95% CI, 0.79 to 0.99; P=0.026). Secondary: The incidence of the composite microvascular outcome was lower in participants assigned to dulaglutide than in those assigned to placebo (3.8 per 100 person-years vs 4.3 per 100 person-years, respectively; HR, 0.87; 95% CI, 0.79 to 0.95). This difference was characterized by fewer composite renal outcomes in the dulaglutide group than in the placebo group (3.5 per 100 person-years vs 4.1 per 100 person-years, respectively; HR, 0.85; 95% CI, 0.77 to 0.93). Dulaglutide did not significantly affect the incidence of all-cause mortality, heart failure, revascularization, hospital admissions, fractures, or cholelithiasis.

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			factor therapy, or vitrectomy) or renal disease (defined as development of a urinary albumin-to-creatinine ratio >33.9 mg/mmol in those with a lower baseline concentration, a sustained 30% or greater decline in eGFR, or chronic renal replacement therapy); hospital admission for unstable angina; each component of the primary composite cardiovascular outcome	
Buse et al.[49] (2011) Exenatide 5 µg SC BID for 4 weeks, followed by 10 µg SC BID vs placebo All patients also received optimized insulin glargine	DB, MC, PC, RCT Type 2 diabetics ≥18 years of age who had been receiving insulin glargine at a minimum of 20 units/day without any other insulin, alone or in combination with a stable dose of metformin or pioglitazone (or	N=261 30 weeks	Primary: Change in baseline HbA_{1c} Secondary: Proportion of patients achieving HbA_{1c} ≤7.0 or ≤6.5%; seven-point self-monitored glucose concentrations; change in baseline body weight, waist	Primary: Exenatide significantly decreased HbA_{1c} compared to placebo (-1.74 vs -1.04%; P<0.001). Secondary: A significantly greater proportion of patients receiving exenatide achieved an HbA_{1c} ≤7.0% (60 vs 35%; treatment difference, 25%; 95% CI, 12 to 39; P<0.001). Similar results were observed with HbA_{1c} ≤6.5% (40 vs 12%; treatment difference, 28%; 95% CI, 17 to 39; P<0.001). With regards to seven-point self-monitored glucose concentrations, exenatide significantly decreased concentrations during morning and evening time points compared to placebo (P<0.001), but not at midday (P=0.320).

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dosing (at randomization, patients with HbA_{1c} levels >8.0% continued to receive current insulin glargine dose; those with HbA_{1c} ≤8.0% decreased their dose by 20%; these doses were maintained for 5 weeks, after which patients began to titrate to achieve a fasting glucose level ≤100 mg/dL).	both agents) for ≥3 months, HbA_{1c} 7.1 to 10.5%, BMI ≤45 kg/m^2, and stable body weight over past 3 months		circumference, and insulin dose; safety	Exenatide significantly decreased body weight compared to placebo (-1.8 vs 1.0 kg; P<0.001), but no difference between treatments was observed in waist circumference (P=0.23). The number of hypoglycemic events per-participant per-year did not differ between the exenatide and placebo (P=0.49).
Rosenstock et al.[50] (2012) Exenatide 5 µg SC BID for 4 weeks, followed by 10 µg SC BID vs placebo All patients also received optimized insulin glargine dosing (at randomization, patients with HbA_{1c} levels >8.0% continued to receive current insulin glargine dose; those	Exploratory analysis of Buse et al.[31] Baseline factors associated with glycemic control and weight loss in type 2 diabetics ≥18 years of age who had been receiving insulin glargine at a minimum of 20 units/day without any other insulin, alone or in combination with a stable dose of metformin or pioglitazone (or both agents) for ≥3 months, HbA_{1c} 7.1 to 10.5%, BMI ≤45	N=259 30 weeks	Primary: Change in baseline HbA_{1c}, weight Secondary: Not reported	Primary: Patients receiving exenatide had achieved significantly greater reductions in HbA_{1c} compared to patients receiving placebo, irrespective of baseline HbA_{1c} (P<0.001). Patients receiving exenatide with longer duration of diabetes and those with lower BMI achieved significantly greater reductions in HbA_{1c} compared to patients receiving placebo (P<0.01). Patients receiving exenatide lost significantly more weight, regardless of baseline HbA_{1c} or BMI compared to patients receiving placebo (P<0.05). Patients receiving exenatide with longer duration of diabetes lost the most weight compared to patients receiving placebo (P<0.001). Secondary: Not reported

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with HbA_{1c} ≤8.0% decreased their dose by 20%; these doses were maintained for 5 weeks, after which patients began to titrate to achieve a fasting glucose level ≤100 mg/dL).	kg/m^2, and stable body weight over past 3 months			
Okerson et al.[51] (2010) Exenatide 5 µg SC BID for 4 weeks, followed by 10 µg SC BID vs placebo or insulin All patients also received existing antidiabetic treatment regimens.	Post-hoc analysis (6 RCTs) Type 2 diabetics ≥18 years of age with HbA_{1c} ≥6.5 to ≤11.0%, BMI ≥25 to ≤45 kg/m^2, and stable body weight	N=2,171 24 to 52 weeks	Primary: Change in baseline BP and pulse pressure Secondary: Not reported	Primary: In the overall study population, by the end of the six month trial period, exenatide was associated with a significantly greater decrease in SBP compared to placebo (-2.20±0.56 vs 0.60±0.56 mm Hg; treatment difference, -2.80±0.75 mm Hg; P=0.002) and insulin (-4.5±0.6 vs -0.9±0.6 mm Hg; treatment difference, -3.7±0.85 mm Hg; P<0.0001). In contrast, DBP was minimally decreased and not different between exenatide and placebo (-0.70±0.33 vs -0.20±0.33 mm Hg; P=0.21) or insulin (-1.60±0.35 vs -0.80±0.36 mm Hg; P=0.16). No differences in the proportions of patients altering the number, type, or intensity of ongoing antihypertensive regimens were observed between treatments (data not reported). Patients with abnormal SBP at baseline achieved the greatest decreases with exenatide (exenatide vs placebo, -8.3 vs -4.5 mm Hg; treatment difference, -3.8 mm Hg; P=0.0004 and exenatide vs insulin, -8.3 vs -4.2 mm Hg; treatment difference, -4.0 mm Hg; P<0.0001). In patients with normal BP at baseline, no differences in the decreases in SBP or DBP were observed between any of the treatments (P values not reported). Pulse pressure effects trended similarly to SBP effects, with the most pronounced decrease occurring in exenatide-treated patients with baseline pulse pressures ≥40 mm Hg. In this subgroup, the reduction in pulse pressure was significantly greater with exenatide compared to placebo (-3.5 vs -0.5 mm Hg; treatment difference, -2.9 mm Hg; P<0.0001) and insulin (-4.0 vs -0.9 mm Hg; treatment difference, -3.0 mm Hg; P<0.0001). By the end of the six month treatment period, a significantly greater proportion of exenatide-treated patients with elevated baseline SBP (26%) achieved the SBP goal for type 2 diabetics compared to insulin (treatment difference, 19%; P=0.03); however, no treatment effect on DBP was

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				observed. In contrast, although no significant exenatide-related shifts were observed in SBP classifications, a significantly greater proportion of exenatide-treated patients were favorably shifted from a baseline classification of "abnormal DBP" to "normal DBP" compared to placebo (treatment difference, 41.4 vs 32.4%; P=0.02). Secondary: Not reported
Guja et al.[52] (2018) DURATION-7 Exenatide 2 mg weekly vs placebo	DB, MC, RCT Patients with type 2 diabetes who were inadequately controlled despite titrated insulin glargine ± metformin	N=464 28 weeks	Primary: Change in HbA_{1c} from baseline to week 28 Secondary: Change in body weight and 2-hour PPG; proportion of patients with HbA_{1c} <7.0% with no weight gain and no major hypoglycemia over the 28 weeks	Primary: Exenatide was associated with a greater HbA_{1c} reduction from baseline to week 28 vs placebo (least-squares mean difference, −0.73%; 95% CI, −0.93 to −0.53%; P<0.001; final HbA_{1c}, 7.55% and 8.24%, respectively). Secondary: Patients receiving exenatide had greater reductions in body weight from baseline to week 28 compared with those receiving placebo (least-squares mean difference, −1.50 kg; 95% CI, −2.17 to −0.84; P<0.001). Reductions in 2-hour PPG were greater with exenatide vs placebo (least-squares mean difference, −1.52 mmol/L; 95% CI, −2.15 to −0.90 mmol/L; P<0.001; final 2-hour PPG, 11.27 mmol/L and 12.72 mmol/L, respectively). More exenatide-treated patients vs placebo-treated patients achieved HbA_{1c} <7.0% (32.5% vs 7.4%, respectively; P<0.001). More patients receiving exenatide vs placebo achieved HbA_{1c} <7.0% with no body weight gain and no major hypoglycemia over the 28-week treatment period (22.1% vs 2.6%, respectively; no hypothesis testing was performed because of the prespecified hierarchical testing sequence; nominal P<0.001).
Holman et al.[53] (2017) EXSCEL Exenatide 2 mg weekly vs placebo	DB, MC, PC, RCT Patients with type 2 diabetes, with or without previous cardiovascular disease	N=14,752 Median of 3.2 years	Primary: First occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke Secondary:	Primary: A primary composite outcome event occurred in 839 of 7,356 patients (11.4%; 3.7 events per 100 person-years) in the exenatide group and in 905 of 7396 patients (12.2%; 4.0 events per 100 person-years) in the placebo group (HR, 0.91; 95% CI, 0.83 to 1.00), with the intention-to-treat analysis indicating that exenatide, administered once weekly, was noninferior to placebo with respect to safety (P<0.001 for noninferiority) and was not superior to placebo with respect to efficacy (P=0.06 for superiority). Secondary:

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Patients were permitted to receive up to three oral glucose-lowering agents or to receive insulin, either alone or in combination with up to two oral glucose-lowering agents.			Death from any cause, death from cardiovascular causes, and the first occurrence of nonfatal or fatal myocardial infarction, nonfatal or fatal stroke, hospitalization for acute coronary syndrome, and hospitalization for heart failure	The risk of death from any cause was 6.9% in the exenatide group and 7.9% in the placebo group (HR, 0.86; 95% CI, 0.77 to 0.97); this difference was not considered to be statistically significant on the basis of the hierarchical testing plan. Causes of death were adjudicated as cardiovascular in 45.4% of the patients in the exenatide group and in 41.3% of the patients in the placebo group, as noncardiovascular in 32.9% and 34.4% of the patients, respectively, and as unknown in 21.7% and 24.3% of the patients. The rates of the first fatal or nonfatal myocardial infarction, fatal or nonfatal stroke, and other secondary outcomes did not differ significantly between the two groups.
Tamborlane et al.[54] (2022) Exenatide 2 mg weekly vs placebo	DB, MC, PG, RCT Youth (aged 10 to <18 years) with type 2 diabetes suboptimally controlled with current treatments. Eligible participants were treated with diet and exercise alone or in combination with a stable dose of an oral glucose-lowering drug (metformin and/or a sulfonylurea) and/or insulin for at least 2 months prior to enrollment.	N=83 24 weeks	Primary: Change in HbA_{1c} Secondary: Changes in fasting plasma glucose levels, body weight, systolic blood pressure, and fasting insulin levels	Primary: At 24 weeks, the least squares mean change in glycated hemoglobin was −0.36% for the exenatide and +0.49% for the placebo groups (between-group difference, −0.85%; 95% CI, −1.51 to −0.19; P=0.012). Secondary: Nonsignificant least squares mean differences from baseline to 24 weeks favoring exenatide were observed: fasting glucose -21.6 mg/dL (95% CI, -49.0 to 5.7; P=0.119), systolic blood pressure -2.8 mmHg (95% CI, -8.0 to 2.4; P=0.284), and body weight -1.22 kg (95% CI, -3.59 to 1.15; P=0.307).
Buse et al.[55] DURATION-6 (2013)	MC, OL, PG, RCT	N=911 26 weeks	Primary: Change in HbA_{1c} at week 26 from	Primary:

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Exenatide 2 mg weekly vs liraglutide 1.8 mg QD	Patients ≥18 years of age with type 2 diabetes treated with lifestyle modification and oral antihyperglycemic drugs (metformin, sulfonylurea, metformin plus sulfonylurea, or metformin plus pioglitazone) with suboptimal glycemic control		baseline between exenatide and liraglutide Secondary: Proportion of patients achieving HbA_{1c} <7%; changes in bodyweight; concentrations of fasting serum glucose; BP; serum lipid concentrations; rates of hypoglycemia; safety and tolerability; patient-reported outcomes	Both drugs were associated with a clinically important decrease in HbA_{1c} from baseline. Change in HbA_{1c} at endpoint was greater in patients taking liraglutide than in those taking exenatide (P=0.02). Secondary: 60% of patients receiving liraglutide and 53% receiving exenatide achieved HbA_{1c} of less than 7% (P=0.0011). Both treatments were associated with progressive decreases in bodyweight. Patients taking liraglutide lost more weight than did those taking exenatide, irrespective of BMI. At 26 weeks, fasting serum glucose significantly decreased in both groups (P<0.0001), but the decrease was greater in patients in the liraglutide group than in those in the exenatide group (P=0.02). Patients in both groups had similar decreases in BP. Improvements in other cardiovascular biomarkers (lipids, C-reactive protein, and brain natriuretic peptide) were similar between groups at endpoint. The most common adverse events were mainly gastrointestinal in both groups, with a greater frequency of nausea, diarrhea, and vomiting in patients in the liraglutide group than in those in the exenatide group.
Gallwitz et al.[56] EUREXA (2012) Exenatide 5 to 10 µg BID vs glimepiride 1 mg initially, titrated to maximum tolerated dose	MC, OL, RCT Overweight patients aged 18 to 85 years with type 2 diabetes on a stable maximum tolerated dose of metformin with HbA_{1c} between 6.5 and 9.0%	N=977 Average treatment was 2 years	Primary: Time to inadequate glycemic control (HbA_{1c} >9% after the first 3 months, or >7% at 2 consecutive visits 3 months apart after the first 6 months) Secondary: Markers of β-cell function, bodyweight, hypoglycemia, surrogate markers of cardiovascular	Primary: Median time to inadequate HbA_{1c} control was 180 weeks with exenatide versus 142.1 weeks with glimepiride (P=0.032). In the exenatide group, 203 (41%) patients had treatment failure compared with 262 (54%) in the glimepiride group (risk difference, 12.4; 95% CI, 6.2 to 18.6; HR, 0.748; CI, 0.623 to 0.899; P=0.002). Secondary: Systolic blood pressure decreased in patients in the exenatide group (change to endpoint -1.9 mmHg; P=0.006), but not in the glimepiride group (1.1 mmHg; P=0.096). Heart rate increased at endpoint in patients given exenatide (1.2 beats per min (bpm); P=0.024), but not in those given glimepiride (0.6 bmp; P=0.282), with no difference between groups at any time.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			risk (blood pressure and heart rate)	Discontinuation because of adverse events (mainly gastrointestinal) was significantly higher (P=0.0005) in the exenatide group than in the glimepiride group in the first six months of treatment, but not thereafter.
Buse et al.[57] (2004) Exenatide 5 µg BID and sulfonylurea (existing therapy) vs exenatide 10 µg BID and sulfonylurea (existing therapy) vs sulfonylurea (existing therapy) and placebo	MC, PC, PG, RCT, TB Type 2 diabetic patients 22 to 76 years of age, treated with maximally effective doses of a sulfonylurea (4 mg/day glimepiride, 20 mg/day glipizide, 10 mg/day glipizide XL, 10 mg/day glyburide, 6 mg/day micronized glyburide, 350 mg/day chlorpropamide, or 500 mg/day tolazamide) for ≥3 months, FPG <240 mg/dL, BMI 27 to 45 kg/m^2, HbA_{1c} 7.1 to 11.0%, stable weight (±10%) for 3 months prior to screening, and no lab value >25% outside of normal value	N=377 30 weeks	Primary: Change in baseline HbA_{1c} Secondary: Change in baseline FPG, weight, fasting concentrations of insulin, proinsulin, and lipoproteins	Primary: Significantly greater decreases in HbA_{1c} were noted with exenatide 10 (-0.86%) and 5 µg (-0.46%) compared to placebo (0.12%; P<0.0002 for pairwise comparison). Secondary: A significantly greater decreases in FPG was reported with exenatide 10 µg at week 30 compared to placebo (-0.6 vs 0.4 mmol/L; P<0.05). There was no difference between exenatide 5 µg and placebo (P value not reported). A significantly greater decrease in body weight was noted with exenatide 10 µg at week 30 compared placebo (-1.6 vs -0.6 kg; P<0.05). There was no difference between exenatide 5 µg and placebo (P value not reported). There were no differences in fasting insulin concentrations between any of the treatments (P value not reported). A significantly greater decrease in fasting proinsulin concentrations was noted with exenatide 10 µg at week 30 compared to placebo (-16 mmol/L; P<0.01). A similar trend was reported with exenatide 5 µg compared to placebo, but no significance was reported (P value not reported). There was a small decrease in LDL-C and apo B (P<0.05 for pairwise comparisons for both values) with exenatide compared to placebo. No differences were observed in other lipid parameters evaluated (P values not reported). Side effects reported by patients receiving exenatide 10 µg included nausea (51%), vomiting (13%), diarrhea (9%), constipation (9%), and hypoglycemia (36%) (P values not reported). There were 13 (10.1%) withdrawals due to adverse event(s) with exenatide 10 µg compared to nine (7.2%) withdrawals with exenatide 5 µg and four (3.3%) withdrawals with placebo (P values not reported). The majority of the events reported were mild to moderate in nature. Serious adverse events were

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				reported in 4, 3, and 8% of patients receiving exenatide 10 µg, exenatide 5 µg, and placebo. Such events included a MI in an exenatide-treated patient and one placebo-treated patient who experienced clinical manifestations of coronary artery disease.
DeFronzo et al.[58] (2005) Exenatide 5 µg BID and metformin (existing therapy) vs exenatide 10 µg BID and metformin (existing therapy) vs metformin (existing therapy) and placebo	MC, PC, PG, RCT, TB Type 2 diabetic patients 19 to 78 years of age, treated with metformin (≥1,500 mg/day) for ≥3 months before screening, FPG <240 mg/dL, BMI 27 to 45 kg/m^2, HbA_{1c} 7.1 to 11.0%, stable weight (±10%) for 3 months prior to screening, and no lab value >25% outside of normal value	N=336 30 weeks	Primary: Change in baseline HbA_{1c} Secondary: Proportion of patients achieving HbA_{1c} ≤7.0%; change in baseline FPG, weight, fasting concentrations of insulin, proinsulin, and lipids	Primary: Significantly greater decreases in HbA_{1c} were reported with exenatide 10 (-0.78%) and 5 µg (-0.40%) compared to placebo (0.08%; P<0.002 for pairwise comparison). Secondary: A significantly greater proportion of patients achieved HbA_{1c}≤7.0% with exenatide 5 (27%) and 10 µg (40%) compared to placebo (11%; P<0.01 for pairwise comparison). Significantly greater decreases in FPG were observed with exenatide 5 (-7.2 mg/dL; P<0.005) and 10 µg (-10.1 mg/dL; P<0.0001) compared to placebo (14.4 mg/dL). Significantly greater decreases in body weight were observed with exenatide 5 (-1.6 kg; P<0.05) and 10 µg (-2.8 kg; P<0.001) compared to placebo (-0.3 kg). There was no difference in fasting insulin or proinsulin concentrations between any of the treatments (P values not reported). No differences in lipid profiles were observed between any of the treatments (P value not reported). Gastrointestinal side effects were most commonly reported with exenatide and included nausea (45%), diarrhea (16%), and vomiting (12%) in exenatide 10 µg-treated patients (P values not reported). The incidence of hypoglycemia was similar with all treatments. Withdrawals due to adverse event(s) occurred in 7.1, 3.6, and 0.9% of patients receiving exenatide 10 µg, exenatide 5 µg, and placebo (P values not reported).
Kendall et al.[59] (2005)	DB, MC, PC, PG, RCT	N=733 30 weeks	Primary: Change in baseline HbA_{1c}	Primary: Significantly greater decreases in HbA_{1c} were achieved with exenatide 5

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Exenatide 5 µg BID and oral hypoglycemic therapy (existing therapy) vs exenatide 10 µg BID and oral hypoglycemic therapy (existing therapy) vs oral hypoglycemic therapy (existing therapy) and placebo	Type 2 diabetic patients 22 to 77 years of age, treated with maximally effective doses of metformin (≥1,500 mg/day) and a sulfonylurea (4 mg/day glimepiride, 20 mg/day glipizide, 10 mg/day glipizide XL, 10 mg/day glyburide, 6 mg/day micronized glyburide, 350 mg/day chlorpropamide, 500 mg/day tolazamide, or 1,500 mg/day tolbutamide) for ≥3 months before screening, FPG <13.3 mmol/L, BMI 27 to 45 kg/m^2, HbA_{1c} 7.5 to 11.0%, stable weight (±10%) for 3 months prior to screening, and no lab value >25% outside of normal value		Secondary: Change in baseline FPG, PPG, and body weight	(-0.55±0.07%) and 10 µg (-0.77±0.08%) compared to placebo (0.23±0.07%; P<0.001 for pairwise comparison). Secondary: Significantly greater decreases in FPG were achieved with exenatide 5 (-0.5±0.2 mmol/L) and 10 µg (-0.6±0.2 mmol/L) compared to placebo (0.8±0.2 mmol/L; P<0.0001 for pairwise comparison). Significantly greater decreases in PPG were achieved with exenatide 5 (P=0.009) and 10 µg (P=0.0004) compared to placebo. Significantly greater decreases in body weight were achieved with exenatide 5 (-1.6±0.2 kg) and 10 µg (-1.6±0.2 kg) compared to placebo (-0.9±0.2 kg; P≤0.01). Nausea was the most commonly reported adverse event and was observed in 48.5, 39.2, and 20.6% of patients receiving exenatide 10 µg, exenatide 5 µg, and placebo (P values not reported). A higher incidence of hypoglycemia was reported with exenatide. Hypoglycemia was reported in 27.8, 19.2, and 12.6% of patients receiving exenatide 10 µg, exenatide 5 µg, and placebo (P values not reported).
Abdul-Ghani et al.[60] (2015) EDICT	OL, RCT Drug-naïve, recently diagnosed (<2 years) subjects	N=221 2 years	Primary: HbA_{1c} Secondary:	Primary: Baseline HbA_{1c} was identical in both groups (8.6%) and during the first six months decreased in both treatment arms. At six months, there was a small but significant HbA_{1c} difference (0.2%, P=0.03) between groups (triple therapy 6.0% vs metformin therapy 6.2%). After six months, HbA_{1c} gradually

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Metformin (escalating dose) vs Triple therapy (metformin/ pioglitazone/ exenatide)	30 to 75 years of age with type 2 diabetes mellitus		Percentage of participants achieving HbA_{1c} <6.5 and <7.0%; decrease in fasting and postprandial plasma glucose; change in body weight; and rate of hypoglycemic events	increased with metformin therapy to 6.5% at 24 months and remained stable at 5.95% with triple therapy; thus, the difference in HbA_{1c} between the two treatments progressively increased with time and was significantly different at two years (change in HbA_{1c} 0.55%; P<0.0001). Secondary: More participants receiving metformin therapy failed to maintain the treatment goal (HbA_{1c} <6.5%) than did those receiving triple therapy (44 vs 17%; P=0.003). A total of 40 participants receiving metformin therapy failed to maintain HbA_{1c} at <6.5% at/after six months compared with only 13 participants receiving triple therapy (P<0.0001). More participants receiving triple therapy (61%) had HbA_{1c} reduced to the normal range (<6.0%) than those receiving metformin therapy (27%; P<0.0001). The median HbA_{1c} of participants receiving triple therapy was 5.9% compared with 6.4% for those receiving metformin therapy. More than 90% of participants receiving triple therapy maintained HbA_{1c} at <7.0% versus <75% of participants receiving metformin therapy. The most common adverse event was hypoglycemia, reported by 46 and 14% of participants receiving metformin and triple therapy, respectively. The overall frequency of hypoglycemic events was greater in participants receiving metformin therapy (2.2 vs 0.31 events/participant per year; P<0.0001).
Schernthaner et al.[61] (2015) EUREXA TZD or glimepiride added to metformin plus exenatide twice daily vs exenatide twice daily added to metformin plus glimepiride	MC, OL, RCT Patients with type 2 diabetes with metformin failure (HbA_{1c} ≥6.5 to ≤9.0%), were 19 to 85 years of age and had a BMI of ≥25 to ≤40 kg/m^2	N=310 Median duration of 2 years	Primary: Changes in HbA_{1c}, BMI, lipids, hypoglycemia, and vital signs Secondary: Not reported	Primary: Significant changes from baseline in HbA_{1c} were observed at 52, 78, 104 and 130 weeks with add-on TZD (all P<0.01), but only at 52 weeks with add-on glimepiride (P=0.001). Significant between-group differences favoring add-on TZD were observed at 78 (P=0.004) and 130 weeks (P=0.001). Among patients re-randomized to add-on glimepiride and add-on TZD, HbA_{1c} ≤7.0% was achieved by 26.0 and 30.7%, respectively, and HbA_{1c} ≤6.5% by 8.2 and 9.3%, respectively (no significant differences between the randomized groups). BMI significantly increased from baseline at 52, 78, 104 and 130 weeks with add-on TZD (all P≤0.01), but significantly increased at 52 and 78 weeks (both P<0.05) and decreased at 130 weeks with add-on glimepiride; the

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				between-group difference was significant at 104 (P=0.022) and 130 weeks (P=0.008). HDL cholesterol significantly increased from baseline to 130 weeks in the TZD add-on group (P<0.001), but not in the add-on glimepiride group; the between-group difference significantly favored TZD (P<0.001). For total and LDL cholesterol, there were no significant within- or between-group changes from baseline to 130 weeks. Systolic blood pressure was significantly increased at 130 weeks with add-on TZD (P=0.043), but not with add-on glimepiride; the between-group difference significantly favored glimepiride (P=0.044). The incidence of any hypoglycemia and nocturnal, non-nocturnal and documented symptomatic hypoglycemia with blood glucose ≤70 mg/dl was significantly higher for glimepiride than TZD as add-on to exenatide plus metformin. Although the proportion of patients reporting documented symptomatic hypoglycemia with blood glucose <50 mg/dl was similar in the add-on glimepiride (1/74; 1.4%) or TZD (1/76; 1.3%) groups, the exposure-adjusted mean rate/year was higher in the glimepiride group (0.10 vs 0.01 events/year of patient exposure). Secondary: Not reported
Zinman et al.[62] (2007) Exenatide 5 µg BID for 4 weeks followed by 10 µg BID vs placebo All patients received existing TZD	MC, PC, RCT Type 2 diabetics 21 to 75 years of age with a stable dose of a TZD (rosiglitazone ≥4 mg/day or pioglitazone ≥30 mg/day) for ≥4 months before screening, alone or in combination with a stable dose of	N=233 16 weeks	Primary: Change in baseline HbA_{1c} Secondary: FPG, body weight, self-monitored blood glucose concentrations, safety	Primary: Exenatide significantly decreased HbA_{1c} compared to placebo (-0.89±0.09 vs 0.09±0.10%; P<0.001). Secondary: Exenatide significantly decreased FPG compared to placebo (-1.59±0.22 vs 0.10±0.21 mmol/L; P<0.001). Exenatide significantly decreased weight compared to placebo (treatment difference, -1.51 kg; P<0.001). Exenatide-treated patients achieved significantly decreased self-monitored blood glucose profiles at each measurement throughout the day at week 16 compared to baseline (P<0.001) and placebo treated patients (P<0.001).

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regimen, with or without metformin.	metformin for 30 days, HbA_{1c} 7.1 to 10.0%, BMI 25 to 45 kg/m^2, and a history of stable body weight (≤10% variation) for ≥3 months before screening			Adverse events that were reported more commonly with exenatide included nausea (39.7 vs 15.2%; 95% CI, 12.7 to 36.3), vomiting (13.2 vs 0.9%; 95% CI, 5.2 to 19.5), and dyspepsia (7.4 vs 0.9%; 95% CI, 0.7 to 12.4).
Ratner et al.[63] (2006) Exenatide 5 µg SC BID for 4 weeks, followed by 10 µg SC BID All patients also received existing metformin therapy.	ES, MC, OL Type 2 diabetic patients 19 to 78 years of age, treated with metformin (≥1,500 mg/day) for ≥3 months before screening, FPG <240 mg/dL, BMI 27 to 45 kg/m^2, HbA_{1c} 7.1 to 11.0%, stable weight (±10%) for 3 months prior to screening, and no lab value >25% outside of normal value	N=150 52 weeks (82 weeks total)	Primary: Changes in baseline HbA_{1c}, body weight, and lipid profile of the completer cohort (those patients who completed 82 weeks of exenatide) and total cohort (ITT population) Secondary: Proportion of patients in the completer cohort with baseline HbA_{1c} >7.0% who achieved an HbA_{1c} ≤7.0%, reduction of weight after stratification by baseline BMI, safety	Primary: At week 30, the completer cohort had significant decreases in HbA_{1c} from baseline of -1.0±0.1%. At week 82, the decrease was -1.3±0.1% (95% CI, -1.5 to -1.0; P<0.05). For the total cohort, the decrease at week 30 was -0.7±0.1% (95% CI, -0.8 to -0.5; P<0.05) and at week 82 was -0.8±0.1% (95% CI, -1.0 to -0.6; P<0.05). At week 30, the completer cohort had significant decreases in body weight from baseline of -3.0±0.6 kg. At week 82, the decrease from baseline was -5.3±0.8 kg (95% CI, -7.0 to -3.7; P<0.05). For the total cohort, the decrease at week 30 was -2.3±0.4 kg and at week 82 was -4.3±0.6 kg (95% CI, -5.5 to -3.2; P<0.05). At week 82, the completer cohort experienced significant decreases in apo B (-5.20 mg/dL; 95% CI, -10.00 to -0.22; P value not reported), a reduction in TG (-73 mg/dL; 95% CI, -107 to -39; P value not reported) and an increase in HDL-C (4.5 mg/dL; 95% CI, 2.3 to 6.6; P value not reported). Secondary: At weeks 30 and 82, the proportion of patients in the completer cohort whose baseline HbA_{1c} was >7.0% and who achieved an HbA_{1c} ≤7.0% was 46 and 59% (P values were not reported). Patients in the completer cohort whose baseline BMI ≥30 kg/m^2 experienced a greater decrease of weight (-6.9±1.1 kg) compared to those whose baseline BMI was <30 kg/m^2 (-2.3±0.8 kg; P values were not reported). The following adverse events were experienced by patients in the total cohort: nausea (14 to 33%), upper respiratory tract infections (3 to 10%),

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				diarrhea (3 to 7%), vomiting (1 to 5%), and dizziness (2 to 6%) (P values were not reported).
Riddle et al.[64] (2006) Exenatide 5 µg SC BID or exenatide 5 µg SC BID for 4 weeks, followed by 10 µg SC BID All patients also received existing metformin and sulfonylurea therapies.	ES, MC, OL Type 2 diabetic patients 19 to 78 years of age, treated with metformin (≥1,500 mg/day) or maximally effective doses of a sulfonylurea (4 mg/day glimepiride, 20 mg/day glipizide, 10 mg/day glipizide XL, 10 mg/day glyburide, 6 mg/day micronized glyburide, 350 mg/day chlorpropamide, or 500 mg/day tolazamide) for ≥3 months before screening, FPG <240 mg/dL, BMI of 27 to 45 kg/m^2, HbA_{1c} 7.1 to 11.0%, stable weight (±10%) for 3 months prior to screening, and no lab value >25% outside of normal value	N=401 52 weeks (82 weeks total)	Primary: Change in baseline HbA_{1c} and FPG in the completer cohort (those patients who completed 82 weeks of exenatide therapy) and total cohort (ITT population) Secondary: Change in baseline weight, change in baseline HbA_{1c} and weight stratified by baseline HbA_{1c} and BMI	Primary: At week 30, the completer cohort experienced a significant decrease in HbA_{1c} of -0.8±0.1% for the original exenatide 5 µg arm and -1.0±0.1% for the original 10 µg arm. At week 82, the decrease was -1.0±0.1% (95% CI, -0.9 to -1.2; P value not reported). For the total cohort group, the decrease at week 82 was -0.7±0.1% (95% CI, -0.8 to -0.5; P value not reported). Results from week 30 week were not reported. At week 30, the completer cohort observed a decrease in FPG of -0.52±0.16 mmol/L (P value not reported). At week 82, the decrease was -0.62±0.19 mmol/L (P value not reported). FPG data for the total cohort were not reported. Secondary: At week 30, the completer cohort group experienced a decrease in body weight of -1.4±0.3 kg for the original exenatide 5 µg arm and -2.1±0.3 kg for the original 10 µg arm. At week 82, the decrease was -4.0±0.3 kg (95% CI, -4.6 to -3.4). The total cohort experienced a decrease in body weight of -3.3±0.2 kg (95% CI, -2.8 to -3.7; P value not reported). At week 82, patients in the completer cohort who had a baseline BMI ≥30 kg/m^2 experienced a greater decrease in mean weight from baseline of -4.4±0.4 kg compared to -3.2±0.5 kg in patients with a baseline BMI <30 kg/m^2 (P values not reported). Of the patients in the completer cohort who had a baseline HbA_{1c} >7.0%, 44% achieved an HbA_{1c} ≤7.0% at week 82. Patients with a baseline HbA_{1c} ≥9.0% experienced a greater decrease (-1.9±0.2%) compared to those with a baseline HbA_{1c}<9.0% (-0.7±0.1%) (P values were not reported). The most common reasons for withdrawal were administrative (study site closure) (12%), withdrawal of consent (11%), and adverse events (7%) (P values were not reported). In the total cohort, nausea and hypoglycemia were reported in ranges of 14 to 27% and 8 to 15% of patients, respectively (P values not reported).
Blonde et al.[65]	IA, MC, OL	N=551	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2006) Exenatide 5 µg SC BID or exenatide 5 µg SC BID for 4 weeks, followed by 10 µg SC BID All patients also received existing metformin and sulfonylurea therapies.	Type 2 diabetics	52 weeks (82 weeks total)	Change in baseline HbA_{1c} and safety in the completer cohort (those patients who completed 82 weeks of exenatide therapy) and total cohort (ITT population) Secondary: Change in baseline FPG and weight, change in baseline weight and HbA_{1c} stratified by baseline BMI and HbA_{1c}, change in lipid profile	At week 30, the completer cohort experienced a significant decrease in HbA_{1c} of -0.9±0.1%, and this decrease was maintained at week 82, with a decrease of -1.1±0.1% (95% CI, -1.0 to -1.3; P value not reported). The total cohort experienced a decrease at week 82 of -0.8±0.1% (95% CI, -0.6 to -0.9; P value not reported). Of the 551 ITT population, 314 (57%) patients completed the ES. Reasons for withdrawal included withdrawal of consent (11%), adverse events (7%), loss of glucose control (4%), and other (21%) (P values were not reported). In the total cohort, nausea and hypoglycemia were reported in ranges of 14 to 29% and 7 to 12% of patients, respectively (P values not reported). Secondary: At week 30, the completer cohort experienced a decrease in FPG of -0.7±0.1 mmol/L (P value not reported). At week 82, the decrease was -0.9±0.2 mmol/L (P value not reported). The total cohort FPG levels were not reported. At week 30, the completer cohort group experienced a decrease in body weight of -2.1±0.2 kg and at week 82 the decrease was -4.4±0.3 kg (95% CI, -3.8 to -5.1; P value not reported). At week 82, the total cohort experienced a decrease in body weight of -3.5±0.2 kg (95% CI, -3.1 to -4.0; P value not reported). At week 82, patients in the completer cohort who had a baseline BMI ≥40 kg/m^2 experienced a decrease of -7 kg compared to -2 kg in patients with a baseline BMI <25 kg/m^2 (P values not reported). In the completer cohort, of those patients whose baseline HbA_{1c} was >7.0%, 39 and 48% achieved HbA_{1c} ≤7.0% at weeks 30 and 82, respectively. At week 82, a greater decrease in HbA_{1c} was achieved in patients who had a baseline HbA_{1c} ≥9.0% (-2.0±0.2) compared to those with a baseline HbA_{1c} <9.0% (-0.8±0.1) (P values were not reported). In the completer cohort, of the lipid levels measured, significant benefits were observed in HDL-C (4 mg/dL; 95% CI, 3.7 to 5.4) and TG (-38.6 mg/dL; 95% CI, -55.5 to -21.6) at week 82 (P values not reported).
Buse et al.[66]	IA, OL	N=521	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2007) Exenatide 5 µg SC BID or exenatide 5 µg SC BID for 4 weeks, followed by 10 µg SC BID All patients also received existing metformin and sulfonylurea therapies.	Type 2 diabetics	104 weeks (2 years total)	Change in baseline HbA_{1c}, weight, and hepatic biomarkers; safety Secondary: Not reported	At week 104, exenatide significantly decreased HbA_{1c} by -1.1% (95% CI, -1.3 to -1.0; P<0.001). At week 104, exenatide significantly decreased weight by -4.7 kg (95% CI, -5.4 to -4.0; P<0.001). At Week 104, exenatide significantly decreased ALT by -5.3 IU/L (95% CI, -7.1 to -3.5; P<0.05) and decreased AST by -2.0 IU/L (95% CI, -3.3 to -0.8; P<0.05). Adverse events with an overall incidence ≥10% during 104 weeks of treatment were reported with the following proportion of patients affected: nausea (8 to 39%), upper respiratory tract infections (2 to 10%), and hypoglycemia (<1 to 13%) (P values were not reported). Secondary: Not reported
Klonoff et al.[67] (2008) Exenatide 5 µg SC BID or exenatide 5 µg SC BID for 4 weeks, followed by 10 µg SC BID All patients also received existing metformin and sulfonylurea therapies.	IA, OE, OL Type 2 diabetics	N=217 156 weeks (3 years total)	Primary: Change in baseline HbA_{1c}, weight, and ALT; safety Secondary: Not reported	Primary: At Week 156, exenatide significantly decreased HbA_{1c} by -1.0±0.1% (P<0.0001). At Week 156, exenatide significantly decreased weight by -5.3±0.4 kg (P<0.0001). At Week 156, exenatide significantly decreased ALT by -10.4±1.5 IU/L in patients with elevated ALT at baseline (P<0.0001). The most frequently reported adverse event was mild to moderate nausea. Secondary: Not reported
Viswanathan et al.[68] (2007) Exenatide 5 µg SC BID vs	RETRO Obese type 2 diabetic patients not adequately controlled despite treatment with oral	N=52 26 weeks	Primary: Change in baseline body weight, HbA_{1c}, and insulin dose Secondary:	Primary: Exenatide-treated patients experienced a significant decrease in body weight of -6.46±0.80 kg (P<0.001) compared to the patients in the control group who experienced a significant weight gain of 2.4±0.6 kg (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
control group (patients who discontinued exenatide therapy within 2 weeks on initiation due to insurance-related, personal or economic reasons) The dosages of rapid-acting and mixed insulin were reduced by 10% in patients with HbA_{1c} <7.5%. Subsequent dosage adjustments were made carefully based on ambient glucose concentrations.	hypoglycemic agents and insulin and HbA_{1c} >7.0%		Change in baseline TC, TG, DBP, SBP, and high-sensitivity CRP; safety	Exenatide-treated patients experienced a decrease in HbA_{1c} (-0.60±0.21%; P=0.007). The patients in the control group also experienced a decrease in HbA_{1c} (-8.4±0.5%; P value not reported). Exenatide-treated patients experienced a significant decrease in rapid-acting insulin requirements from 50.4±6.7 to 36.6±5.1 units (P<0.02) and for mixed insulin from 72.9±15.6 to 28.3±14.8 units (P<0.02). Insulin requirements for the control group were not reported. Secondary: Exenatide-treated patients experienced a significant decrease in TC from 163.9±8.2 to 149.8±5.9 mg/dL (P=0.03) compared to the patients in the control group who experienced a decrease from 168.1±16.3 to 144.33±10.39 mg/dL (P=0.08). Exenatide-treated patients experienced a significant decrease in TG from 202.5±28.8 to 149.9±17.3 mg/dL (P=0.01) compared to the patients in the control group who experienced a decrease from 182.7±23.9 to 171.1±39.2 mg/dL (P=0.91). Exenatide-treated patients experienced a significant decrease in SBP of -9.2±3.3 mm Hg (P=0.02). Data for the control group were not reported. Neither group experienced a reduction in DBP. Exenatide-treated patients experienced a significant decrease in high-sensitivity CRP of -34.0±14.3% (P=0.05). Data for the control group were not reported. Four patients receiving exenatide experienced severe nausea during treatment which led to discontinuation. Mild nausea was experienced by several other patients that did not interfere with therapy. Hypoglycemia (glucose <60 mg/dL) was rare and did not lead to any hospital admissions. No other adverse events were observed.
Grimm et al.[69] (2013) Exenatide once weekly	MA (post-hoc) (DURATION 1 through 6 trials)	N=1,379 24 to 30 weeks	Primary: Effects of 24 to 30 weeks of treatment with weekly exenatide on	Primary: At the end of the 24 to 30 week assessment period, 59% of population (compared with 3% at baseline) had achieved an HbA_{1c} level <7%, and 39% (compared with <1% at baseline) had achieved an HbA_{1c} level ≤6.5%. FPG levels also progressively declined over time and were significantly reduced at

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	Patients with type 2 diabetes, age ≥ 16 years, baseline HbA_{1c} level of 7.1% to 11%, a history of stable body weight, and a BMI≤ 45 kg/m^2		glycemic control, body weight, and CV risk factors Secondary: Not reported	endpoint. Modest but significant reductions in CV risk factors, including BP and fasting lipid levels, were observed following 24 to 30 weeks of exenatide once weekly treatment. Treatment with exenatide was also associated with progressive reductions in body weight. Patients experienced a least-squares mean reduction (95% CI) in body weight of −2.5 kg (−2.8 to −2.3 kg) at endpoint. At endpoint, 76% of the population experienced weight loss. Secondary: Not reported
Marre et al.[70] (2009) LEAD-1 Liraglutide 0.6, 1.2, and 1.8 mg SC QD plus glimepiride 2 to 4 mg/day and placebo vs placebo plus glimepiride 2 to 4 mg/day vs placebo plus glimepiride 2 to 4 mg/day and rosiglitazone 4 mg/day	AC, DB, DD, MC, PG, RCT Type 2 diabetic patients 18 to 80 years of age treated with an oral glucose-lowering agent for ≥3 months, HbA_{1c} 7.0 to 11.0% (previously on oral glucose lowering agent monotherapy) or 7.0 to 10.0% (previously on oral glucose lowering agent combination therapy), and BMI ≤45 kg/m^2	N=1,041 26 weeks	Primary: Change in baseline HbA_{1c} Secondary: Proportion of patients reaching HbA_{1c} (<7.0 and ≤6.5%), FPG (5.0 to ≤7.2 mmol/L), and PPG (10.0 mmol/L) targets; change in baseline body weight, FPG, mean PPG, β cell function, and BP	Primary: After 26 weeks, HbA_{1c} decreased by -1.1% with both liraglutide 1.2 and 1.8 mg, respectively, compared to placebo (0.2%) and rosiglitazone (-0.4%). Estimated treatment differences compared to placebo were: liraglutide 1.8 mg, -1.4% (95% CI, 1.6 to -1.1; P<0.0001); liraglutide 1.2 mg, -1.3% (95% CI, 1.5 to -1.1; P<0.0001); liraglutide 0.6 mg, -0.8% (95% CI, -1.1 to -0.6; P<0.0001); and rosiglitazone, -0.7% (95% CI, -0.9 to -0.4; P<0.0001). Additionally, the two higher doses of liraglutide (1.2 and 1.8 mg) were more efficacious compared to treatment with rosiglitazone (P<0.0001 for both measures). Decreases in HbA_{1c} were greater in patients previously on an oral glucose lowering agent monotherapy. Secondary: The proportion of patients reaching HbA_{1c} targets with liraglutide was dose-dependent. At week 26, 42, and 21% of patients receiving liraglutide 1.8 mg reached HbA_{1c} <7.0 and ≤6.5% compared to 8 and 4% of patients receiving placebo. Estimated proportions of patients receiving liraglutide 1.2 and 1.8 mg reaching HbA_{1c} targets were greater compared to patients receiving placebo (P<0.0001) and rosiglitazone (P<0.0003), respectively. More patients reached <7.0% with liraglutide 1.8 mg compared to 1.2 mg (P=0.018). The proportions of patients achieving FPG targets were significantly greater with liraglutide 0.6 mg (19%; P=0.002), 1.2 mg (37%; P<0.001), and 1.8 mg (38%; P=0.002) compared to placebo (7%). Compared to patients receiving rosiglitazone (26%), significantly more patients receiving liraglutide 1.2 and 1.8 mg achieved FPG targets (P=0.007 and P=0.01, respectively).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The proportion of patients with one, two, or three PPG target measurements were significantly greater for all doses of liraglutide compared to placebo (P<0.05), but not rosiglitazone (P value not reported). Mean decreases in weight were -0.2 kg with liraglutide 1.8 mg and -0.1 kg with placebo. Mean increases in weight were 0.7 kg with liraglutide 0.6 mg, 0.3 kg with liraglutide 1.2 mg, and 2.1 kg with rosiglitazone. Differences between rosiglitazone and liraglutide were significant (P<0.0001), although there were no differences compared to placebo (P value not reported). Decreases in the proinsulin:insulin ratio were significantly greater with liraglutide 1.2 and 1.8 mg compared to rosiglitazone and placebo (P≤0.02). HOMA-B increased with liraglutide 1.2 and 1.8 mg compared to rosiglitazone (P<0.05), and increases were only significant compared to placebo with liraglutide 1.2 mg (P=0.01). No differences between treatments were observed for changes in HOMA-IR. Decreases in SBP with liraglutide 1.2 and 1.8 mg (-2.6 to -2.8 mm Hg) were not different compared to placebo or rosiglitazone (-0.9 to -2.3 mm Hg; P values not reported).
Tamborlane et al.[71] (2019) ELLIPSE Liraglutide vs placebo	DB, MC, RCT Patients were 10 to <17 years of age at the time of randomization, had type 2 diabetes, had HbA_{1c} levels between 7.0 and 11.0% if they were being treated with diet and exercise alone or between 6.5 and 11.0% if they were being treated with metformin (with or without insulin),	N=134 26 weeks	Primary: Change in baseline HbA_{1c} Secondary: Change in fasting plasma glucose levels from baseline, the percentage of patients who reached a HbA_{1c} level of less than 7.0%, and the change from baseline in the BMI z score, adverse events	Primary: At the 26-week analysis of the primary efficacy end point, the mean glycated hemoglobin level had decreased by 0.64 percentage points with liraglutide and increased by 0.42 percentage points with placebo, for an estimated treatment difference of -1.06 percentage points (P<0.001). Secondary: The superiority of liraglutide to placebo in reducing fasting plasma glucose levels by 26 weeks was also shown. Moreover, 63.7% of the patients in the liraglutide group, as compared with 36.5% in the placebo group, attained HbA_{1c} <7.0% (P<0.001). In contrast, the statistical superiority of liraglutide to placebo in lowering the BMI z score was not shown; the estimated treatment difference at week 26 was −0.05 (95% CI, −0.15 to 0.06), which subsequently increased at week 52 to −0.18 (95% CI, −0.33 to −0.03). Similarly, mean body weight decreased in both groups at week 26 (−2.3 kg with liraglutide and −0.99 kg with placebo) but was maintained only with liraglutide at week 52 (−1.91 kg with liraglutide vs 0.87 kg with placebo).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	and had a body-mass index (BMI) greater than the 85th percentile			The number of patients who reported adverse events was similar in the two groups (56 [84.8%] with liraglutide and 55 [80.9%] with placebo), but the overall rates of adverse events and gastrointestinal adverse events were higher with liraglutide.
Nauck et al.[72] (2009) LEAD-2 Liraglutide 0.6, 1.2, and 1.8 mg SC QD vs placebo vs glimepiride 4 mg/day All patients also received metformin 1,500 to 2,000 mg/day.	AC, DB, DD, MC, PG, RCT Type 2 diabetic patients 18 to 80 years of age with HbA_{1c} 7.0 to 11.0% (pre-trial oral glucose lowering agent monotherapy ≥3 months) or 7.0 to 10.0% (pre-trial oral glucose lowering agent combination therapy ≥3 months), and BMI ≤40 kg/m^2	N=1,091 26 weeks	Primary: Change in baseline HbA_{1c} Secondary: Changes in baseline body weight, FPG, seven-point self-monitored glucose concentrations, and β cell function	Primary: HbA_{1c} decreased by -0.7±0.1% with liraglutide 0.6 mg, -1.0±0.1% with liraglutide 1.2 and 1.8 mg, and increased by 0.1±0.1% with glimepiride and placebo. Based on the estimated treatment differences, liraglutide had more efficacious glycemic control compared to placebo (liraglutide 0.6 mg vs placebo, -0.8%; 95% CI, -1.0 to -0.6 and liraglutide 1.2 and 1.8 mg vs placebo, -1.1%; 95% CI, -1.3 to -0.9; P values not reported). Analysis of the estimated treatment difference in HbA_{1c} between liraglutide and glimepiride demonstrated that liraglutide 1.2 and 1.8 mg were noninferior to treatment with glimepiride. Secondary: Weight loss was dose-dependent with liraglutide (liraglutide 0.6 mg, -1.8±0.2 kg; liraglutide 1.2 mg, -2.6±0.2 kg; liraglutide 1.8 mg, -2.8±0.2 kg). Reductions in weight with liraglutide were significantly different compared to glimepiride (-1.0±0.2 kg; P<0.001). Weight loss with liraglutide 1.2 and 1.8 mg was significantly greater compared to placebo (1.5±0.3 kg; P≤0.01). Decreases in FPG with liraglutide (-1.1, -1.6, and -1.7 mmol/L with liraglutide 0.6, 1.2, and 1.8 mg) were significantly greater compared to the increase with placebo (0.4 mmol/L; P<0.0001). Decreases with liraglutide were similar to glimepiride (-1.3 mmol/L; P value not reported). Mean baseline PPG values decreased with all liraglutide doses and glimepiride (liraglutide 0.6 mg, -1.7 mmol/L; liraglutide 1.2 mg, -2.3 mmol/L; liraglutide 1.8 mg, -2.6 mmol/L; glimepiride, -2.5 mmol/L; placebo, -0.6 mmol/L; P<0.001 for comparisons of all liraglutide doses vs placebo). The decreases observed with liraglutide 1.2 and 1.8 mg were comparable to glimepiride (P values not reported). No differences in the fasting C-peptide values were observed between liraglutide and glimepiride or placebo (P values not reported).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Decreases in the proinsulin: insulin ratio with all three liraglutide doses (-0.1) were comparable to glimepiride (P value not reported), and were significantly greater compared to placebo (0.1; P<0.0001). Liraglutide 0.6, 1.2, and 1.8 mg had improvements in HOMA-B of 63, 70, and 71%. Glimepiride had similar improvements, and there were no improvements with placebo. No differences were observed between any of the treatments (P values not reported).
Zinman et al.[73] (2009) LEAD-4 Liraglutide 1.2 and 1.8 mg SC QD vs placebo All patients also received metformin 2,000 mg/day and rosiglitazone 8 mg/day.	DB, MC, PC, PG, RCT Type 2 diabetic patients 18 to 80 years of age with HbA_{1c} 7.0 to 11.0% (pre-trial oral glucose lowering agent monotherapy ≥3 months) or 7.0 to 10.0% (pre-trial oral glucose lowering agent combination therapy for ≥3 months), and BMI ≤45 kg/m^2	N=533 26 weeks	Primary: Change in baseline HbA_{1c} Secondary: Change in baseline body weight, FPG, seven-point self-monitored glucose concentrations, β cell function, and lipids	Primary: The mean baseline HbA_{1c} for the overall population decreased by -1.5±0.1% with liraglutide 1.2 (95% CI, -1.1 to -0.8; P value not reported) and 1.8 mg (95% CI, -1.1 to -0.8; P value not reported) compared to -0.5±0.1% with placebo. Secondary: Weight loss with liraglutide was significantly greater compared to placebo (liraglutide 1.2 mg, -1.0±0.3 kg and liraglutide 1.8 mg, -2.0±0.3 kg; P<0.0001 for both). Decreases in FPG with liraglutide (liraglutide 1.2 mg, -2.2 mmol/L and liraglutide 1.8 mg, -2.4 mmol/L) were significantly greater compared to placebo (-0.4 mmol/L; P<0.0001 for both). Decreases in mean PPG were significantly greater with liraglutide compared to placebo (liraglutide 1.2 mg, -2.6 mmol/L; liraglutide 1.8 mg, -2.7 mmol/L; and placebo, -0.8 mmol/L; P<0.001 for both). The decrease in proinsulin:insulin ratio with liraglutide was significantly greater compared to placebo (liraglutide 1.2 mg, -0.029±0.026; liraglutide 1.8 mg -0.085±0.260; placebo, 0.036±0.029; P<0.05 for both). The increase in C-peptide was significantly greater with liraglutide compared to placebo (liraglutide 1.2 mg, 131±32; liraglutide 1.8 mg, 144±31; placebo, 51±34 pmol/L; P<0.05 for both). Increases in HOMA-B with liraglutide were significantly greater compared to placebo (P<0.05), but decreases with HOMA-IR were not different between treatments (P values not reported).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Decreases in FFA were significantly greater with liraglutide 1.2 mg (-0.03±0.02 mmol/L; P<0.05) and liraglutide 1.8 mg (-0.05±0.02 mmol/L; P<0.05) compared to placebo (0.02±0.02). Other significant decreases in lipid profiles with liraglutide compared to placebo were LDL-C (liraglutide 1.2 mg, -0.28±0.07 vs -0.10±0.07 mmol/L; P<0.05) and TG (liraglutide 1.2 mg, -0.38±0.10 vs -0.13±0.11 mmol/L; P<0.05).
Marso et al.[74] (2016) LEADER Liraglutide 1.8 mg SC QD vs placebo	DB, MC, RCT Patients ≥50 years of age with type 2 diabetes with at least one cardiovascular coexisting condition (coronary heart disease, cerebrovascular disease, peripheral vascular disease, chronic kidney disease of stage 3 or greater, or chronic heart failure of New York Heart Association class II or III) or an age of 60 years or more with at least one cardiovascular risk factor, as determined by the investigator	N=9,340 Median follow-up of 3.8 years	Primary: First occurrence of death from cardiovascular causes, nonfatal (including silent) myocardial infarction, or nonfatal stroke Secondary: Not reported	Primary: The primary composite outcome occurred in fewer patients in the liraglutide group (608 of 4668 patients [13.0%]) than in the placebo group (694 of 4672 [14.9%]) (HR, 0.87; 95% CI, 0.78 to 0.97; P<0.001 for noninferiority; P=0.01 for superiority). Secondary: Not reported
Russell-Jones et al.[75] (2009) LEAD-5	PC, PG, RCT Type 2 diabetic patients 18 to 80 years of age with	N=581 26 weeks	Primary: Change in baseline in HbA_{1c} Secondary:	Primary: Decreases in HbA_{1c} were -1.33, -0.24, and -1.09% with liraglutide, placebo, and insulin. Decreases achieved with liraglutide were significantly greater compared to placebo and insulin (differences for liraglutide vs placebo, -

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Liraglutide 1.8 mg SC QD vs placebo vs insulin glargine (OL) All patients also received metformin 2,000 mg/day and glimepiride 4 mg/day.	oral glucose lowering agents ≥3 months before screening, HbA_{1c} 7.5 to 10.0% (previous oral glucose lowering agent monotherapy) or 7.0 to 10.0% (previous oral glucose lowering agent combination therapy), and BMI ≤45 kg/m^2		Change in baseline body weight, waist circumference, FPG, eight-point self-monitored glucose concentrations, β cell function, and BP	1.09%; 95% CI, -1.28 to -0.90; P<0.0001 and differences for liraglutide vs glargine, -0.24%; 95% CI, -0.39 to -0.08; P=0.0015). Secondary: The decrease in body weight with liraglutide (-1.8 kg) was significantly greater compared to placebo (0.42 kg; treatment difference, -1.39 kg; 95% CI, -2.10 to -0.69; P=0.0001). Additionally, patients gained weight with insulin (1.6 kg; treatment difference, -3.43 kg; 95% CI, -4.00 to -2.86; P<0.0001). The decrease in waist circumference with liraglutide (-1.50 cm) was significantly greater compared to insulin (0.89 cm; treatment difference, -2.40 cm; 95% CI, -3.14 to -1.65; P<0.0001), but not compared to placebo (-0.62 cm; treatment difference, -0.88 cm; 95% CI, -1.81 to 0.04; P=0.0608). Final decreases in FPG were -1.55, -1.79, and -0.53 mmol/L with liraglutide, insulin, and placebo. The decrease with liraglutide, and the likelihood of achieving American Diabetes Association targets (FPG 5.0 to 7.2 mmol/L) was significantly greater compared to placebo (treatment difference, -2.08 mmol/L; 95% CI, 2.53 to -1.64; P<0.0001; OR, 4.99; 95% CI, 2.65 to 9.39), but not compared to insulin (data not reported). Decreases in PPG were achieved with liraglutide (-1.81 mmol/L) and insulin (-1.61 mmol/L), with liraglutide being significantly greater compared to placebo (0.03 mmol/L; treatment difference, -1.84 mmol/L; 95% CI, -2.63 to -1.33; P<0.0001), but not compared to insulin (data not reported). Significant improvements in β cell function as demonstrated by the proinsulin:C-peptide ratio compared to insulin (treatment difference, -0.00366; 95% CI, -0.00597 to -0.00136; P=0.0019) and placebo (treatment difference, -0.00671; 95% CI, -0.00964 to -0.00377; P<0.0001) were achieved with liraglutide. A significant decrease in SBP was achieved with liraglutide (-4.00 mm Hg) compared to insulin (-0.54 mm Hg; treatment difference, -4.51 mm Hg; 95% CI, -6.82 to -2.20; P=0.001), but not compared to placebo (-1.4 mm Hg; treatment difference, -2.53 mm Hg; 95% CI, -5.36 to 0.29; P=0.0791). No

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				significant decreases in DBP were achieved with liraglutide relative to either placebo or insulin.
Kaku et al.[76] (2010) Liraglutide 0.6 and 0.9 mg SC QD vs placebo All patients received existing sulfonylurea therapy.	DB, MC, PG, RCT Japanese type 2 diabetics ≥20 years of age currently treated with a sulfonylurea for ≥8 weeks, HbA_{1c} 7.0 to <10.0%, and BMI <35 kg/m^2	N=264 52 weeks (initial 24 week DB period, followed by 28 week OL period to assess the long-term safety and efficacy of liraglutide)	Primary: Change in baseline HbA_{1c} at 24 weeks Secondary: seven-point self-monitored glucose concentrations, body weight, FPG, PPG, lipid profile, biomarkers for cardiovascular effects, proportion of patients reaching an HbA_{1c} <7.0 or <6.5% (post-hoc analysis)	Primary: Liraglutide significantly decreased and sustained HbA_{1c} compared to placebo. The decrease at week 24 was greater with liraglutide 0.9 mg (-1.56±0.84%) compared to the other treatments (liraglutide 0.6 mg, -1.46±0.95% and placebo, -0.40±0.93%). HbA_{1c} at week 24 were significantly lower with liraglutide compared to placebo (7.02 and 6.75% with liraglutide 0.6 and 0.9 mg compared to 8.02% with placebo) with the treatment differences of -1.00% (95% CI, -1.24 to -0.75) with liraglutide 0.6 mg and -1.27% (95% CI, -1.51 to -1.02) with liraglutide 0.9 mg. Secondary: Improvements in metabolic controls were apparent in the seven-point self monitored glucose concentration profiles at week 24, with significant reductions in glucose. Plasma glucose was significantly lower with liraglutide compared to placebo (P<0.0001). Body weight did not change with liraglutide (0.6 mg, 0.06 kg and 0.9 mg, -0.37 kg) despite the improvements seen in glycemic control (P values not reported). Weight decreased with placebo (-1.12 kg). Full impact on FPG levels was achieved at the first two visits at week four, and levels were significantly lower with liraglutide at week 24 compared to placebo. FPG with liraglutide 0.6 and 0.9 mg was significantly lower compared to placebo (7.34±0.19, 7.01±0.19, and 8.81±0.19 mmol/L, respectively; P<0.0001). The estimated means of PPG at week 24 at all time points with liraglutide were lower compared to placebo, with much lower mean values occurring with liraglutide 0.9 mg (P values not reported). The means of $AUC_{0\text{-}3hr}$ at week 24 were also significantly lower with liraglutide compared to placebo (P<0.0001). No significant treatment effects were observed in any of the parameters of the lipid profile. The cardiovascular biomarker BNP was significantly lower with liraglutide compared to placebo (liraglutide 0.6 mg vs placebo; P=0.0018 and liraglutide 0.9 mg vs placebo; P=0.0157). High-sensitivity CRP was significantly lower with liraglutide 0.6 mg compared to placebo (P=0.0218), but no difference was observed between liraglutide 0.9 mg and placebo

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				(P=0.8143). No treatment effect was seen in the estimated mean of PAI-1 at week 24 (P values not reported). A significantly greater proportion of patients receiving liraglutide achieved HbA_{1c} values <7.0 and <6.5% compared to placebo (P values not reported).
Ahmann et al.[77] (2015) Liraglutide 1.8 mg SC QD vs placebo added to their pre-existing basal insulin analogue (≥20 U/day) ± metformin (≥1500 mg/day)	DB, MC, RCT Adults with inadequately controlled type 2 diabetes (HbA_{1c} of 7.0 to 10.0%)	N=451 26 weeks	Primary: Change in baseline HbA_{1c} Secondary: HbA_{1c} <7 or ≤6.5%, FPG, seven-point self-measured plasma glucose values, body weight, SBP, adverse events	Primary: After 26 weeks of treatment, HbA_{1c} was reduced more with liraglutide than with placebo (−1.3 vs −0.1%), with an estimated treatment difference of −1.2% (95% CI, −1.4 to −1.0%; P<0.0001). Secondary: More subjects on liraglutide reached HbA_{1c} targets: <7.0% (59 vs 14%; P<0.0001) and ≤6.5% (43 vs 4%; P<0.0001) using slightly less insulin (35.8 vs 40.1 IU). Greater decreases from baseline (estimated treatment differences vs placebo; P<0.0001) occurred in fasting plasma glucose (−1.3 mmol/l), seven-point glucose profiles (−1.6 mmol/l), body weight (−3.1 kg) and systolic blood pressure (−5.0 mmHg). Transient gastrointestinal adverse events (nausea: 22.2 vs 3.1%) and minor hypoglycemia (18.2 vs 12.4%) were more frequent with liraglutide than placebo, and pulse increased (4.5 beats/min) compared with placebo. No severe hypoglycemia or pancreatitis occurred.
Drucker et al.[78] (2008) DURATION-1 Exenatide ER 2 mg SC once weekly vs exenatide 5 µg SC BID for 28 days, followed by 10 µg BID	AC, OL, NI, RCT Type 2 diabetics for ≥2 months prior to screening; ≥16 years of age; HbA_{1c} 7.1 to 11.0%; FPG <16 mmol/L; BMI 25 to 45 kg/m^2; and therapy with diet modification and exercise, or treatment with metformin, sulfonylurea, TZD, or any combination of 2 of these agents	N=303 30 weeks	Primary: Change in baseline HbA_{1c} Secondary: Safety and tolerability; FPG and PPG; body weight; fasting glucagon; fasting lipids; BP; proportion of patients achieving HbA_{1c} ≤7.0, ≤6.5, and ≤6.0%; exenatide antibodies	Primary: Both treatments achieved significant decreases in HbA_{1c}, with a decrease at week 30 of -0.33±0.10% (95% CI, -0.54 to -0.12). Decreases were significantly greater with exenatide ER compared to exenatide (-1.9±0.1 vs -1.5±0.1%; P=0.0023). Significant decreases with both treatments were observed as early as week six, and the mean decrease was significantly greater with exenatide ER compared to exenatide by week 10, and the difference persisted throughout the remainder of the trial. Overall, decreases were consistent across all treatment background therapies and did not vary notably with sex or age (>65 years vs <65 years). Secondary: Adverse events reported in >10% of patients include nausea (26.4 vs 34.5%), vomiting (10.8 vs 18.6%), injection site pruritus (17.6 vs 1.4%), upper respiratory tract infection (8.1 vs 17.2%), diarrhea (13.5 vs 13.1%), constipation (10.8 vs 6.2%), injection site bruising (4.7 vs 10.3%), and urinary tract infection (10.1 vs 8.3%). Gastrointestinal complaints were the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				most frequently reported adverse events with exenatide. Treatment-related nausea was reported in significantly fewer patients receiving exenatide ER (P value not reported). Reported nausea with both treatments was predominantly mild in intensity, and no severe nausea was reported with exenatide ER. Injection site pruritus with either treatment was typically mild in intensity, and resolved with continued treatment. No episodes of major hypoglycemia were reported with either treatment, and the incidence of minor hypoglycemia was low. Withdrawals due to adverse events were 6.1 vs 4.8% (P value not reported). No clinically significant abnormalities in vital signs; electrocardiogram reports; or hematological, chemistry, or urinalysis values were reported. The incidence of serious adverse events was low (5.4 vs 3.4%). No cases of pancreatitis were reported with either treatment. Both treatments achieved significant decreases in FPG and PPG, with exenatide ER achieving significantly greater decreases in FPG compared to exenatide (-2.3±0.2 vs -1.4±0.2 mmol/L; 95% CI, -1.3 to -5.2; P<0.0001). Analysis across all background treatments revealed similar results. Similar results were observed with PPG (data reported in graphical form only). Both treatments resulted in significant improvements in 7-point self-monitored glucose concentrations profiles. Body weight decreased progressively with both treatments (-3.7±0.5 vs -3.6±0.5 kg; 95% CI, -1.3 to 1.1; P=0.89). At week 30, the mean percentage of weight loss from baseline was -3.6 vs -3.7% with exenatide ER and exenatide (P>0.05). Both treatments significantly decreased FPG and PPG (P values not reported). Exenatide ER achieved significantly greater decreases in TC (-0.31±0.06 vs -0.10±0.06 mmol/L) and LDL-C (-0.13±0.05 vs 0.03±0.05 mmol/L) compared to exenatide (P values not reported). TG decreased with both treatments (-15 vs -11%; P value not reported). Both treatments achieved significant improvements in SBP and DBP (P values not reported).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				A significantly greater proportion of patients receiving exenatide ER achieved an HbA_{1c} ≤7.0% compared to patients receiving exenatide (77 vs 61%; P=0.0039). Forty nine and 25% of patients receiving exenatide ER achieved HbA_{1c} ≤6.5 and ≤6.0%. Anti-exenatide antibody levels were significantly higher with exenatide ER compared to exenatide (P=0.0002), but most antibodies were either not detectable or of low titer.
Buse et al.[79] (2010) DURATION-1 Exenatide ER 2 mg SC once weekly (continued exenatide ER) vs exenatide ER 2 mg SC once weekly (switched to exenatide ER) Patients enrolled in DURATION-1 who were randomized to exenatide 10 µg SC BID were transitioned to exenatide ER 2 mg SC once weekly after the initial 30 week trial period.	ES (DURATION-1[44]) Type 2 diabetics for ≥2 months prior to screening; ≥16 years of age; HbA_{1c} 7.1 to 11.0%; FPG <16 mmol/L; BMI 25 to 45 kg/m^2; and therapy with diet modification and exercise, or treatment with metformin, sulfonylurea, TZD, or any combination of 2 of these agents	N=258 22 weeks (52 weeks total)	Primary: Efficacy, body weight, glucose control, lipid and BP profile, safety and tolerability Secondary: Not reported	Primary: During the 22 weeks, patients who continued exenatide ER maintained improvements in HbA_{1c}, with a decrease of -2.1% (95% CI, -2.2 to -1.9) at week 30 and -2.0% (95% CI, -2.1 to -1.8) at week 52. Patients who switched to exenatide ER (week 30 HbA_{1c} decrease, -1.8%; 95% CI, -1.9 to -1.6) exhibited further improvements in glycemic control and achieved the same reduction (-2.0%) and mean HbA_{1c} (6.6%) at week 52 compared to patients who continued exenatide ER. After 52 weeks, 71 and 54% of all patients achieved an HbA_{1c} ≤7.0 and ≤6.5% (similar between the two cohorts). In patients with a baseline HbA_{1c} <9.0%, the decrease at week 52 was -1.2 (95% CI, -1.4 to -1.1) and -1.3% (95% CI, -1.5 to -1.2) in patients who continued exenatide ER and in those who switched to exenatide ER. Larger decreases in HbA_{1c} were observed in patients with a baseline HbA_{1c} ≥9.0% (-2.8 [95% CI, -3.1 to -2.5] vs -2.6% [95% CI, -3.0 to -2.3]). Body weight decreased similarly with both treatments. At week 52, the decreases in body weight were -4.1 (95% CI, -5.3 to -2.9) vs -4.5 kg (95% CI, -5.7 to -3.3) in patients who continued exenatide ER and those who switched to exenatide ER. In patients who continued exenatide ER, the decreases in FPG achieved at week 30 (-46 mg/dL; 95% CI, -52 to -40) were maintained throughout the 52 weeks (-47 mg/dL; 95% CI, -53 to -41). Patients who switched to exenatide ER achieved a similar decrease in FPG at week 52 (-43 mg/dL; 95% CI, -49 to -37). Subsequent to week 30, patients switched to exenatide ER experienced a transient rise in mean FPG followed by a rapid decreases within two weeks after switching treatment. Clinically significant improvements in BP were observed in patients who continued exenatide ER for 52 weeks. (SBP, -6.2 mm Hg; 95% CI, -8.5 to -

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				3.9 and DBP, -2.8 mm Hg; 95% CI, -4.3 to -1.3) and in patients who switched to exenatide ER (SBP, -3.8 mm Hg; 95% CI, -6.1 to -1.5 and DBP, -1.8 mm Hg; 95% CI, -3.2 to -0.3). Fifty and 36% of patients in the two treatment groups who had elevated SBP at baseline achieved normal SBP at week 52. Improvements in lipid profiles were achieved in both treatment groups, with clinically significant decreased in TC (-9.6 [95% CI, -14.8 to -4.3] and -9.0 mg/dL [95% CI, -14.5 to -3.6]) and TG (-15%; 95% CI, -21 to -9). Treatment-emergent adverse events that occurred for the first time or worsened during the 22 week long second phase were similar to those observed during the initial 30 weeks of treatment. Nausea was predominantly mild, and no severe cases were reported. Twenty one patients (four vs 17) reported injection site-related adverse events. Mild to moderate injection site pruritus was observed after switching from exenatide to exenatide ER in six patients. No cases of pancreatitis were reported. Secondary: Not reported
Blevins et al.[80] (2011) DURATION-5 Exenatide ER 2 mg SC once weekly vs exenatide 5 µg SC BID for 4 weeks, followed by 10 µg SC BID	AC, MC, OL, RCT Type 2 diabetics ≥18 years of age treated for ≥2 months with diet and exercise alone or with a stable, maximally effective regimen of metformin, sulfonylurea, TZD, or a combination of these medications; HbA_{1c} 7.1 to 11.0%; FPG <280 mg/dL; and BMI 25 to 45 kg/m^2	N=252 24 weeks	Primary: Change in baseline HbA_{1c} Secondary: Proportion of patients achieving HbA_{1c} <7.0 and <6.5% and FPG ≤126 mg/dL, body weight, FPG, BP, lipid profile, safety and tolerability	Primary: Decreases in HbA_{1c} were significantly greater with exenatide ER compared to exenatide (-1.6±0.1 vs -0.9±0.1%, treatment difference, -0.7%; 95% CI, -0.9 to -0.4). At week 24, HbA_{1c} was 7.1±0.1 and 7.7±0.1% with exenatide ER and exenatide. Secondary: A significantly greater proportion of patients receiving exenatide ER achieved HbA_{1c} <7.0 (58.1 vs 30.1%; P<0.0001) and <6.5% (41.1 vs 16.3%; P<0.0001) compared to exenatide. Similar results were achieved for FPG ≤126 mg/dL (50.4 vs 30.9%; P=0.0008). Both treatments resulted in progressive decreases in body weight through 24 weeks (between group difference, -0.95 kg; 95% CI, -1.9 to 0.01). By week 24, 77 and 63% of patients receiving exenatide ER and exenatide experienced weight loss, whereas 71 and 51% of patients experienced both weight loss and a decrease in HbA_{1c}.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Decreases in FPG were significantly greater with exenatide ER compared to exenatide (-35±5 vs -12±5 mg/dL; P=0.0008). Decreases in SBP were significant with exenatide ER (-2.9±1.1 mm Hg; 95% CI, -5.2 to -0.7), but not with exenatide. No significant decreases in DBP were observed with either treatment. Decreases in TC (-15.4±2.6 mg/dL; 95% CI, -20.5 to -10.2) and LDL-C (-6.4±2.1 mg/dL; 95% CI, -10.7 to -2.2) were significant with exenatide ER, and no significant changes were observed with exenatide. Nausea, the adverse event most commonly reported with both treatments (14 vs 35%), occurred at a lower incidence in patients receiving exenatide ER. Injection site-related adverse events were more common with exenatide ER (13 vs 10%), with one patient receiving exenatide ER withdrawing from treatment due to mild injection site pruritus. There were no major hypoglycemic episodes. The incidences of serious adverse events were low (2 vs 4%). During the course of treatment there was substantial variability in pancreatic-amylase and lipase concentrations. The incidence of adverse events, including gastrointestinal symptoms was similar between patients with normal and abnormal post-baseline amylase and lipase measured at any post-baseline time point.
Wysham et al.[81] (2018) DURATION-NEO-1 Exenatide 2 mg once weekly via autoinjector vs exenatide 5 µg SC BID for 4 weeks, followed by 10 µg SC BID	MC, OL, RCT Adults (≥18 years of age) with type 2 diabetes who were treated with diet and exercise alone or with a stable regimen of metformin, sulfonylurea, pioglitazone or any combination of 2 of these agents and had an HbA_{1c} level of 7.1 to ≤11.0%	N=375 28 weeks	Primary: Change in HbA_{1c} from baseline Secondary: Proportion of patients achieving HbA_{1c} < 7.0% by 28 weeks, change in FPG and body weight from baseline to week 28; adverse events	Primary: HbA_{1c} was reduced with both exenatide weekly (−1.39% ± 0.09%) and exenatide BID treatment (−1.02% ± 0.11%). The reduction in HbA_{1c} after 28 weeks was greater with exenatide weekly (difference, −0.37% ± 0.13; 95% CI, −0.63 to −0.10%; P=0.0072). Secondary: There was no statistical difference in the proportion of patients who achieved HbA_{1c} <7.0% with exenatide weekly (49.3%) or exenatide BID (43.2%; P=0.225). FPG decreased comparably with both treatments by week two (the first post-baseline measurement) and remained below baseline for the duration of the study. After 28 weeks, the change in FPG was −32.7 ± 3.9 mg/dL for exenatide weekly and −22.5 ± 4.9 mg/dL for exenatide BID (difference, −10.2 ± 5.8 mg/dL; P=0.083).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Body weight was reduced from baseline with both exenatide weekly (−1.49 ± 0.28 kg) and exenatide BID (−1.89 ± 0.36 kg). After 28 weeks, there was no significant between-group difference in change in body weight (difference, 0.4 ± 0.4 kg; P=0.37). Gastrointestinal adverse events were reported in 22.7% (exenatide weekly) and 35.6% (exenatide BID) of patients. Injection site-related adverse events were more frequent overall with exenatide weekly (26.6%) than with exenatide BID (4.1%).
Jabbour et al.[82] (2018) DURATION-8 extension Exenatide 2 mg once weekly by subcutaneous injection plus dapagliflozin 10 mg oral tablets daily vs exenatide once weekly with dapagliflozin-matched oral placebo daily vs dapagliflozin daily with exenatide once weekly–matched placebo injections	DB, MC, RCT Adults (≥18 years of age) with type 2 diabetes and inadequate glycemic control (HbA_{1c} 8.0 to 12.0%) despite stable metformin monotherapy (≥1,500 mg/day)	N=695 52 weeks	Primary: Glycemic parameters Secondary: Safety and tolerability	Primary: Treatment with exenatide once weekly plus dapagliflozin resulted in greater mean reductions in HbA_{1c} from baseline to week 28, which were maintained through week 52 (least squares mean change from baseline, −1.75%) compared with exenatide once weekly plus placebo (−1.38%; P=0.006) or dapagliflozin plus placebo (−1.23%; P<0.001). At week 52, mean HbA_{1c} was 6.87% with exenatide once weekly plus dapagliflozin, 7.21% with exenatide once weekly plus placebo, and 7.36% with dapagliflozin plus placebo. The proportions of patients who achieved glycemic goals with exenatide once weekly plus dapagliflozin were generally similar at 28 and 52 weeks. At 52 weeks, more patients achieved an HbA_{1c} level of <7.0% or ≤6.5%, respectively, with exenatide once weekly plus dapagliflozin (37.7% and 26.3%) than with exenatide once weekly plus placebo (30.0% and 17.2%) or dapagliflozin plus placebo (16.5% and 8.7%). Secondary: Exenatide once weekly plus dapagliflozin was well tolerated; similar proportions of patients experienced an adverse event over 52 weeks across all treatment groups. The most common adverse events reported with exenatide once weekly plus dapagliflozin were injection-site nodule, urinary tract infection, headache, and nausea. Most adverse events were mild or moderate in intensity. Patients who received exenatide once weekly plus dapagliflozin and exenatide once weekly plus placebo experienced more gastrointestinal or injection site–related adverse events than those who received dapagliflozin plus placebo.
Buse et al.[83] (2009) LEAD-6	AC, MC, OL, PG, RCT	N=464 26 weeks	Primary: Change in baseline HbA_{1c}	Primary: Decreases in HbA_{1c} with liraglutide were more efficacious compared to exenatide (-1.12 vs -0.79%; treatment difference, -0.33; 95% CI, -0.47 to -

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Liraglutide 1.8 mg SC QD vs exenatide 10 µg SC BID Background oral glucose-lowering agents were maintained at pre-trial doses unless unacceptable hypoglycemia occurred, in which case sulfonylurea doses could be reduced to no less than 50% of the starting dose.	Type 2 diabetic patients 18 to 80 years of age with HbA_{1c} 7.0 to 11.0%; BMI ≤45 kg/m^2; and stable on treatment with maximally tolerated doses of metformin, sulfonylurea, or both for ≥3 months		Secondary: Proportion of patients reaching HbA_{1c} targets (<7.0 and ≤6.5%); change in baseline FPG, seven-point self-monitored glucose concentrations, body weight, β cell function, glucagon, BP, and lipid profiles	0.18; P value not reported). Data in the ITT population demonstrated similar decreases with liraglutide and exenatide (-1.16 vs -0.87%; estimated treatment difference, -0.29%; 95% CI, -0.45 to -0.13; P<0.0001). Secondary: The proportion of patients achieving target HbA_{1c} was significantly greater with liraglutide compared to exenatide (HbA_{1c} <7.0%, 54 vs 43%; OR, 2.02; 95% CI, 1.31 to 3.11; P value not reported and HbA_{1c} ≤6.5%, 35 vs 21%; OR, 2.73; 95% CI, 1.68 to 4.43; P value not reported). Significant decreases in FPG were achieved with liraglutide compared to exenatide (-1.61 vs -0.60 mmol/L; treatment difference, -1.01 mmol/L; 95% CI, -1.37 to -0.65; P<0.0001). In contrast, exenatide decreased PPG significantly more compared to liraglutide after breakfast (treatment difference, -1.33 mmol/L; 95% CI, 0.80 to 1.86; P<0.0001) and dinner (treatment difference, -1.01 mmol/L; 95% CI, 0.44 to 1.57; P=0.0005). After lunch differences between the two treatments were not significant (data not reported). Both treatments were associated with decreases in body weight (-3.24 vs -2.87 kg; treatment difference, -0.37 kg; 95% CI, -0.99 to 0.23; P=0.2235). Increases in HOMA-B were significant with liraglutide compared to exenatide (32.12 vs 2.74%; treatment difference, 29.38%; 95% CI, 16.81 to 41.93; P<0.0001). Decreases in fasting glucagon were not different between the two treatments (-19.44 vs -12.33 ng/L; treatment difference, -7.11 ng/L; 95% CI, -16.66 to 2.43; P=0.1436). No differences were observed between the two treatments in terms of decreases in SBP (P=0.6409) or DBP (P=0.1610). In terms of lipid profiles, significant changes favoring liraglutide were observed only for VLDL-C (P=0.0277), TG (P=0.0485), and FFA (P=0.0014). All other lipid parameters were similar between the two treatments.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Buse et al.[84] (2010) Liraglutide 1.8 mg SC QD (continued liraglutide) vs liraglutide 1.8 mg SC QD (switched to liraglutide) Patients enrolled in LEAD-6 who were randomized to exenatide 10 µg SC BID were transitioned to liraglutide 1.8 mg SC QD after the initial 26 week trial period.	ES (LEAD-6) Type 2 diabetic patients 18 to 80 years of age with HbA_{1c} 7.0 to 11.0%; BMI ≤45 kg/m^2; and stable on treatment with maximally tolerated doses of metformin, sulfonylurea, or both for ≥3 months	N=376 14 weeks (40 weeks total)	Primary: Change in baseline HbA_{1c}, FPG, body weight, and SBP; adverse events Secondary: Not reported	Primary: HbA_{1c} decreased further from 7.2% at week 26 to 6.9±0.32% at week 40 (P<0.0001) after switching from exenatide to liraglutide, but remained similar with continued liraglutide treatment (7.0 to 6.9±-0.06%; P=0.1222). Additional patients reached HbA_{1c} targets after switching from exenatide to liraglutide. After switching from exenatide to liraglutide, further decreases in FPG (-0.9±0.16 mmol/L; P<0.0001), body weight (-0.9±0.15 kg; P<0.0001), and SBP (-3.8±0.84 mmHg; P<0.0001) occurred, while HOMA-B increased (14.5±4.4%; P=0.001), consistent with FPG reductions. With continued liraglutide treatment, reductions in FPG (-0.2±0.11 mmol/L; P=0.0973), body weight (-0.4±0.15 kg; P=0.0089), and SBP (-2.2±0.88 mmHg; P=0.0128) occurred. No significant changes in PPG occurred in either treatment group (P value not reported). Similar numbers of patients reported one or more adverse events during the ES (37.6 vs 37.4%; P value not reported). Most adverse events were mild in severity. Nausea and diarrhea occurred in 1.5% of patients who continued liraglutide and 3.2% of patients who switched from exenatide to liraglutide, whereas vomiting occurred in 2.0% of patients who continued liraglutide and 0.5% of patients who switched from exenatide to liraglutide. One major hypoglycemic episode occurred in a patient continuing liraglutide. Four patients who switched from exenatide to liraglutide had seven severe adverse events (cardiac failure, MI, cataract, chest discomfort, COPD, and dyspnea). Five patients continuing liraglutide had eight severe adverse events (cerebral infarction, cerebrovascular accident, TIA, acute coronary syndrome, coronary artery occlusion, portal vein thrombosis, rectal cancer, and depression). Calcitonin levels remained at the lower level of the normal range (<1 pg/mL) and did not differ between treatment groups. No medullary thyroid carcinoma or pancreatitis cases were reported. Secondary: Not reported
Capehorn et al.[85] (2019)	MC, OL, RCT	N=577	Primary: Changes in HbA_{1c}	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
SUSTAIN 10 Liraglutide 1.2 mg SC once-daily vs semaglutide 1.0 SC mg once-weekly	Adults with type 2 diabetes (HbA_{1c} 7.0 to 11.0%) on one to three oral antidiabetic drugs	30 weeks	Secondary: Changes in body weight, safety	Mean HbA_{1c} (baseline 8.2%) decreased over time for both treatment arms, and from baseline to week 30 by 1.7% with semaglutide and 1.0% with liraglutide (estimated treatment difference (ETD) at week 30, -0.69%; 95% CI, -0.82 to -0.56; P<0.0001 for superiority). Secondary: Mean body weight (baseline 96.9 kg) decreased over time for both treatment arms, and from baseline to week 30 by 5.8 kg vs 1.9 kg with semaglutide vs liraglutide (ETD, -3.83 kg; 95% CI, -4.57 to -3.09; P<0.0001). The proportions of subjects achieving glycemic targets of <7.0% and 6.5%, weight loss of 5% and 10%, and a composite endpoint of HbA_{1c} <7.0% without severe or blood glucose-confirmed symptomatic hypoglycemia and no weight gain were greater with semaglutide vs liraglutide (all P<0.0001). Both treatments had similar safety profiles, except for more frequent gastrointestinal disorders (the most common adverse events and adverse events leading to premature treatment discontinuation with semaglutide vs liraglutide (43.9% vs 38.3% and 11.4% vs 6.6%, respectively).
Heine et al.[86] (2005) Exenatide 5 µg BID for 4 weeks, then 10 µg BID vs insulin glargine QD at bedtime All patients were receiving existing metformin and/or sulfonylurea regimens.	OL, RCT Patients 30 to 75 years of age with type 2 diabetes not adequately controlled (defined as HbA_{1c} 7.0 to 10.0%) with combination metformin and sulfonylurea therapy at maximally effective doses, BMI 25 to 45 kg/m^2 and a history of stable body weight (≤10% variation for ≥3 months before screening)	N=551 26 weeks	Primary: Change in HbA_{1c} Secondary: Change in FPG, fasting glucose <100 mg/dL and body weight loss	Primary: At 26 weeks, similar reductions in HbA_{1c} were noted between exenatide and insulin glargine (–1.11%, CI, –0.123 to 0.157). Secondary: A significantly reduction in FPG from baseline was observed in the insulin glargine group (–51.5 mg/dL; P<0.001). The reduction from baseline in the exenatide group was not significant (–25.7 mg/dL). A significant reduction was observed in the insulin group when compared to the exenatide group (95% CI, 20 to 34 mg/dL). A significantly greater proportion of patients taking insulin glargine (21.6%) achieved fasting glucose of <100 mg/dL than those taking exenatide (8.6%; P<0.001). A significant weight loss was experienced in the exenatide group (–2.3 kg) compared to a gain of +1.8 kg in the insulin group (CI, –4.6 to –3.5 kg; P<0.001). Similar rates of hypoglycemia were reported with both agents (CI, –1.3 to 3.4 events/patient-year). Exenatide patients had a higher incidence of daytime

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				hypoglycemia (CI, 0.4 to 4.9 events/patient-year), and a lower rate of nocturnal hypoglycemia than insulin glargine patients (CI, –2.3 to –0.9 events/patient-year). A significantly higher incidence of gastrointestinal side effects, including nausea (57.1 vs 8.6%; P<0.001), vomiting (17.4 vs 3.7%; P<0.001) and diarrhea (8.5 vs 3%; P=0.006), upper abdominal pain (P=0.012), constipation (P=0.011), dyspepsia (P=0.011), decreased appetite (P=0.021), and anorexia (P=0.002) were reported in the exenatide group vs the insulin group. Withdrawals due to adverse events occurred in 9.5% of exenatide patients vs 0.7% of insulin patients.
Secnik Boye et al.[87] (2006) Exenatide 5 µg BID for 4 weeks, then 10 µg BID vs insulin glargine QD at bedtime All patients were receiving existing metformin and/or sulfonylurea regimens.	MC, OL, RCT Secondary analysis on patients with type 2 diabetes inadequately controlled (defined as an HbA_{1c} 7.0 to 10.0%) with sulfonylurea and metformin therapy at maximally effective doses, enrolled in a previous 26 week study	N=455 26 weeks	Primary: Patient-reported health outcome measures: Diabetes Symptom Checklist-revised, DTSQ, EQ-5D, Medical Outcomes Study 36-Item Short-Form Health Survey, Diabetes Treatment Flexibility Score Secondary: Not reported	Primary: Both exenatide and insulin glargine groups experienced a significant improvement from baseline in patient-reported health outcome measures as demonstrated by Diabetes Symptom Checklist-revised overall scores, DTSQ, EQ-5D and Medical Outcomes Study 36-Item Short-Form Health Survey scores (P<0.05 for all measures). There was not a statistical difference between treatment groups in any of the outcome measures (P>0.05 for all measures). Neither the exenatide nor the insulin glargine group experienced a significant improvement in Treatment Flexibility Score scores (P=0.93 for both groups). Secondary: Not reported
Nauck et al.[88] (2007) Exenatide 5 µg BID for 4 weeks, then 10 µg BID vs insulin aspart BID	MC, OL, RCT Patients 30 to 75 years of age who had suboptimal glycemic control despite receiving optimally effective metformin and	N=501 52 weeks	Primary: Mean change in HbA_{1c} levels, weight, fasting serum glucose levels, PPG levels, adverse events	Primary: There was not a significantly different change from baseline in mean HbA_{1c} levels between the exenatide (–1.04%) and insulin aspart groups (–0.89%, 95% CI, −0.32% to 0.01%; P=0.067). Patients in the exenatide group experienced a gradual weight loss of –2.5 kg, compared to a gradual weight gain of 2.9 kg in the insulin aspart group, (95% CI, −5.9 to −5.0; P<0.001) at the end of 52 weeks.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
All patients were receiving existing metformin and/or sulfonylurea regimens.	sulfonylurea therapy for ≥3 months, HbA_{1c} levels ≥7.0 and ≤11.0%, a BMI ≥25 and ≤40 kg/m^2, and a history of stable body weight (≤10% variation for ≥3 months)		Secondary: Not reported	Patients in both exenatide (–1.8 mmol/L) and insulin aspart (–1.7 mmol/L) groups had a significant decrease in fasting serum glucose compared to baseline (P<0.001 for both groups). There was not a significant difference between groups (CI, −0.6 to 0.4; P=0.689). Patients in the insulin aspart group had significantly lower mean glucose values at pre-breakfast (P=0.037), pre-lunch (P=0.004) and 03.00 hours (P=0.002). Patients in the exenatide group had a greater reduction in PPG excursions following morning (P<0.001), midday (P=0.002) and evening meals (P<0.001). The withdrawal rate was 21.3% in the exenatide group and 10.1% in the insulin aspart group. Adverse events that were more commonly reported in the exenatide vs insulin aspart group included: nausea (33.2 vs 0.4%), vomiting (15.0 vs 3.2%), diarrhea (9.5 vs 2%) and other clinically relevant adverse events (13.4 vs 6.4%). Secondary: Not reported
Diamant et al.[89] (2010) DURATION-3 Exenatide ER 2 mg SC once weekly vs insulin glargine SC QD All patients received existing background oral glucose-lowering regimens.	OL, PG, RCT Type 2 diabetics ≥18 years of age with suboptimum glycemic control despite maximum tolerated doses of metformin (stable dose of ≥1,500 mg for ≥8 months) or combined metformin and sulfonylurea treatment ≥3 months, HbA_{1c} 7.1 to 11.0%, BMI 25 to 45 kg/m^2, and a	N=456 26 weeks	Primary: Change in baseline HbA_{1c} Secondary: Proportion of patients achieving HbA_{1c} <7.0 or <6.5%, fasting serum glucose, self-monitored blood glucose concentrations, body weight, fasting lipid profile, BP, markers of cardiovascular risk, β cell function,	Primary: Decreases in HbA_{1c} were significantly greater with exenatide ER (-1.5±0.05%) compared to insulin glargine (-1.3±0.06%; treatment difference, -0.16±0.07%; 95% CI, -0.29 to -0.03; P=0.017). In patients receiving exenatide ER or insulin glargine plus metformin only, HbA_{1c} was decreased by -1.5±0.06 and -1.4±0.07% (treatment difference, -1.8±0.08%; 95% CI, -0.34 to -0.02; P=0.031). Secondary: Significantly greater proportions of exenatide ER-treated patients achieved HbA_{1c} <7.0 (60 vs 48%; P=0.010) and <6.5% (35 vs 23%; P=0.004) compared to insulin glargine treated patients. Fasting serum glucose decreased with both treatments (-2.1±0.2 vs -2.8±0.2 mmol/L); however, insulin glargine significantly decreased values compared to exenatide ER (treatment difference, -0.6 mmol/L; 95% CI, 0.2 to 1.0; P=0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	stable body weight ≥3 months		insulin profile, patient-reported QOL, safety	With regards to self-monitored blood glucose concentrations, both treatments significantly decreased FPG and PPG at all eight time points (P<0.0001 for all). Significantly lower concentrations with insulin glargine compared to exenatide ER were observed at 0300 hour (P=0.022) and before breakfast (P<0.0001), and significantly lower concentrations with exenatide ER were observed after dinner (P=0.004). Exenatide ER resulted in significantly greater reductions in post-prandial glucose excursions compared to insulin glargine after morning (P=0.001) and evening meals (P=0.033). Seventy nine percent of patients receiving exenatide ER experienced both a decrease in HbA_{1c} and body weight compared to 63% of patients receiving insulin glargine who experienced a decrease in HbA_{1c} and increase in body weight. Only exenatide ER resulted in a significant decrease in TC (-0.12 mmol/L; P<0.05). There were no differences between the two treatments in the decreases in TC (treatment difference, -0.07 mmol/L; 95% CI, -0.21 to 0.06) and LDL-C (treatment difference, -0.09 mmol/L; 95% CI, -0.21 to 0.03), and the increase in HDL-C (treatment difference, -0.02; 95% CI, -0.05 to 0.02) observed. Only exenatide ER resulted in a significant decrease in SBP (-3 mm Hg; P<0.05). There were no differences between the two treatments in the decreases in SBP (treatment difference, -2 mm Hg; 95% CI, -4 to 1) and DBP (treatment difference, 0 mm Hg; 95% CI, -2 to 1) observed. Only exenatide ER resulted in a significant decrease in high-sensitivity CRP (-2.0 mg/dL; P<0.05). There were no differences between the two treatments in the decreases in high-sensitivity CRP (-1.2 mg/dL; 95% CI, -2.8 to 0.3) and urinary albumin:creatinine ratio (0.06 mg/mmoL; 95% CI, -1.70 to 1.80) observed. Both treatments resulted in improvements in IWQOL-Lite, binge eating scale, and DTSQ total scores, with only patients receiving exenatide ER achieving significant improvements on the EQ-5D index. Significant improvements with exenatide ER compared to insulin glargine were observed for one of the IWQOL-Lite domains (self-esteem) and one EQ-5D dimension (usual activities) (data not reported).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Gastrointestinal events including nausea and diarrhea were among the most common reported adverse events with exenatide ER, with nasopharyngitis and headache being the most commonly reported with insulin glargine. Gastrointestinal events were all mild or moderate and no serious adverse events were reported by more than one patient, except chest pain (two patients).
Diamant et al.[90] (2012) DURATION-3 Exenatide ER 2 mg SC once weekly vs insulin glargine SC QD All patients received existing background oral glucose-lowering regimens.	ES of DURATION-3[60] Type 2 diabetics ≥18 years of age with suboptimum glycemic control despite maximum tolerated doses of metformin (stable dose of ≥1,500 mg for ≥8 months) or combined metformin and sulfonylurea treatment ≥3 months, HbA_{1c} 7.1 to 11.0%, BMI 25 to 45 kg/m^2, and a stable body weight ≥3 months	N=390 84 weeks	Primary: Change in baseline HbA_{1c} Secondary: Proportions of patients achieving HbA_{1c} <7.0 and ≤6.5%, body weight, incidence of hypoglycemia, safety	Primary: At 84 weeks, HbA_{1c} decreased from baseline by -1.2% with exenatide ER compared to -1.0% with insulin glargine (P=0.029). Secondary: The proportions of patients who achieved end point HbA_{1c} targets <7.0 and ≤6.5% were 44.6 and 36.8% with exenatide ER and insulin glargine (P=0.084) and 31.3 and 20.2% with exenatide ER and insulin glargine (P=0.009), respectively. Patients receiving exenatide ER lost 2.1 kg of body weight compared to patients receiving insulin glargine who gained 2.4 kg (P<0.001). Among patients receiving metformin plus a sulfonylurea, the incidence of minor hypoglycemia was 24 and 54% with exenatide ER and insulin glargine (P<0.001). Among adverse events occurring in ≥5% of all patients, diarrhea (12 vs 6%) and nausea (15 vs 1%) occurred more frequently (P<0.05) with exenatide ER compared to insulin glargine.
Derosa et al.[91] (2011) Exenatide 5 µg SC BID, titrated up to 10 µg SC BID vs	MC, RCT, SB Patients ≥18 years of age with type 2 diabetes intolerant to metformin at the highest dosages (2,500 to 3,000 mg/day)	N=111 12 months	Primary: Change in baseline body weight, glycemic control, insulin resistance Secondary: Not reported	Primary: There was decrease of body weight and BMI after six, nine, and 12 months (P<0.05, P<0.01, P<0.001, respectively) with exenatide, not obtained with glimepiride. BMI reached with exenatide was significantly lower compared to glimepiride (P<0.05). A similar decrease in HbA_{1c}, FPG, and PPG after nine (P<0.05 for all), and after 12 months (P<0.01 for all) with both treatments, without significant differences between the two treatments.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
glimepiride 1 mg TID, titrated up to 2 mg TID				Exenatide resulted in a reduction of fasting plasma insulin, and HOMA-IR after 12 months (P<0.05 for both), not observed with glimepiride; fasting plasma insulin increased with glimepiride. Values reached with exenatide were significantly lower compared to values reached with glimepiride after 12 months (P<0.05). Exenatide, but not glimepiride, gave an increase of adiponectin after 12 months (P<0.05), and the value registered with exenatide was significantly higher compared to the value recorded with glimepiride at trial end (P<0.05). A decrease of tumor necrosis factor-α was observed after 12 months (P<0.05) with exenatide, but no with glimepiride; furthermore the value obtained with exenatide was significantly better compared to the value obtained with glimepiride after 12 months (P<0.05). Exenatide, but not glimepiride, gave a reduction of high sensitivity CRP after nine and 12 months (P<.0.05 and P<0.01) compared to baseline and glimepiride (P<0.05). Secondary: Not reported
Yang et al.[92] (2011) Liraglutide 0.6, 1.2, or 1.8 mg QD vs glimepiride 4 mg QD All patients received metformin.	AC, DB, DD, RCT Adult patients with type 2 diabetes	N=929 16 weeks	Primary: Change in baseline HbA_{1c} Secondary: Proportions of patients achieving HbA_{1c} <7.0 and ≤6.5%, body weight, BP, hypoglycemia, adverse events	Primary: Baseline HbA_{1c} was significantly reduced with all treatments. Treatment with liraglutide 1.2 and 1.8 mg was non-inferior to glimepiride (mean reduction: 1.36, 1.45, 1.39% points, respectively). Secondary: No significant difference was shown in the proportion of patients achieving HbA_{1c} <7.0 or ≤6.5% between liraglutide 1.2 and 1.8 mg and glimepiride. Liraglutide resulted in a mean reduction in weight of -1.8 to -2.4 kg compared to 0.1 kg weight gain with glimepiride. Liraglutide significantly reduced SBP compared to glimepiride. Two patients receiving glimepiride experienced major hypoglycemia compared to zero patients receiving liraglutide. Liraglutide was associated with a 10-fold lower incidence of minor hypoglycemia compared to glimepiride.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Gastrointestinal disorders were the most commonly reported adverse events with liraglutide therapy; events were transient and resulted in few withdrawals.
Bergenstal et al.[93] (2010) DURATION-2 Exenatide ER 2 mg SC once weekly vs sitagliptin 100 mg QD vs pioglitazone 45 mg QD All patients received existing metformin therapy.	DB, DD, MC, PG, RCT Type 2 diabetics ≥18 years of age, receiving a stable metformin therapy for ≥2 months, HbA_{1c} 7.1 to 11.0%, and BMI 25 to 45 kg/m^2	N=514 26 weeks	Primary: Change in baseline HbA_{1c} Secondary: Proportion of patients achieving an HbA_{1c} ≤6.5 or ≤7.0%, FPG, six-point self-monitored glucose concentrations, body weight, fasting lipid profile, fasting insulin profile, BP, cardiovascular risk markers, patient-reported QOL, safety	Primary: Exenatide ER (-1.5%; 95% CI, -1.7 to -1.4) significantly decreased HbA_{1c} compared to sitagliptin (-0.9% [95% CI, -1.1 to -0.7]; treatment difference, -0.6% [95% CI, -0.9 to -0.4]; P<0.0001) and pioglitazone (-1.2% [95% CI, -1.4 to -1.0]; treatment difference, -0.3% [95% CI, -0.6 to -0.1]; P=0.0165). Secondary: A significantly greater proportion of patients receiving exenatide achieved HbA_{1c} targets of ≤6.5 (P<0.0001 and P=0.0120) or ≤7.0% (P<0.0001 and P=0.0015) compared to patients receiving sitagliptin or pioglitazone. Exenatide ER (-1.8 mmol/L; 95% CI, -2.2 to -1.3) achieved significantly greater decreases in FPG compared to sitagliptin (-0.9 mmol/L [95% CI, -1.3 to -0.5]; treatment difference, -0.9 mmol/L [95% CI, -0.3 to -1.4]; P=0.0038), but not pioglitazone (-1.5 mmol/L [95% CI, -1.9 to -1.1]; treatment difference, -0.2 mmol/L [95% CI, -0.8 to 0.3]; P=0.3729). A significantly greater proportion of patients receiving exenatide ER (60%) achieved the FPG goal of ≤7 mmol/L compared to patients receiving sitagliptin (35%; P<0.0001), but no difference was observed between patients receiving pioglitazone (52%; P=0.1024). In all measurements of the six-point self-monitored glucose concentrations profile, decreases at week 26 were significantly greater with exenatide ER compared to sitagliptin, but not pioglitazone (P values not reported). Weight loss with exenatide ER (-2.3 kg; 95% CI, -2.9 to -1.7) was significantly greater compared to sitagliptin (difference, -1.5 kg; 95% CI, -2.4 to -0.7; P=0.0002) and pioglitazone (difference, -5.1 kg; 95% CI, -5.9 to -4.3; P<0.0001). Pioglitazone was the only treatment to achieve significant decreases in TG (-16%; 95% CI, -21 to -11) and increases in TC (0.16 mmol/L; 95% CI, 0.04 to 0.28), the former of which was significantly different compared to exenatide ER (-5%; 95% CI, -11 to 0).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Fasting insulin was significantly increased after 26 weeks with exenatide ER (3.6 µIU/mL; 95% CI, 1.6 to 5.6) compared to sitagliptin (0.4 µIU/mL [95% CI, -1.6 to 2.3]; treatment difference, 3.2 µIU/mL [95% CI, 0.6 to 5.8]; P=0.0161) and pioglitazone (-3.9 µIU/mL [95% CI, -5.9 to -2.0]; treatment difference, 7.5 µIU/mL [95% CI, 4.9 to 10.1]; P<0.0001). Decreases in SBP with exenatide ER were significantly greater compared to sitagliptin (treatment difference, -4 mm Hg; 95% CI, -6 to -1), but not pioglitazone (data reported in graphical form only). All treatments achieved significant improvements in high-sensitivity CRP and adiponectin. Exenatide ER was the only treatment to achieve a significant improvement in BNP and albumin:creatinine ratio, with the changes in BNP being significantly greater compared to sitagliptin and pioglitazone (P values not reported). All five domains of weight-related QOL and IWQOL total score were significantly improved with exenatide ER (IWQOL total score, 5.15; 95% CI, 3.11 to 7.19) and sitagliptin (4.56; 95% CI, 2.56 to 6.57), but not pioglitazone (1.20; 95% CI, -0.87 to 3.28), which improved only on self-esteem. Improvements in IWQOL with exenatide ER were significantly greater compared to sitagliptin (treatment difference, 3.94; 95% CI, 1.28 to 6.61; P=0.0038). All treatments achieved improvements in all domains of the PGWB and DTSQ total score, with greater improvement in overall satisfaction recorded with exenatide ER (3.96; 95% CI, 2.78 to 5.15) compared to sitagliptin (2.35 [95% CI, 1.19 to 3.51]; treatment difference, 1.61 [95% CI, 0.07 to 3.16]; P=0.0406). The most commonly reported adverse events with exenatide ER and sitagliptin were nausea (24 vs 10%, respectively) and diarrhea (18 vs 10%, respectively). Upper respiratory tract infection (10%) and peripheral edema (8%) were the most commonly reported adverse events with pioglitazone. No episodes of major hypoglycemia were reported.
Gadde et al.[94] (2017) DURATION-NEO-2	MC, OL, RCT Type 2 diabetics ≥18 years of age, receiving a stable	N=365 28 weeks	Primary: Change in baseline HbA_{1c} Secondary:	Primary: Exenatide led to greater HbA_{1c} reduction from baseline to week 28 vs sitagliptin (least-squares mean difference, −0.38%; 95% CI, −0.70 to −0.06%; P=0.021) or placebo (−0.72%; 95% CI, −1.15 to −0.30%; P=0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Exenatide 2 mg once-weekly suspension for autoinjection vs sitagliptin 100 mg QD vs placebo	metformin therapy for ≥2 months, HbA_{1c} 7.1 to 11.0%		Proportion of patients achieving HbA_{1c} <7.0% and change in FPG and body weight from baseline	Secondary: At week 28, a higher proportion of exenatide-treated patients (43.1%) achieved HbA_{1c} < 7.0% than did sitagliptin- (32.0%) or placebo-treated patients (24.6%). Exenatide resulted in numerically greater FPG reductions than sitagliptin and greater FPG reductions than placebo (P<0.001). The difference in FPG reduction for exenatide vs sitagliptin was not statistically significant. Body weight decreased over the 28-week treatment period with exenatide QWS-AI and sitagliptin, with no difference observed between groups (nominal P=0.8625).
Wyshman et al.[95] (2011) DURATION-2 Exenatide ER 2 mg SC once weekly (continued exenatide ER) vs exenatide ER 2 mg SC once weekly (switched to exenatide ER) Patients enrolled in DURATION-2 who were randomized to sitagliptin 100 mg QD or pioglitazone 45 mg QD were transitioned to exenatide ER 2 mg	ES (DURATION-2) Type 2 diabetics ≥18 years of age, receiving stable metformin therapy for ≥2 months, HbA_{1c} 7.1 to 11.0%, and BMI 25 to 45 kg/m^2	N=319 26 weeks (52 weeks total)	Primary: Change in baseline HbA_{1c}, FPG, body weight, proportion of patients achieving an HbA_{1c} <7.0 or ≤6.5%, proportion of patients achieving FPG <7 mmol/L, and markers of cardiovascular risk at week 52 and from week 26 to 52; safety Secondary: Not reported	Primary: Patients who continued exenatide ER demonstrated significant 52 week improvements in HbA_{1c} (-1.6±0.1%), FPG (-1.8±0.3 mmol/L), and body weight (-1.8±0.5 kg; P=0.0002 vs baseline). Patients originally receiving sitagliptin who switched to exenatide ER demonstrated significant incremental improvements in HbA_{1c} (-0.3±0.1%; P=0.0010), FPG (-0.7±0.2 mmol/L; P=0.0017), and body weight (-1.1±0.3 kg; P=0.0006). Patients originally receiving pioglitazone who switched to exenatide ER maintained HbA_{1c} and FPG improvements (week 52, -1.6±0.1% and -1.7±0.3 mmol/L, with significant weight loss; -3.0±0.3 kg; P<0.0001). No differences in the proportions of patients achieving target HbA_{1c} <7.0 or ≤6.5% were observed between weeks 26 and 52 in patients who continued exenatide ER and who switched to exenatide ER from pioglitazone. A significantly greater proportion of patients achieved both targets after switching from sitagliptin to exenatide ER (P<0.05 for both). Similar results were observed for the FPG target (<7 mmol/L) (P=0.0002). Patients who continued exenatide ER achieved greater SBP improvements at week 52 (-12.2 mm Hg; 95% CI, -16.1 to -8.3). Patients with abnormal SBP at 26 weeks who were receiving sitagliptin and pioglitazone, achieved greater SBP decreases (-11.3 [95% CI, -14.9 to -7.7] and -9.4 mm Hg [95% CI, -13.4 to -5.3], respectively) at week 52. Patients who continued exenatide ER maintained improvements in HDL-C at week 52; all other lipid variables

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
SC once weekly after the initial 26 week trial period.				were not different from baseline. Patients switched to exenatide ER from sitagliptin maintained HDL-C improvements and achieved a significant decrease in TC at week 52. Patients switched to exenatide ER from pioglitazone achieved significant decreases in HDL-C, LDL-C, and TC at week 52. Patients who continued exenatide ER achieved improvements in urinary albumin/creatinine ratio, BNP, and high-sensitivity CRP. The urinary albumin/creatinine ratio was significantly decreased for all treatment groups by week 52. Patients who switched to exenatide ER from sitagliptin and pioglitazone achieved significant reductions in BNP, with high-sensitivity CRP and plasminogen activator inhibitor-1 improvements observed after 26 weeks of initial treatment with pioglitazone were not maintained once switched to exenatide ER. Exenatide ER was well tolerated and adverse events were predominantly mild or moderate in intensity. Nausea was the most frequent adverse event (continued exenatide ER, 5%; switched to exenatide ER from sitagliptin, 11%; switched to exenatide ER from pioglitazone, 10%). No major cases of hypoglycemia or pancreatitis were reported. Secondary: Not reported
Garber et al.[96] (2009) LEAD-3 Liraglutide 1.2 and 1.8 mg SC QD vs glimepiride 8 mg/day	AC, DB, DD, MC, PG, RCT Type 2 diabetic patients 18 to 80 years of age treated previously with diet and exercise or up to half the highest dose of an oral glucose lowering agent monotherapy including sulfonylureas, meglitinides, amino acid derivatives, biguanides, α-	N=746 52 weeks	Primary: Change in baseline HbA_{1c} Secondary: Change in baseline body weight, FPG, eight-point self-measured glucose concentrations, BP, β cell function, fasting glucagon, and patient-reported QOL	Primary: Decreases in HbA_{1c} were -0.84±1.23% with liraglutide 1.2 mg, -1.14±1.24% with liraglutide 1.8 mg, and -0.51±1.20% with glimepiride. Decreases with liraglutide were significantly greater compared to glimepiride. Differences between glimepiride and liraglutide 1.2 mg were -0.62% (95% CI, -0.83 to -0.42; P<0.0001) and liraglutide 1.8 mg were -0.33% (95% CI, -0.53 to -0.13; P=0.0014). Additionally, decreases with liraglutide 1.8 mg were significantly greater compared to liraglutide 1.2 mg (-0.29%; 95% CI, -0.50 to -0.09; P=0.0046). Secondary: Liraglutide-treated patients lost body weight and those receiving glimepiride gained weight (P values not reported). The weight loss with liraglutide after 16 weeks was sustained throughout the 52 weeks.

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	glucosidase inhibitors, and TZDs for ≥2 months; and HbA_{1c} 7.0 to 11.0% (previous diet and exercise) or 7.0 to 10.0% (previous oral glucose lowering agent monotherapy)			Decreases in FPG with liraglutide (1.2 mg, -0.84 mmol/L; P=0.027 and 1.8 mg, -1.42 mmol/L; P=0.0001) were significantly greater compared to glimepiride (-0.29 mmol/L). Decreases in PPG occurred with all three treatments (liraglutide 1.2 mg vs glimepiride; P=0.1616, liraglutide 1.8 mg vs glimepiride; P=0.0038, and liraglutide 1.8 mg vs liraglutide 1.2 mg; P=0.1319). Decreases in SBP were -0.7 mm Hg with glimepiride compared to -0.1 mm Hg with liraglutide 1.2 mg (P=0.2912) and -3.6 mm Hg with liraglutide 1.8 mg (P<0.0118). Mean DBP decreased but not significantly with any treatment. HOMA-IR and fasting glucagon significantly decreased with liraglutide, but increased with glimepiride. HOMA-IR was decreased by -0.65% with liraglutide 1.2 mg and by -1.35% with liraglutide 1.8 mg, and increased by 0.85% with glimepiride (P=0.0249 and P=0.0011 for liraglutide 1.2 and 1.8 mg vs glimepiride). Patients receiving liraglutide 1.8 mg reported improved QOL scoring for physical and emotional domains compared to glimepiride (P=0.02). Improvements were largely as a result of improvements in weight image and weight concern (P<0.01).
Garber et al.[97] (2011) LEAD-3 Liraglutide 1.2 mg and 1.8 mg SC QD vs glimepiride 8 mg/day	ES (LEAD-3) Type 2 diabetic patients 18 to 80 years of age treated previously with diet and exercise or up to half the highest dose of an oral glucose lowering agent monotherapy including sulfonylureas, meglitinides, amino acid derivatives,	N=440 52 weeks	Primary: Change in baseline HbA_{1c} Secondary: Change in baseline body weight, FPG, β cell function, fasting glucagon, and BP	Primary: The decrease in HbA_{1c} was significantly greater with liraglutide 1.2 mg (-0.9 vs -0.6%; P=0.0376) and 1.8 mg (-1.1 vs -0.6%; P=0.0016) compared to glimepiride over two years of treatment. Secondary: Over two years, patients receiving liraglutide 1.2 or 1.8 mg experienced weight loss compared to weight gain with patients receiving glimepiride (-2.3 and -2.8 vs 1.0 kg, respectively; P<0.001 for both comparisons). Compared to glimepiride (-1.8 mmol/L), both liraglutide 1.2 (-1.9 mmol/L) and 1.8 mg (-2.6 mmol/L) were significantly more effective at decreasing FPG over the course of the extension period (P=0.0015 and P=0.0001, respectively).

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	biguanides, α-glucosidase inhibitors, and TZDs for ≥2 months; and HbA_{1c} 7.0 to 11.0% (previous diet and exercise) or 7.0 to 10.0% (previous oral glucose lowering agent monotherapy)			In patients who completed two years of treatment, baseline HOMA-IR decreased by -1.1% with liraglutide 1.2 mg and -0.8% with liraglutide 1.8 mg, and increased by 0.8% with glimepiride (P=0.0451 for liraglutide 1.2 mg vs glimepiride). The proinsulin:insulin ratio increased slightly with all treatments, by 0.108 with liraglutide 1.2 mg, 0.018 with liraglutide 1.8 mg, and 0.141 with glimepiride (P values not reported). After two years, all three treatments had increases in HOMA-B, fasting insulin, and fasting C-peptide; and had decreases in fasting glucagon, but there were no differences between treatments (P values not reported). No differences between treatments in change in pulse, DBP, and SBP were observed in any patient completing two years of treatment.
Bode et al.[98] (2010) LEAD-3 Liraglutide 1.2 and 1.8 mg SC QD vs glimepiride 8 mg/day	Post-hoc analysis (LEAD-3) Type 2 diabetic patients 18 to 80 years of age treated previously with diet and exercise or up to half the highest dose of oral glucose lowering agent monotherapy including sulfonylureas, meglitinides, amino acid derivatives, biguanides, α-glucosidase inhibitors, and TZDs for ≥2 months and HbA_{1c} 7.0 to 11.0% (previous diet and exercise) or	N=746 52 weeks	Primary: Impact of treatment on patient-reported perceptions of body image, weight, and weight concern; psychological well-being and distress, cognitive functioning and health Secondary: Not reported	Primary: Both measures of weight perception (weight assessment and weight concern) were more favorable with liraglutide compared to glimepiride. Baseline-adjusted mean weight assessment compared to the reference point "my weight is just right" was significantly more favorable (i.e., shifted from more overweight to less overweight) with liraglutide 1.8 mg (P=0.002). Furthermore, weight concern decreased markedly with liraglutide, with mean scores significantly less compared to glimepiride (liraglutide 1.2 mg; P<0.0001 and liraglutide 1.8 mg; P<0.001). Logistic regression estimates indicated that patients receiving liraglutide 1.8 mg were 52% less likely to report feeling either "somewhat" or "very overweight" vs "just right", "somewhat underweight," or "very overweight" during treatment compared to patients receiving glimepiride (OR, 0.480; 95% CI, 0.331 to 0.696; P value not reported). Also, liraglutide 1.8 mg-treated patients were 39% less likely to report being "somewhat worried", "very worried," or "extremely worried" vs "a little concerned" or "not concerned at all" about their weight during treatment compared to glimepiride treated patients (OR, 0.608; 95% CI, 0.440 to 0.850; P value not reported). There were no differences between liraglutide and glimepiride for the body image scales (body size evaluation and body appearance distress) or for any

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	7.0 to 10.0% (previous oral glucose lowering agent monotherapy)			of the cognitive functioning and performance scales during treatment (P values not reported). The health-related QOL composite score significantly improved more favorably with liraglutide 1.8 mg compared to glimepiride (P=0.004). Favorable improvements were seen in the composite scales of mental and emotional healthy, psychological well-being, psychological distress, and general perceived health (P<0.05 for all). The higher scores with liraglutide 1.8 mg for mental and emotional health reflected greater improvement in both domains of psychological well-being and psychological distress compared to glimepiride. There were no differences for these scales between liraglutide 1.2 mg and glimepiride (P values not reported). However, there was a significant difference between liraglutide 1.2 mg and glimepiride in general health status favoring liraglutide (P=0.006). Correlation analyses using data pooled from all treatments confirmed that decreases in BMI were correlated with improvements in both weight assessment and weight concern (P<0.0001 for both), indicating that patients' reports were valid representations of actual weight losses. Decreases in HbA_{1c} corresponded to improvements in general perceived health (P<0.0001), cognitive functioning composite score (P=0.006), and cognitive performance (P=0.004). Correlations of change in HbA_{1c} within treatment groups with change in patient-reported measures were strongest with liraglutide 1.8 mg. Secondary: Not reported
Charbonnel et al.[99] (2013) Sitagliptin starting at 100 mg/day, with glimepiride added if further glucose control needed (oral) vs	AC, OL, RCT Patients with type 2 diabetes mellitus aged 18 to 79 years, on a stable dose of metformin monotherapy ≥1,500 mg/day for ≥12 weeks, with	N=653 (per protocol patients were analyzed, N=522) 26 weeks	Primary: Change in HbA_{1c} (non-inferiority) Secondary: FPG, plasma lipids, safety	Primary: HbA_{1c} decreased over 26 weeks in both treatment strategy groups, with a larger initial reduction at week 12 in the injectable strategy group. The mean change in HbA_{1c} at week 26 was -1.3% in the oral group and -1.4% in the injectable group. The primary hypothesis was met to declare that the oral treatment was non-inferior to the injectable in lowering HbA_{1c}. Secondary: Significant reductions in FPG at week 26 were observed in both groups, with a greater reduction observed in the injectable group. No meaningful between-

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liraglutide starting at 0.6 mg/day, up-titrated to 1.2 mg/day after 1 week (injectable)	an HbA_{1c} ≥7.0% and ≤11.0% and a fasting fingerstick glucose <15 mmol/L at the randomization visit, deemed capable by the investigator of using a Victoza pen injection device			group differences were found in any lipid variable or in the incidence of clinical adverse effects overall. The incidence of drug-related adverse events or adverse events leading to discontinuation was greater in the injectable group than in the oral group. These differences were mainly related to the significantly higher incidence of gastrointestinal adverse events, such as abdominal pain, diarrhea, nausea, and vomiting, in the injectable group.
Amori et al.[100] (2007) Incretin therapy (exenatide, liraglutide, sitagliptin and vildagliptin*) vs non-incretin-based therapy (placebo or hypoglycemic agent)	MA (29 RCTs) Type 2 diabetics	N=12,996 Duration varied (12 to 52 weeks)	Primary: Change in baseline HbA_{1c} Secondary: FPG, proportion of patients achieving an HbA_{1c} <7.0%	Primary: Pooled analysis of trials comparing GLP-1 analogues to placebo demonstrated a significant difference in the decrease in HbA_{1c} favoring GLP-1 analogues (WMD, -0.97; 95% CI, -1.13 to -0.81). Specifically, no difference in the HbA_{1c} was found in OL non-inferiority trials between exenatide and insulin glargine or biphasic aspart (WMD, -0.06; 95% CI, -0.22 to 0.10). Liraglutide demonstrated similar HbA_{1c} efficacy compared to OL glimepiride titrated to glycemic goals or DB maximum dose metformin (data not reported). Secondary: Compared to placebo, FPG was significantly decreased with GLP-1 analogues (WMD, -27 mg/dL; 95% CI, -33 to -21). Exenatide-treated patients were more likely to achieve an HbA_{1c} <7.0% compared to placebo treated patients (45 vs 10%, respectively; RR, 4.2; 95% CI, 3.2 to 5.5), while no difference in the proportions of patients achieving this goal was observed between exenatide and insulin therapy in non-inferiority trials (39 vs 35%, respectively; RR, 1.1; 95% CI, 0.8 to 1.5). Data with liraglutide were not reported.
Pinelli et al.[101] (2008) Exenatide in combination with other antidiabetic agents	MA (22 RCTs) Patients with type 2 diabetes receiving combination therapy	N=9,325 ≥24 weeks	Primary: Mean change in baseline HbA_{1c} Secondary: Proportion of patients	Primary: There were small reductions in HbA_{1c} across the trials. The WMD were -0.80% (95% CI, -1.10 to -0.50) with TZD and -0.60% (95% CI, -1.04 to -0.16) with exenatide.

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vs TZD in combination with other antidiabetic agents			reaching HbA_{1c} <7.0%, mean change from baseline in FPG and body weight, hypoglycemia, gastrointestinal adverse events	When only PC trials were analyzed, there were greater reductions in HbA_{1c} with both TZDs (WMD, -1.14%; 95% CI -1.30 to -0.98) and exenatide (WMD, -0.97%; 95% CI -1.11 to -0.83). When only TZD AC trials were analyzed, there was a significant difference in HbA_{1c} levels from baseline (WMD, -0.38%; 95% CI -0.75 to -0.01). There was no difference in HbA_{1c} reduction between exenatide and insulin comparators in OL, NI trials. Secondary: TZD and exenatide-based therapies were associated with OR of 2.27 (95% CI, 1.22 to 4.24) and 2.90 (95% CI, 1.28 to 6.55), respectively, for reaching HbA_{1c} <7.0%. FPG concentrations were reduced from baseline with TZD-based regimens (WMD, -29.58 mg/dL; 95% CI, -39.27 to -19.89), but did not reach significance with exenatide (WMD, -8.77 mg/dL; 95% CI, -28.85 to 11.31). Severe hypoglycemia was rare in the one exenatide and four TZD trials that identified a total of nine participants experiencing hypoglycemic episodes. In these five trials, participants reporting an event were also receiving an insulin secretagogue. The OR for developing nonsevere hypoglycemia with TZDs was not significantly different from other treatment arms (OR, 1.59; 95% CI, 0.76 to 3.32). In TZD trials, there was a nonsignificant difference in body weight from baseline compared to other treatment groups (WMD, 1.51 kg; 95% CI, -0.12 to 3.15). Mean change in body weight from baseline was reduced significantly with exenatide-based regimens (WMD, -2.74 kg; 95% CI, -4.85 to -0.64). The most commonly reported adverse effects were gastrointestinal disorders in the exenatide trials. ORs greater than one for nausea, vomiting, and diarrhea were observed with exenatide with pooled ORs of 9.02 (95% CI, 3.66 to 22.23), 4.56 (95% CI, 3.13 to 6.65), and 2.96 (95% CI, 2.05 to 4.26), respectively. Nausea occurred in 47% of patients receiving exenatide and 11% in the comparator arms. Vomiting occurred in 15% of patients receiving

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				exenatide and 4% of patients receiving comparator. Diarrhea occurred in 12% of patients receiving exenatide and 4% in patients receiving comparator.
Bolli et al.[102] (2014) GETGOAL-F1 Lixisenatide 10 µg QD for two weeks, then 20 µg QD thereafter vs lixisenatide 10 µg QD for week, 15 µg QD for one week and then 20 µg QD thereafter vs placebo	DB, MC, PC, PG, RCT Patients 24 to 79 years of age with type 2 DM (≥1 year since diagnosis) receiving at least 1.5 g/day of metformin as monotherapy for at least three months and a HbA_{1c} ≥7% to ≤10%	N=484 24 weeks	Primary: HbA_{1c} Secondary: Members achieving glycemic goals, FPG, changes in body weight and safety evaluations	Primary: The one-step protocol arm resulted in greater decreases in mean HbA_{1c} from 64 ± 9.6 mmol/mol at baseline to 54 ± 9.3 mmol/mol at week 24 (LS mean change [± SE]: –10 ± 1.1 mmol/mol) compared to placebo (64 ± 9.1 mmol/mol to 60 ± 10.1 mmol/mol; LS mean change: –5 ± 1.1 mmol/mol). The LS mean change difference vs. placebo was –5 mmol/mol (–0.5%) (*P*<0.0001) for lixisenatide one-step. Secondary: The HbA_{1c} targets of <53 mmol/mol (<7.0%) and ≤48 mmol/mol (≤6.5%) were both achieved by more participants in both the lixisenatide one-step and two-step groups compared with the combined placebo group (P<0.001 for both). Both lixisenatide one- and two-step groups achieved significantly greater reductions in FPG at week 24 vs the combined placebo group. Mean body weight was reduced from 90.3 ± 19.0 kg at baseline to 87.7 ± 18.7 kg at week 24 with lixisenatide one-step (LS mean change: –2.6 ± 0.4 kg), from 88.1 ± 16.8 to 85.4 ± 16.8 kg with lixisenatide two-step (LS mean change: –2.7 ± 0.4 kg), and from 87.9 ± 17.3 to 86.3 ± 17.4 kg with placebo combined (LS mean change: –1.6 ± 0.4 kg) at 24 weeks. At week 24, adverse events were reported by 67.7, 70.8 and 65.6% of participants treated with lixisenatide one-, two-step and placebo, respectively, nausea and vomiting being reported most frequently.
Rosenstock et al.[103] (2013) GETGOAL-X Lixisenatide 20 µg QD vs exenatide 10 µg BID	AC, DB, MC, OL, PG, Patients 21 to 84 years of age with type 2 DM (≥1 year since diagnosis) receiving at least 1.5 g/day of metformin as	N=634 24 weeks	Primary: HbA_{1c} Secondary: Proportion of patients achieving glycemic goals, FPG, body weight and adverse events	Primary: Lixisenatide was found to be non-inferior to exenatide meeting 0.4% margin in reduction from baseline (-0.73% vs -0.90%), however, the agent provided statistically less reduction HbA_{1c} (P=0.0175). A similar proportion of patients in each group achieved HbA_{1c} goals of <7.0% at week 24 (48.5% lixisenatide and 49.8% exenatide); the number with HbA_{1c} ≤6.5% was 28.5% in the lixisenatide group compared with 35.4% in the exenatide group.

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	monotherapy for at least three months and a HbA_{1c} ≥7% to ≤10%			The agent also had lower decreases in FPG (-19.79 mg/dL vs -24.19 mg/dL) and body weight (-2.74 kg vs -3.72 kg). Incidence of adverse events was similar for lixisenatide and exenatide, as was incidence of serious events (2.8 and 2.2%, respectively). In the lixisenatide group, fewer participants experienced symptomatic hypoglycemia (2.5 vs 7.9%; P<0.05), with fewer gastrointestinal events (especially nausea; 24.5% vs 35.1%; P<0.05).
Rosenstock et al.[104] (2014) GETGOAL-S Lixisenatide 20 µg QD vs placebo	DB, MC, PC, PG, RCT Patients 20 to 79 years of age with type 2 DM receiving a sulfonylurea with or without metformin and a HbA_{1c} ≥7% to ≤10%	N=859 24 weeks	Primary: HbA_{1c} Secondary: Proportion of patients achieving glycemic goals, FPG, body weight and adverse events	Primary: Lixisenatide provided a reduction in HbA_{1c} at week 24 versus placebo (LS mean, -0.85% vs -0.10%; P<0.0001). Secondary: More patients receiving lixisenatide compared to placebo achieved HbA_{1c} <7.0% (36.4% vs 13.5%; P<0.0001). Lixisenatide lowered FPG (-17.09 mg/dL vs -10.36 mg/dL, respectively; P=0.0114) and body weight (-1.63 kg vs -0.83, respectively; P=0.0005) compared to placebo. The percentage of adverse events was 68.3% for lixisenatide and 61.1% for placebo; and for severe adverse events: 3.5% vs 5.6%, respectively. Lixisenatide did not significantly increase symptomatic hypoglycemia vs placebo (15.3% vs 12.3%, respectively).
Pinget et al.[105] (2013) GETGOAL-P Lixisenatide 20 µg QD vs placebo	DB, MC, PC, PG, RCT Patients with type 2 DM (diagnosed for at least one year) receiving pioglitazone at a stable dose of ≥30 mg/day with or without metformin for at least the previous three months and a	N=484 24 weeks	Primary: HbA_{1c} Secondary: Proportion of patients achieving glycemic goals, FPG, body weight and adverse events	Primary: After 24 weeks, lixisenatide once daily improved HbA_{1c} (-0.56% vs placebo; P<0.0001). Secondary: Lixisenatide was associated with an increased proportion of patients achieving HbA_{1c} <7% compared with placebo (52.3% vs. 26.4%, respectively; P<0.0001) and improved FPG (-0.84 mmol/L vs placebo; P<0.0001). There was a small decrease in body weight with lixisenatide once daily and a small increase with placebo, with no statistically significant difference between the two groups (-0.11 kg vs 0.26 kg; P=0.1864).

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	HbA_{1c} ≥7% to ≤10%			Overall, lixisenatide once daily was well tolerated, with a similar proportion of adverse events and serious events between groups. Symptomatic hypoglycemia rates were also relatively low in both groups (lixisenatide 3.4% and placebo 1.2%), with no severe episodes.
Riddle et al.[106] (2013) GETGOAL-L Lixisenatide 20 µg QD vs placebo	DB, MC, PC, PG, RCT Patients with type 2 DM (diagnosed for at least one year) receiving basal insulin with or without metformin at a stable dose of ≥30 units/day for at least the previous two months and a HbA_{1c} ≥7% to ≤10%	N=496 24 weeks	Primary: HbA_{1c} Secondary: Proportion of patients achieving glycemic goals, body weight and adverse events	Primary: With lixisenatide, the placebo-corrected change of HbA_{1c} from baseline was -0.4% (95% CI, -0.6 to -0.2; P=0.0002), and mean HbA_{1c} at end point was 7.8%. Secondary: HbA_{1c} <7.0% was attained by more lixisenatide than placebo (28% vs 12%, respectively; P<0.0001). Reductions in body weight was greater with lixisenatide (placebo corrected, -1.3 kg; P<0.0001). Main adverse events with lixisenatide were gastrointestinal. Symptomatic hypoglycemia was 28% for lixisenatide and 22% for placebo; 4 of 328 subjects (1.2%) had severe hypoglycemia with lixisenatide compared to 0 of 167 with placebo.
Riddle et al.[107] (2013) GETGOAL-DUO 1 Lixisenatide 20 µg QD vs placebo After enrollment, participants continued metformin and a TZD if previously used but stopped any secretagogue.	DB, MC, PC, PG, RCT Adult patients with type 2 DM (diagnosed for at least one year) receiving metformin at a stable dose of ≥1.5 g/day alone or in combination with a sulfonylurea, TZD or a glinide for at least the previous three months and a HbA_{1c} ≥7% to ≤10% and BMI>20 kg/m^2	N=446 24 weeks	Primary: HbA_{1c} Secondary: Proportion of patients achieving glycemic goals, post-prandial glucose, body weight and adverse events	Primary: HbA_{1c} had decreased during run-in from 8.6% to 7.6%; adding lixisenatide further reduced HbA_{1c} by 0.71% vs 0.40% with placebo (LS mean difference, -0.32%; 95% CI, -0.46 to -0.17; P<0.0001). Secondary: More participants attained HbA_{1c} <7% with lixisenatide (56 vs 39%; P<0.0001). Lixisenatide reduced plasma glucose 2 hour after a standardized breakfast (difference vs. placebo -3.2 mmol/L; P<0.0001) and had a favorable effect on body weight (difference vs placebo -0.89 kg; P=0.0012). Nausea, vomiting, and symptomatic hypoglycemia were more common with lixisenatide.

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Morning administration of insulin glargine was started at 10 units QD and was titrated weekly, targeting a fasting range of 80 to 100 mg/dL. At completion of the 12-week run-in, participants were eligible for randomization if they had HbA_{1c} ≥7% and ≤9% and fasting self-measurement of plasma-referenced glucose for the past seven days averaging ≤126 mg/dL early in the trial or ≤140 mg/dL after a protocol amendment in July 2010.				
Rosenstock et al.[108] (2016) GETGOAL-DUO 2 Lixisenatide 20 µg QD vs insulin glulisine QD vs.	AC, MC, OL Adult patients with type 2 DM (diagnosed for at least one year) uncontrolled on ≥6 months' basal insulin, with or without one to three oral antidiabetic agents	N=298 24 weeks	Primary: Noninferiority of lixisenatide versus insulin glulisine once daily in HbA_{1c} reduction; and for lixisenatide vs. insulin glulisine thrice daily, either noninferiority in HbA_{1c} reduction or superiority of	Primary: All coprimary end points were met. HbA_{1c} improved from 8.5% to 7.9% with glargine optimization and further to 7.2%, 7.2%, and 7.0% with lixisenatide and glulisine once daily and thrice daily, respectively. Lixisenatide demonstrated statistical superiority in change from baseline at week 26 in body weight compared with insulin glulisine thrice daily (coprimary end point LS mean treatment difference, –2.0 kg (95% CI, –2.59 to –1.40; P<0.0001). Secondary:

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insulin glulisine TID On run-in entry, oral antidiabetic drugs other than metformin (DPP-4 inhibitors, sulfonylureas, and glinides) were discontinued, and insulin glargine was optimally titrated. After the run-in phase, if HbA_{1c} remained between ≥7% to ≤9% and mean FPG was ≤140 mg/dL patients were randomized.	and a HbA_{1c} ≥7% to ≤9% at study start and BMI> 20 and ≤40 kg/m^2		lixisenatide vs. insulin glulisine thrice daily in body weight change. Secondary: Percentage of patients achieving glycemic goals, FPG, post-prandial glucose, body weight and adverse events	At week 26, the change from baseline in body weight in the three treatment groups was –0.6, 1.0 and 1.4 kg, for lixisenatide and insulin glulisine once daily and thrice daily, respectively. LS mean reductions from baseline in 2-hour post prandial glucose after a standardized breakfast at week 26 were greater in the lixisenatide arm compared with the insulin glulisine. Symptomatic hypoglycemia was lower in lixisenatide compared to glulisine patients. More gastrointestinal events occurred with lixisenatide.
Pfeffer et al.[109] (2015) ELIXA Lixisenatide 20 µg QD vs placebo Glycemic control was managed by the investigators in accordance with	DB, MC, PC, RCT Patients with type 2 DM who had had an MI or who had been hospitalized for unstable angina within the previous 180 days	N=6,068 Median follow-up of 25 months	Primary: Composite of the first occurrence of any of the following: death from cardiovascular causes, nonfatal MI, nonfatal stroke, or hospitalization for unstable angina Secondary: Composite	Primary: A primary end-point event occurred in 406 patients (13.4%) in the lixisenatide group and in 399 (13.2%) in the placebo group (HR, 1.02; 95% CI, 0.89 to 1.17), which showed the noninferiority of lixisenatide to placebo (P<0.001) but did not show superiority (P=0.81). A total of 156 patients in the lixisenatide group and 158 in the placebo group died from cardiovascular causes (HR, 0.98; 95% CI, 0.78 to 1.22), a total of 270 patients in the lixisenatide group and 261 in the placebo group had a fatal or nonfatal MI (HR, 1.03; 95% CI, 0.87 to 1.22), a total of 67 patients in the lixisenatide group and 60 in the placebo group had a fatal or nonfatal stroke (HR, 1.12; 95% CI, 0.79 to 1.58), and a total of 11 patients in the lixisenatide group and 10 in the placebo group were hospitalized for unstable angina (HR, 1.11; 95% CI, 0.47 to 2.62).

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local clinical practice guidelines by the adjustment of concomitant glucose-lowering agents or the addition of new antidiabetic medications with the exception of other incretin therapies.			of the primary end point or hospitalization for HF and a composite of the primary end point, hospitalization for HF, or coronary revascularization procedures, death from any cause and safety evaluations	Sensitivity analyses that excluded events occurring more than 30 days after discontinuation of lixisenatide or placebo and that were adjusted for baseline imbalances produced similar results. Secondary: When hospitalization for HF was added to the primary composite end point, 456 patients (15.0%) in the lixisenatide group and 469 (15.5%) in the placebo group had an event in this expanded end point (HR, 0.97; 95% CI, 0.85 to 1.10). The further addition of coronary revascularization procedure to the expanded composite end point resulted in 661 patients (21.8%) in the lixisenatide group and 659 (21.7%) in the placebo group having at least one of these adjudicated cardiovascular end points (HR, 1.00; 95% CI, 0.90 to 1.11). Death from any cause was reported in 211 patients (7.0%) in the lixisenatide group and in 223 (7.4%) in the placebo group (HR, 0.94; 95% CI, 0.78 to 1.13). Lixisenatide was not associated with a higher rate of serious adverse events or severe hypoglycemia, pancreatitis, pancreatic neoplasms or allergic reactions than was placebo.
Pratley et al.[110] (2018) SUSTAIN 7 Semaglutide 0.5 or 1 mg SC weekly vs dulaglutide 0.75 or 1 mg SC weekly	OL, MC, RCT Patients ≥18 years with type 2 diabetes with HbA_{1c} 7.0 to 10.5% on metformin monotherapy	N=1,201 40 weeks	Primary: Change in HbA_{1c} Secondary: Change in body weight	Primary: From baseline, mean percentage HbA_{1c} was reduced by 1.5 percentage points with semaglutide 0.5 mg vs 1.1 percentage points with dulaglutide 0.75 mg. At the higher doses, semaglutide 1.0 mg reduced HbA_{1c} by 1.8 percentage points vs 1.4 percentage points with dulaglutide 1.5 mg. The estimated treatment difference for semaglutide 0.5 mg vs dulaglutide 0.75 mg was −0.40 percentage points (95% CI, −0.55 to −0.25) and for semaglutide 1.0 mg vs dulaglutide 1.5 mg was −0.41 percentage points (95% CI, −0.57 to −0.25); both P<0.0001 for non-inferiority and superiority Secondary: From baseline, mean bodyweight was reduced at week 40 by 4.6 kg with semaglutide 0.5 mg vs 2.3 kg with dulaglutide 0.75 mg (treatment difference, −2.26; 95% CI, −3.02 to −1.51; P<0.0001), and by 6.5 kg with semaglutide 1.0 mg vs 3.0 kg with dulaglutide 1.5 mg (−3.55 kg; 95% CI, –4.32 to −2.78; P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Ahmann et al.[111] (2018) SUSTAIN 3 Semaglutide 1 mg SC weekly vs exenatide ER 2 mg SC weekly Subjects with unacceptable hyperglycemia were to be offered metformin (first choice) or other antidiabetic medications (not GLP-1, DPP-4 inhibitors or amylin analogs) as add-on to their randomized treatment (rescue medication) at the discretion of the investigator.	AC, MC, OL, RCT Patients ≥18 years with type 2 DM inadequately controlled with two oral antidiabetic drugs (metformin and/or TZD and sulfonylurea) ≥90 days before screening and an HbA_{1c} ≥7% to ≤10.5%	N=813 56 weeks	Primary: Change in HbA_{1c} Secondary: Change in body weight, FPG, SMPG, BMI, waist circumference, SBP and safety evaluations.	Primary: Mean HbA_{1c} decreased over time by 1.5% with semaglutide and 0.9% with exenatide ER at 56 weeks (estimated treatment difference vs exenatide ER, –0.62%; 95% CI –0.80 to –0.44; P<0.0001 for noninferiority and superiority). Secondary: Mean body weight (95.8 kg at baseline) was reduced by 5.6 kg with semaglutide and 1.9 kg with exenatide ER (estimated treatment difference, -3.78 kg; 95% CI, -4.58 to -2.98; P<0.0001). More subjects treated with semaglutide achieved HbA_{1c} <7.0% versus those taking exenatide ER (67% vs 40%; P<0.0001). Both treatments had similar safety profiles, but gastrointestinal adverse events were more common in semaglutide-treated subjects (41.8%) than in exenatide ER-treated subjects (33.3%); injection-site reactions were more frequent with exenatide ER (22.0%) than with semaglutide (1.2%).
Aroda et al.[112] (2017) SUSTAIN 4 Semaglutide 0.5 mg SC weekly vs	AC, MC, OL, PG Patients ≥18 years with type 2 DM inadequately controlled with metformin with or without a sulfonylurea ≥90 days before	N=1,089 30 weeks	Primary: HbA_{1c} Secondary: Change in body weight, FPG, SMPG, BMI, waist circumference, SBP and safety evaluations.	Primary: Treatment with semaglutide 0.5 mg and 1 mg once weekly resulted in a reduction in HbA_{1c} compared with the insulin glargine (1.2% and -1.5% and -0.9%; P<0.0001). Secondary: The mean changes from baseline to week 30 were -3.2 kg, -4.7 kg and 0.9 kg in the semaglutide 0.5 mg, 1 mg, and insulin glargine arms, respectively.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
semaglutide 1 mg SC weekly vs insulin glargine 10 units QD titrated to a pre-breakfast SMPG target of 72 to 99 mg/dL Subjects with unacceptable hyperglycemia were to be offered metformin (first choice) or other antidiabetic medications (not GLP-1, DPP-4 inhibitors or amylin analogs) as add-on to their randomized treatment (rescue medication) at the discretion of the investigator.	screening, an HbA_{1c} ≥7% to ≤10% and who were insulin naïve			The semaglutide treatment had significantly greater reductions in FPG (only semaglutide 1 mg), mean 8-point SMPG (only semaglutide 1 mg), mean prandial increment (across all meals) of the 8-point SMPG, BMI and waist circumference. Further, the odds of achieving HbA_{1c} targets and categorical weight loss targets were significantly greater with semaglutide 0.5 mg or 1 mg compared with insulin glargine. The most frequently reported adverse events were nausea with semaglutide, reported in 77 (21%) patients with 0.5 mg and in 80 (22%) with 1.0 mg, and nasopharyngitis reported in 44 (12%) patients with insulin glargine.
Kellerer et al.[113] (2022) SUSTAIN 11 Semaglutide once weekly vs	MC, OL, PG, RCT Adults with inadequately controlled type 2 diabetes (HbA_{1c} >7.5% to ≤10.0%) with IGlar and metformin ± one additional oral	N=1,748 52 weeks	Primary: HbA_{1c} Secondary: Occurrence of severe hypoglycemic episodes and change in body weight	Primary: HbA_{1c} (randomization: 8.6%) decreased by 1.5% points and 1.2% points with semaglutide (n=874) and IAsp (n=874), respectively (estimated treatment difference [ETD], -0.29% points; 95% CI, -0.38 to -0.20; P<0.0001 for non-inferiority). Secondary: Few severe hypoglycemic episodes were recorded in either group, with no statistically significant difference between the groups. Change in body weight from randomization (87.9 kg) to week 52 was in favor of semaglutide (-4.1

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
insulin aspart (IAsp) thrice-daily (TID) Treatments as add-on to optimized insulin glargine (IGlar) and metformin	antihyperglycaemic drug (OAD), who were willing to undergo individualized treatment intensification toward an HbA_{1c} target of 6.5% to 7.5%			kg) versus IAsp (+2.8 kg) (ETD, -6.99 kg; 95% CI, -7.41 to -6.57). A higher proportion of participants experienced adverse events with semaglutide (58.5%) versus IAsp (52.1%); most were mild to moderate.
Ahrén et al.[114] (2017) SUSTAIN 2 Semaglutide 0.5 mg SC weekly vs semaglutide 1 mg SC weekly vs sitagliptin 100 mg QD Subjects with unacceptable hyperglycemia were to be offered metformin (first choice) or other antidiabetic medications (not GLP-1, DPP-4 inhibitors or amylin	DB, MC, AC, PG, RCT Patients ≥18 years with type 2 DM inadequately controlled with metformin, TZD or metformin and a TZD for ≥90 days before screening and an HbA1c ≥7% to ≤10.5%	N=1,231 56 weeks	Primary: HbA_{1c} Secondary: Change in body weight, FPG, SMPG, BMI, waist circumference, SBP and safety evaluations.	Primary: Treatment with semaglutide 0.5 mg and 1 mg once weekly resulted in a reduction in HbA1c compared to sitagliptin 100 mg daily (-1.3% and 1.5% vs -0.7%; P<0.0001). Secondary: The semaglutide groups had greater body weight reduction vs sitagliptin and significantly greater reductions in FPG, mean 7-point SMPG, mean prandial increment (across all meals) of the 7-point SMPG (only semaglutide 1 mg), BMI, waist circumference and systolic blood pressure. There were also significantly greater odds of achieving A_{1c} targets and categorical weight loss targets with semaglutide 0.5 mg or 1 mg vs sitagliptin. The most frequently reported adverse events in both semaglutide groups were gastrointestinal in nature: nausea was reported in 73 (18%) who received semaglutide 0.5 mg, 72 (18%) who received semaglutide 1.0 mg, and 30 (7%) who received placebo, and diarrhoea was reported in 54 (13%) who received semaglutide 0.5 mg, 53 (13%) who received semaglutide 1.0 mg, and 29 (7%) who received placebo.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
analogs) as add-on to their randomized treatment (rescue medication) at the discretion of the investigator.				
Rodbard et al.[115] (2018) SUSTAIN 5 Semaglutide 0.5 mg SC weekly vs semaglutide 1 mg SC weekly vs placebo Subjects with unacceptable hyperglycemia were to be offered metformin (first choice) or other antidiabetic medications (not GLP-1, DPP-4 inhibitors or amylin analogs) as add-on to their randomized treatment (rescue medication) at the discretion of the investigator.	DB, MC, PC, PG, RCT Patients ≥18 years with type 2 DM inadequately controlled with insulin with or without metformin ≥90 days before screening, an HbA_{1c} ≥7% to ≤10% and who were experiencing ≥3 episodes of severe hypoglycemia within six months prior to screen and/or hypoglycemic unawareness	N=397 30 weeks	Primary: HbA_{1c} Secondary: Change in body weight, FPG, SMPG, BMI, waist circumference, SBP, and safety evaluations.	Primary: At week 30, mean HbA_{1c} values with semaglutide 0.5 and 1.0 mg were 6.9% and 6.5%, vs 8.3% with placebo, corresponding to reductions of 1.4% and 1.8% vs 0.1% with placebo (estimated treatment difference vs placebo, –1.35%; 95% CI, –1.61 to –1.10; and estimated treatment difference, –1.75%; 95% CI, –2.01 to –1.50; both P<0.0001). Secondary: Severe or blood glucose-confirmed hypoglycemic episodes were reported in 11 patients (17 events) and 14 patients (25 events) with semaglutide 0.5 and 1.0 mg, respectively, vs seven patients (13 events) with placebo (estimated rate ratio vs placebo, 2.08; 95% CI, 0.67 to 6.51 and estimated rate ratio vs placebo, 2.41; 95% CI, 0.84 to 6.96 for 0.5 and 1.0 mg; both P=nonsignificant). Mean body weight decreased with semaglutide 0.5 and 1.0 mg vs placebo from baseline to end of treatment: 3.7, 6.4, and 1.4 kg (estimated treatment difference, -2.31; 95% CI, -3.33 to -1.29 and estimated treatment difference, -5.06; 95% CI, -6.08 to -4.04 kg; both P<0.0001). Premature treatment discontinuation due to adverse events was higher for semaglutide 0.5 and 1.0 mg vs placebo (4.5%, 6.1%, and 0.8%), mainly due to gastrointestinal disorders.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Marso et al.[116] (2016) SUSTAIN 6 Semaglutide 0.5 mg SC weekly vs semaglutide 1 mg SC weekly vs insulin glargine 10 units QD titrated to a pre-breakfast SMPG target of 72 to 99 mg/dL Subjects with unacceptable hyperglycemia were to be offered metformin (first choice) or other antidiabetic medications (not GLP-1, DPP-4 inhibitors or amylin analogs) as add-on to their randomized treatment (rescue medication) at the discretion of the investigator.	DB, MC, PC, PG, RCT Patients ≥50 years with type 2 DM inadequately and established cardiovascular disease, chronic heart failure or chronic kidney disease or ≥60 years with at least one cardiovascular risk factor, antihyperglycemic drug-naïve, or treated with one or two oral antihyperglycemic agents, with or without basal or pre-mixed insulin and HbA_{1c} ≥7%	N=3,297 N=104	Primary: MACE Secondary: Safety evaluations	Primary: The total number of primary component MACE endpoints was 254 (108 [6.6%] with semaglutide and 146 [8.9%] with placebo). For the MACE components, the results for non-fatal MI (HR, 0.74; 95% CI, 0.51 to 1.08; P=0.12) and non-fatal stroke (HR, 0.61; 95% CI, 0.38 to 0.99; P=0.04) contributed to the favorable overall treatment effect of semaglutide on MACE. The occurrence of cardiovascular death was similar with semaglutide and placebo (HR, 0.98; 95% CI, 0.65 to 1.48; P=0.92). Rates of new or worsening nephropathy were lower in the semaglutide group, but rates of retinopathy complications (vitreous hemorrhage, blindness, or conditions requiring treatment with an intravitreal agent or photocoagulation) were significantly higher (HR, 1.76; 95% CI, 1.11 to 2.78; P=0.02). Secondary: Fewer serious adverse events occurred in the semaglutide group, although more patients discontinued treatment because of adverse events, mainly gastrointestinal.
Lingvay et al.[117] (2019)	DB, MC, RCT	N=788	Primary: Change in	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
SUSTAIN 8 Semaglutide 1.0 mg subcutaneous once weekly vs canagliflozin 300 mg orally once daily	Adults with uncontrolled type 2 diabetes (HbA_{1c} 7.0 to 10.5%) on stable daily metformin therapy	52 weeks	HbA_{1c} from baseline Secondary: Change in body weight from baseline	Treatment with semaglutide led to greater reductions in HbA_{1c} compared with those with canagliflozin, with an estimated change from baseline to week 52 of −1.5 percentage points (standard error [SE], 0.06; −16.0 mmol/mol, SE 0.65) with semaglutide and −1.0 percentage points (0.06; −10.7 mmol/mol, 0.61) with canagliflozin. The estimated treatment difference (ETD) was −0.49 percentage points (95% CI, −0.65 to −0.33; −5.34 mmol/mol, 95% CI −7.10 to −3.57; P<0.0001). Greater proportions of patients achieved prespecified HbA_{1c} targets with semaglutide than with canagliflozin (66% vs 45% achieved HbA_{1c} <7.0% [<53 mmol/mol], OR, 2.77; 95% CI, 1.98 to 3.85; P<0.0001; 53% vs 24% achieved HbA_{1c} ≤6.5% [≤48 mmol/mol], 4.19, 2.97 to 5.92; P<0.0001). Secondary: From an overall mean baseline of 90.2 kg, estimated change in bodyweight was −5.3 kg with semaglutide and −4.2 kg with canagliflozin (ETD, −1.06 kg; 95% CI, −1.76 to −0.36; P=0.0029).
Rodbard et al.[118] (2019) PIONEER 2 Semaglutide 14 mg orally QD vs empagliflozin 25 mg QD All patients randomized to oral semaglutide initiated treatment with 3 mg QD with dose escalations every four weeks until the randomized maintenance dose was achieved.	AC, DB, MC, PG, RCT Adults with type 2 DM insufficiently controlled with diet and exercise and HbA_{1c} 7.0 to 10.5% and on a stable dose of metformin ≥90 days before screening	N=822 52 weeks	Primary: Change in HbA_{1c} from baseline Secondary: Changes in measures of glucose control, achievement of an HbA_{1c} target of ,7% or ≤6.5% and achievement of weight loss of at least 5% or 10%, as well as C-reactive protein, fasting lipid levels from baseline and safety	Primary: Treatment with semaglutide resulted in a statistically significant reduction in HbA_{1c} compared to empagliflozin 25 mg once daily (-1.3% vs -0.9%, respectively; P<0.001). Secondary: The mean changes from baseline to week 26 were -3.8 kg and -3.7 kg in the semaglutide 14 mg and empagliflozin 25 mg arms, respectively (95% CI -0.1, -0.7 to 0.5). Select secondary endpoints involving measures of glycemic control, weight loss and lipid levels favored semaglutide over empagliflozin, however select comparisons demonstrated no difference.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Rosenstock et al.[119] (2019) PIONEER 3 Semaglutide 3 mg orally QD vs semaglutide 7 mg orally QD vs semaglutide 14 mg orally QD vs sitagliptin 100 mg QD All patients randomized to oral semaglutide initiated treatment with 3 mg QD with dose escalations every four weeks until the randomized maintenance dose was achieved.	AC, DB, MC, PG, RCT Adults with type 2 DM insufficiently controlled with diet and exercise and HbA_{1c} 7.0 to 10.5% and on a stable dose of metformin (with or without a SU) ≥90 days before screening	N=1,864 78 weeks	Primary: Change in HbA_{1c} from baseline at week 26 Secondary: Changes in measures of glucose control, achievement of an HbA_{1c} target of ,7% or ≤6.5% [and achievement of weight loss of at least 5% or 10%, as well as C-reactive protein, fasting lipid levels from baseline (at weeks 26, 52 and 78) and safety	Primary: Treatment with semaglutide 7 mg and 14 mg once daily for 26 weeks resulted in a statistically significant reduction in HbA_{1c} compared to sitagliptin 100 mg once daily (-1.0% and -1.3% vs -0.8%; P<0.001 for both comparisons). At week 78, HbA_{1c} reductions from baseline remained statistically significantly greater with semaglutide, 7 mg/day and 14mg/day compared to sitagliptin. Secondary: The mean changes in weight from baseline to week 26 were -2.2 kg and -3.1 kg in the semaglutide 7 and 14 mg groups and -0.6 kg in sitagliptin group, respectively (95% CI, -1.1 to -2.0 and -2.0 to -3.0, respectively).[1] The body weight reductions at week 78 remained statistically significantly greater with all dosages of semaglutide compared with sitagliptin. For fasting plasma glucose and mean self-measured whole-blood glucose, the reductions from baseline were significantly greater in the 14 mg/day semaglutide group at weeks 26 and 78 compared with sitagliptin. In the 7 mg/day-and 14 mg/day semaglutide groups, significantly greater proportions of patients and achieved HbA1c levels lower than 7.0%, and body weight loss of 5% or greater. The most frequent adverse events by system organ class were gastrointestinal disorders in the 14 mg/day semaglutide group and infections and infestations in the 3 mg/day and 7 mg/day semaglutide and sitagliptin groups.
Pratley et al.[120] (2019) PIONEER 4 Semaglutide 14 mg orally QD	AC, DB, MC, PG, RCT Adults with type 2 DM insufficiently controlled with diet	N=711 52 weeks	Primary: Change in HbA_{1c} from baseline at week 26	Primary: Treatment with semaglutide 14 mg once daily for 26 weeks resulted in non-inferior reductions in HbA_{1c} compared to liraglutide 1.8 mg (-1.2% vs -1.1; P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs liraglutide 1.8 mg QD vs placebo All patients randomized to oral semaglutide initiated treatment with 3 mg QD with dose escalations every four weeks until the randomized maintenance dose was achieved.	and exercise and HbA_{1c} 7.0 to 9.5% and on a stable dose of metformin (with or without an SGLT2) ≥90 days before screening		Secondary: Changes in measures of glucose control, achievement of an HbA_{1c} target of <7% or ≤6.5% [and achievement of weight loss of at least 5% or 10% and safety	At 52 weeks, decreases in HbA_{1c} were significantly greater with oral semaglutide than with both subcutaneous liraglutide (difference, –0.3%; 95% CI, –0.5 to –0.1; P=0.0002) and placebo (difference, –1.0%; 95% CI, –1.2 to –0.8; P<0.0001) Secondary: The mean changes from baseline to week 26 were -0.5 kg, -3.1 kg and -4.4 kg in the placebo, liraglutide 1.8 mg, and semaglutide 14 mg arms, respectively. The difference between semaglutide and liraglutide was considered significant, favoring semaglutide (P<0.0003). While most secondary endpoints favored semaglutide over placebo, select endpoints involving measures of glycemic control, weight loss and lipid levels favored semaglutide over liraglutide, however select comparisons demonstrated no difference. Adverse events were more frequent with semaglutide (n=229 [80%]) and liraglutide (n=211 [74%]) than with placebo (n=95 [67%]).
Mosenzon et al.[121] (2019) PIONEER 5 Semaglutide 14 mg orally QD vs placebo All patients randomized to oral semaglutide initiated treatment with 3 mg QD with dose escalations every four weeks	DB, MC, PC, PG, RCT Adults with type 2 DM insufficiently controlled with diet and exercise and HbA_{1c} 7.0 to 9.5% and moderate renal impairment (glomerular filtration rate: 30 to 59 mL/min/ 1.73 m^2) doses of one of the following regimens for 90 days before	N=324 26 weeks	Primary: Change in HbA_{1c} from baseline at week 26 Secondary: Changes in measures of glucose control, achievement of an HbA_{1c} target of <7% or ≤6.5% [and achievement of weight loss of at least 5% or 10% and safety	Primary: Treatment with semaglutide 14 mg once daily for 26 weeks resulted in a statistically significant reduction in HbA_{1c} from baseline compared to placebo (-1.0% vs -0.2%, respectively; P<0.001). Secondary: The mean changes from baseline to week 26 were -0.9 kg and -3.4 kg in the placebo and semaglutide 14 mg arms, respectively. The difference from placebo for semaglutide 14 mg was -2.5 kg (95% CI, -3.2 to -1.8). Other secondary endpoints involving measures of glycemic control, weight loss and lipid levels generally favored semaglutide over placebo. More patients taking oral semaglutide than placebo had adverse events (120 [74%] of 163 vs 105 [65%] of 161), and discontinued treatment as a result (24 [15%] vs eight [5%]). GI events, mainly mild-to-moderate nausea, were more common with oral semaglutide than with placebo.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
until the randomized maintenance dose was achieved.	screening: metformin (≥1,500 mg or maximum tolerated dose), a SU (at least half of the maximum approved dose or maximum tolerated dose), or both; or basal insulin with or without metformin			
Husain et al.[122] (2019) PIONEER 6 Semaglutide oral once-daily (target dose, 14 mg) vs placebo	DB, MC, RCT Patients with type 2 diabetes ≥50 years of age with established cardiovascular disease or chronic kidney disease or ≥60 years of age with cardiovascular risk factors only	N=3,183 Median time in the trial was 15.9 months	Primary: Time from randomization to the first occurrence of a major adverse cardiovascular event, a composite of death from cardiovascular causes (including undetermined causes of death), nonfatal myocardial infarction, or nonfatal stroke Secondary: Time from randomization to the first occurrence of the following: an expanded composite outcome consisting of the primary outcome	Primary: Major adverse cardiovascular events occurred in 61 of 1591 patients (3.8%) in the oral semaglutide group and 76 of 1592 (4.8%) in the placebo group (HR, 0.79; 95% CI, 0.57 to 1.11; P<0.001 for noninferiority). Secondary: The hazard ratio for the expanded outcome was similar to that for the primary outcome (with events in 83 of 1591 patients [5.2%] in the oral semaglutide group and 100 of 1592 [6.3%] in the placebo group; HR, 0.82; 95% CI, 0.61 to 1.10). Results for components of the primary outcome were as follows: death from cardiovascular causes, 15 of 1591 patients (0.9%) in the oral semaglutide group and 30 of 1592 (1.9%) in the placebo group (HR, 0.49; 95% CI, 0.27 to 0.92); nonfatal myocardial infarction, 37 of 1591 patients (2.3%) and 31 of 1592 (1.9%), respectively (HR, 1.18; 95% CI, 0.73 to 1.90); and nonfatal stroke, 12 of 1591 patients (0.8%) and 16 of 1592 (1.0%), respectively (HR, 0.74; 95% CI, 0.35 to 1.57). Death from any cause occurred in 23 of 1591 patients (1.4%) in the oral semaglutide group and 45 of 1592 (2.8%) in the placebo group (HR, 0.51; 95% CI, 0.31 to 0.84). Gastrointestinal adverse events leading to discontinuation of oral semaglutide or placebo were more common with oral semaglutide.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			plus unstable angina resulting in hospitalization or heart failure resulting in hospitalization; a composite of death from any cause, nonfatal myocardial infarction, or nonfatal stroke; and the individual components of these composite outcomes	
Pieber et al.[123] (2019) PIONEER 7 Sitagliptin 100 mg once daily vs semaglutide orally with flexible dose adjustments to 3, 7, or 14 mg once daily	MC, OL, RCT Adults with type 2 diabetes (diagnosed ≥90 days before screening), HbA_{1c} of 7.5 to 9.5%, and were inadequately controlled on stable daily doses of one or two oral glucose-lowering drugs (for 90 days or more before screening)	N=504 52 weeks	Primary: Achievement of HbA_{1c} < 7% and change in bodyweight from baseline to week 52 according to two efficacy-related estimands were prespecified: treatment policy (regardless of treatment discontinuation or use of rescue medication) and trial product (on treatment and without use of rescue medication) Secondary:	Primary: A greater proportion of participants achieved an HbA_{1c} <7% with oral semaglutide than did with sitagliptin (treatment policy estimand: 58% vs 25%; and trial product estimand: 63% vs 28%). The odds of achieving an HbA_{1c} <7% was better with oral semaglutide than sitagliptin (treatment policy estimand: odds ratio [OR] 4.40; 95% CI, 2.89 to 6.70; P<0.0001; and trial product estimand: 5.54; 3.54 to 8.68; P<0.0001). The odds of decreasing mean bodyweight from baseline to week 52 were higher with oral semaglutide than with sitagliptin (estimated mean change in bodyweight, treatment policy estimand: -2.6 kg vs -0.7 kg, estimated treatment difference, -1.9 kg; 95% CI, -2.6 to -1.2; P<0.0001; and trial product estimand: -2.9 kg vs -0.8 kg; estimated treatment difference, -2.2 kg; -2.9 to -1.5; P<0.0001). Secondary: Adverse events occurred in 197 (78%) of 253 participants in the oral semaglutide group versus 172 (69%) of 250 in the sitagliptin group, and nausea was the most common adverse event with oral semaglutide (53 [21%]). Two deaths occurred in the sitagliptin group during the trial.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Safety	
Zinman et al.[124] (2019) PIONEER 8 Semaglutide 3 mg orally QD vs semaglutide 7 mg orally QD vs semaglutide 14 mg orally QD vs placebo All patients randomized to oral semaglutide initiated treatment with 3 mg QD with dose escalations every four weeks until the randomized maintenance dose was achieved.	DB, MC, PC, PG, RCT Adults with type 2 DM with HbA_{1c} 7.0 to 9.5% and on a stable regimen of basal, basal-bolus (in any combination), or premixed insulin (including combinations of soluble insulin) at ≥10 units/day for ≥90 days before screening. If used, concomitant metformin was required to be at a stable dosage (≥1,500 mg daily or the maximum tolerated dosage) for ≥90 days before screening	N=731 52 weeks	Primary: Change in HbA_{1c} from baseline at week 26 Secondary: Changes in measures of glucose control, achievement of an HbA_{1c} target of <7% or ≤6.5% [and achievement of weight loss of at least 5% or 10% and safety	Primary: Treatment with semaglutide 7 mg and 14 mg once daily for 26 weeks resulted in a statistically significant reduction in HbA_{1c} from baseline compared to placebo once daily (-0.9% and -1.3% vs. -0.1%, respectively; P<0.001 for both comparisons). Secondary: The mean changes from baseline to week 26 were -0.4 kg, -2.4 kg and -3.7 kg in the placebo, semaglutide 7 mg, and semaglutide 14 mg arms, respectively. The difference from placebo for semaglutide 7 mg was -2.0 kg (95% CI, -3.0 to -1.0), and for semaglutide 14 mg was -3.3 kg (95% CI, -4.2 to -2.3). Significantly greater dose-dependent HbA1c and body weight reductions versus placebo were achieved with oral semaglutide at weeks 26 and 52. Other secondary endpoints involving measures of glycemic control, weight loss and lipid levels generally favored semaglutide over placebo. The most frequent adverse event with oral semaglutide was nausea (11.4 to 23.2% of patients vs 7.1% with placebo; mostly mild to moderate).
GRADE Study Research Group[125] (2022) Insulin glargine U-100 administered	MC, PG, RCT Participants with type 2 diabetes of less than 10 years' duration who were	N=5,047 5 years	Primary: Cumulative incidence of a glycated hemoglobin level of 7.0% or higher	Primary: Over the mean 5-year follow-up, 71% of the cohort had a primary metabolic outcome event, with the highest frequency in the sitagliptin group (77%), intermediate frequency in the glimepiride group (72%), and the lowest frequency in the liraglutide (68%) and glargine (67%) groups. The between-

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
daily at an initial dose of up to 20 U and adjusted according to glucose levels vs glimepiride, increased from 1 to 2 mg to a maximum of 8 mg per day, administered in divided doses and adjusted according to glucose levels vs liraglutide initiated at a dose of 0.6 mg, with escalation to a maximum dose of 1.8 mg daily, depending on gastrointestinal side effects vs sitagliptin at a dose of 100 mg, with the dose adjusted according to kidney function	receiving metformin and had glycated hemoglobin levels of 6.8 to 8.5%		Secondary: Cumulative incidence of a glycated hemoglobin level of 7.5% or higher	group differences in the Kaplan–Meier estimates of the cumulative incidence of a primary-outcome event were significant (P<0.001 by the log-rank test). Secondary: The differences among the groups with respect to a glycated hemoglobin level greater than 7.5% (the secondary outcome) paralleled those of the primary outcome. A secondary-outcome event occurred in 55% of the participants in the sitagliptin group over a mean follow-up of 5 years, followed by glimepiride (in 50%), liraglutide (in 46%), and glargine (in 39%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Metformin was supplied to all the participants				
GRADE Study Research Group[126] (2022) Insulin glargine U-100 administered daily at an initial dose of up to 20 U and adjusted according to glucose levels vs glimepiride, increased from 1 to 2 mg to a maximum of 8 mg per day, administered in divided doses and adjusted according to glucose levels vs liraglutide initiated at a dose of 0.6 mg, with escalation to a maximum dose of 1.8 mg daily, depending on gastrointestinal side effects vs	MC, PG, RCT Participants with type 2 diabetes of less than 10 years' duration who were receiving metformin and had glycated hemoglobin levels of 6.8 to 8.5%	N=5,047 5 years	Primary: Hypertension and dyslipidemia, confirmed moderately or severely increased albuminuria or an estimated glomerular filtration rate of less than 60 ml/min/1.73 m^2, diabetic peripheral neuropathy, cardiovascular events (major adverse cardiovascular events [MACE], hospitalization for heart failure, or an aggregate outcome of any cardiovascular event), and death Secondary: Not reported	Primary: There were no material differences among the interventions with respect to the development of hypertension or dyslipidemia or with respect to microvascular outcomes; the mean overall rate (i.e., events per 100 participant-years) of moderately increased albuminuria levels was 2.6, of severely increased albuminuria levels 1.1, of renal impairment 2.9, and of diabetic peripheral neuropathy 16.7. The treatment groups did not differ with respect to MACE (overall rate, 1.0), hospitalization for heart failure (0.4), death from cardiovascular causes (0.3), or all deaths (0.6). There were small differences with respect to rates of any cardiovascular disease, with 1.9, 1.9, 1.4, and 2.0 in the glargine, glimepiride, liraglutide, and sitagliptin groups, respectively. When one treatment was compared with the combined results of the other three treatments, the hazard ratios for any cardiovascular disease were 1.1 (95% confidence interval [CI], 0.9 to 1.3) in the glargine group, 1.1 (95% CI, 0.9 to 1.4) in the glimepiride group, 0.7 (95% CI, 0.6 to 0.9) in the liraglutide group, and 1.2 (95% CI, 1.0 to 1.5) in the sitagliptin group. Secondary: Not reported

<table>
<tr><th>Study and Drug Regimen</th><th>Study Design and Demographics</th><th>Study Size and Study Duration</th><th>End Points</th><th>Results</th></tr>
<tr><td>sitagliptin at a dose of 100 mg, with the dose adjusted according to kidney function

Metformin was supplied to all the participants</td><td></td><td></td><td></td><td></td></tr>
<tr><td>SURPASS Clinical Trials Program[127-131]

Tirzepatide

vs

comparators</td><td>Adult patients with type 2 diabetes mellitus</td><td colspan="3">
<table>
<tr><th>Trial (size)</th><th>Background Therapy</th><th>Key Comparator</th><th colspan="2">Key Glycemic Efficacy Comparison (HbA1c % decrease)</th><th colspan="2">Key Body Weight Comparison Loss (kg)</th></tr>
<tr><td colspan="7">Efficacy and Safety Confirmatory Trials</td></tr>
<tr><td rowspan="3">SURPASS-1 (N=478)</td><td rowspan="3">Diet/exercise alone</td><td rowspan="3">Placebo</td><td>5 mg</td><td>-1.87% vs 0.04% (P<0.0001)</td><td>5 mg</td><td>-7.0 vs -0.7 (P<0.001)</td></tr>
<tr><td>10 mg</td><td>-1.89% vs 0.04% (P<0.0001)</td><td>10 mg</td><td>-7.8 vs -0.7 (P<0.0001)</td></tr>
<tr><td>15 mg</td><td>-2.07% vs 0.04% (P<0.0001)</td><td>15 mg</td><td>-9.5 vs -0.7 (P<0.0001)</td></tr>
<tr><td rowspan="3">SURPASS-2 (N=1,878)</td><td rowspan="3">Metformin</td><td rowspan="3">Semaglutide 1 mg weekly</td><td>5 mg</td><td>-2.01% vs -1.86% (P=0.02)</td><td>5 mg</td><td>-7.6 vs -5.7 (P<0.001)</td></tr>
<tr><td>10 mg</td><td>-2.24% vs -1.86% (P<0.001)</td><td>10 mg</td><td>-9.3 vs -5.7 (P<0.001)</td></tr>
<tr><td>15 mg</td><td>-2.30% vs -1.86% (P<0.001)</td><td>15 mg</td><td>-11.2 vs -5.7 (P<0.001)</td></tr>
<tr><td rowspan="3">SURPASS-3 (N=1,437)</td><td rowspan="3">Metformin (w/ or w/o SGLT2)</td><td rowspan="3">Insulin degludec QD</td><td>5 mg</td><td>-1.93% vs -1.34% (P<0.0001)</td><td>5 mg</td><td>-7.5 vs +2.3 (P<0.001)</td></tr>
<tr><td>10 mg</td><td>-2.20% vs -1.34% (P<0.0001)</td><td>10 mg</td><td>-10.7 vs +2.3 (P<0.001)</td></tr>
<tr><td>15 mg</td><td>-2.37% vs -1.34% (P<0.0001)</td><td>15 mg</td><td>-12.9 vs +2.3 (P<0.001)</td></tr>
<tr><td rowspan="2">SURPASS-4 (N=1,995)</td><td rowspan="2">Metformin or sulfonylurea, or SGLT2</td><td rowspan="2">Insulin glargine QD</td><td>5 mg</td><td>-2.24 vs -1.44 (P<0.0001)</td><td>5 mg</td><td>-7.1 vs +1.9 (P<0.0001)</td></tr>
<tr><td>10 mg</td><td>-2.43 vs -1.44 (P<0.0001)</td><td>10 mg</td><td>-9.5 vs +1.9 (P<0.0001)</td></tr>
</table>
</td></tr>
</table>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points		Results			
					15 mg	-2.58 vs -1.44 (P<0.0001)	15 mg	-11.7 vs +1.9 (P<0.0001)
		SURPASS-5 (N=475)	Insulin glargine (w/ or w/o metformin)	Placebo	5 mg	-2.11 vs -0.86 (P<0.001)	5 mg	-5.4 vs +1.6 (P<0.001)
					10 mg	-2.40 vs -0.86 (P<0.001)	10 mg	-7.5 vs +1.6 (P<0.001)
					15 mg	-2.34 vs -0.86 (P<0.001)	15 mg	-8.8 vs +1.6 (P<0.001)

*Agent is not available in the United States.
Drug regimen abbreviations: BID=twice daily, ER=extended-release, QD=once daily, SC=subcutaneous, XL=extended-release
Study abbreviations: AC=active-comparator, DB=double-blind, DD=double-dummy, ES=extension study, IA=interim analysis, MC=multicenter, NI=noninferiority, OE=open-ended, OL=open-label, PC=placebo-controlled, PG=parallel-group, RCT=randomized-controlled trial, RETRO=retrospective, SB=single-blind, SR=systematic review, TB=triple-blind, XO=cross-over
Miscellaneous abbreviations: ALT=alanine aminotransferase, apo B=apolipoprotein B, AST=aspartate aminotransferase, AUC=area under the curve, BMI=body mass index, BNP=brain natriuretic peptide, BP=blood pressure, CI=confidence interval, COPD=chronic obstructive pulmonary disease, CRP=C-reactive protein, DBP=diastolic blood pressure, DPP-4 inhibitor=dipeptidyl peptidase-4 inhibitor, DTSQ=Diabetes Treatment Satisfaction Questionnaire, EQ-5D=EuroQol Quality of Life, FFA=free fatty acid, FPG=fasting plasma glucose, GLP-1=glucagon-like peptide 1, HbA_{1c}=glycosylated hemoglobin, HDL-C=high density lipoprotein cholesterol, HOMA-B=homeostasis model assessment-beta, HOMA-IR=homeostasis model assessment-insulin resistance, HOMA-S=homeostasis model assessment-insulin sensitivity, ITT=intention-to-treat, IWQOL=Impact of Weight on Quality of life Questionnaire, LDL-C=low density lipoprotein cholesterol, LSM=least squares mean, MACE= MI=myocardial infarction, PAI-1=plasminogen activator inhibitor-1, OR=odds ratio, PPG=post-prandial glucose, QOL=quality of life, RR=relative risk, SBP=systolic blood pressure, TC=total cholesterol, TG=triglycerides, TIA=transient ischemic attack, TZD=thiazolidinedione, 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 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 13. Relative Cost of the Incretin Mimetics

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Dulaglutide	injection	Trulicity®	$$$$$	N/A
Exenatide	injection	Byetta®, Bydureon®	$$$$$	N/A
Liraglutide	injection	Victoza®	$$$$$	N/A
Semaglutide	injection, tablet	Ozempic®, Rybelsus®	$$$$$	N/A
Tirzepatide	injection	Mounjaro®	$$$$$	N/A

N/A=Not available

X. Conclusions

The incretin mimetics are approved for use as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus. Some agents are also approved to reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in adults with type 2 diabetes mellitus who have established cardiovascular disease or multiple cardiovascular risk factors.[9] There are no generic products in this class.

Mounjaro® (tirzepatide) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. This agent has a novel mechanism of action that targets GIP and GLP-1 receptors.[1,7] In the SURPASS trials, tirzepatide achieved superior improvements in HbA_{1c} vs placebo, semaglutide, insulin degludec, and insulin glargine. In addition, improvements in body weight were greater than with placebo,

semaglutide, and insulin.[7,127-131] However, the agent is associated with gastrointestinal side effects and a boxed warning for the risk of medullary thyroid tumors.[7]

The goal of treatment for type 2 diabetes is to control hyperglycemia and reduce the risk of long-term complications. A notable new theme in diabetes treatment guidelines is an emphasis on a complication-centric approach, beyond glucose levels, to frame decisions regarding first-line pharmacologic choices for the treatment of persons with diabetes. Pharmacologic therapy should be guided by person-centered treatment factors, including comorbidities and treatment goals. In adults with type 2 diabetes and established/high risk of atherosclerotic cardiovascular disease, heart failure, and/or chronic kidney disease, the treatment regimen should include agents that reduce cardiorenal risk. Pharmacologic approaches that provide adequate efficacy to achieve and maintain treatment goals should be considered, such as metformin or other agents, including combination therapy.[11-14] Guidelines recommend that for patients with type 2 diabetes and atherosclerotic cardiovascular disease (e.g., those with prior myocardial infarction, stroke, or any revascularization procedure) or indicators of high risk, a GLP-1 receptor agonist or SGLT2 inhibitor with proven cardiovascular benefit should be the initial treatment option.[11,14] The incretin mimetics are also listed as very high/high efficacy for glucose lowering to achieve glycemic goals in combination with metformin. These agents are also considered to have very high (semaglutide, tirzepatide), high (dulaglutide, liraglutide), or intermediate (exenatide) efficacy for weight loss in patients needing to achieve weight-based goals.[11]

A variety of clinical trials have been conducted evaluating the incretin mimetics. The incretin mimetics have been evaluated in combination with and in comparison to a variety of antidiabetic therapies. In these studies, the more aggressive treatment regimens improved glycemic parameters to a greater extent than the less-intensive treatment regimens. Overall, the incretin mimetics are effective in improving glycosylated hemoglobin (HbA_{1c}), fasting plasma glucose, post-prandial glucose, and body weight. Efficacy data comparing the incretin mimetics to other antidiabetic agents are not consistent, with the incretin mimetics achieving significantly greater or comparable benefits in glycemic outcomes. However, in general, all incretin-based therapies, including the incretin mimetics, consistently demonstrate a beneficial effect on body weight compared to other antidiabetic agents. A limited number of head-to-head clinical trials have been conducted within the class. Results from these trials do not consistently demonstrate that one incretin mimetic is more effective than another.[18-101] Dulaglutide has been demonstrated to be non-inferior to liraglutide therapy in two clinical trials.[19,42]

Gastrointestinal-related adverse events are common with incretin mimetics.[1-9] There have been postmarketing reports of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, in patients taking these agents.[1-7] There have also been postmarketing reports of altered renal function, including increased serum creatinine, renal impairment, worsened chronic renal failure, and acute renal failure, sometimes requiring hemodialysis or kidney transplantation.[1-7] Patients may develop antibodies to the incretin mimetics consistent with the potentially immunogenic properties of protein and peptide pharmaceuticals.[1-7]

There is insufficient evidence to support that one brand incretin mimetic is safer or more efficacious than another within its given indication. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process. The incretin mimetics that have demonstrated cardiovascular disease benefit should be available for treatment of patients with type 2 diabetes and cardiovascular disease.

Therefore, all brand products 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 incretin mimetic 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 Insulins
AHFS Class 682008
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I. Overview

Diabetes mellitus is a chronic condition which results in hyperglycemia. It is differentiated into four main classes: 1) type 1 diabetes; 2) type 2 diabetes; 3) gestational diabetes; and 4) other types (drug- or chemical-induced, genetic defects in β-cell function or insulin action, and diseases of the exocrine pancreas). Type 2 diabetes is the most prevalent form of the disease in the United States. Inadequate glycemic control may lead to both acute and long-term complications, including microvascular and macrovascular events. There are a variety of oral and injectable antidiabetic agents currently available to treat diabetes. The antidiabetic agents are categorized into 12 different American Hospital Formulary Service (AHFS) classes, which differ with regards to their mechanism of action, efficacy, safety profiles, tolerability, and ease of use.

Insulins stimulate peripheral glucose uptake by skeletal muscle and fat, decrease hepatic glucose production, inhibit lipolysis and proteolysis, and enhance protein synthesis.[1-3] There are two types of insulin preparations currently available: human insulin and insulin analogs. Human insulin is derived from a biosynthetic process and is structurally identical to endogenous insulin. Insulin analogs are structurally different than human insulin. Each insulin analog differs in the addition, deletion, or substitution of amino acids on the B chain. These modifications lead to a faster onset and shorter duration of action (for rapid-acting insulin analogs) or slower absorption and a longer duration of action (for long-acting insulin analogs) than human insulins.[1,2]

The insulin preparations are further categorized based on their duration of action. Rapid- and short-acting insulins are administered as a bolus prior to meals to control postprandial glucose excursions. They may also be administered continuously via an infusion pump. Intermediate- and long-acting insulins are administered once or twice daily. They act as basal insulin to decrease hepatic glucose production and lower fasting plasma glucose concentrations.[1,2]

Insulin therapy is usually administered by subcutaneous injection, which allows for prolonged absorption and less pain compared to intramuscular injection.[1,2] Regular insulin is also formulated as an inhalation. Inhaled insulin powder is formulated in disposable, single-use cartridges, known as Technosphere®, which provide a more efficient inhalation device than what has been used in the past.[3] Regular insulin as used in Afrezza® is rapid-acting. Following pulmonary absorption into systemic circulation, the metabolism and elimination are comparable to regular human insulin.[3] Tresiba® (insulin degludec) is a long-acting human insulin analog which forms multi-hexamers when injected into the subcutaneous tissue resulting in a depot. The protracted time action profile (>42 hours) is predominantly due to delayed absorption into the systemic circulation and to a lesser extent due to binding to circulating albumin.[1-3] All insulin products have at least one formulation with a concentration of 100 units/mL (U-100). Two agents are also formulated with a higher concentration, regular insulin as 500 units/mL (U-500; Humulin® R U-500) and insulin glargine as 300 units/mL (U-300; Toujeo®).[1,2] Toujeo® shows a more flat-line pharmacokinetic profile and prolonged duration of activity versus insulin glargine U-100 (Lantus®).[3]

Fiasp® (insulin aspart injection) is a rapid-acting human insulin analog.[3] This agent can be dosed at the beginning of a meal or within 20 minutes after starting a meal. Fiasp® is a newer formulation of NovoLog® (insulin aspart) in which the addition of niacinamide (vitamin B3) helps to increase the speed of the initial insulin absorption, resulting in an onset of appearance in the blood in approximately 2.5 minutes.[1-3] Basaglar® (insulin glargine) is a long-acting human insulin analog and is the first insulin product approved through an abbreviated approval pathway under the Federal Food, Drug, and Cosmetic Act 505(b)(2), based upon similarity to Lantus® (insulin glargine).[1-4] It is not categorized as a biosimilar having not been approved under the 351 (k) pathway.[4] Admelog® (insulin lispro) is a rapid-acting human insulin analog and is the first short-acting insulin approved as a "follow-on" product (submitted through the agency's 505(b)(2) pathway).[1-3,5] The application for Admelog® relied, in part, on the FDA's finding of safety and effectiveness for Humalog® (insulin lispro injection) to support approval.[5] Xultophy® (insulin degludec/liraglutide) is a combination of insulin degludec, a long-acting human insulin analog, and liraglutide, a glucagon-like peptide 1 (GLP-1) receptor agonist, indicated as an adjunct to diet and exercise to

improve glycemic control in adults with type 2 diabetes mellitus.[1-3] Soliqua® (insulin glargine/lixisenatide) is a combination of insulin glargine, a long-acting human insulin analog, and lixisenatide, a GLP-1 receptor agonist, indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.[1-3]

Lyumjev® (insulin lispro-aabc) is a rapid-acting human insulin analog indicated to improve glycemic control in adults with diabetes mellitus. The profile of action is designed to have a quicker onset of action and shorter duration of action overall compared to Humalog® (insulin lispro).[1-3] Specifically, the prescribing information supports that Lyumjev® (insulin lispro-aabc) can be administered at the start of the meal or within 20 minutes. Conversely, Humalog® (insulin lispro) should be administered within 15 minutes before a meal or immediately after a meal.[3] Myxredlin® (Insulin Human in 0.9% Sodium Chloride Injection). Myxredlin® is the first ready-to-use insulin for IV infusion. Semglee® (insulin glargine-yfgn) is the first interchangeable biosimilar product and is interchangeable with Lantus® (insulin glargine).[1-3] Rezvoglar® (insulin glargine-aglr) is the second interchangeable biosimilar product and is also interchangeable with Lantus® (insulin glargine).[1-3]

The insulins that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Several products are available over-the-counter. This class was last reviewed in November 2021.

Table 1. Insulins Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Rapid-Acting Insulins			
Insulin aspart	injection	Fiasp®, NovoLog®*	insulin aspart, NovoLog®
Insulin glulisine	injection	Apidra®, Apidra Solostar®	none
Insulin lispro	injection	Admelog®, Humalog®*, Lyumjev®	none
Short-Acting Insulins			
Insulin regular, human	inhalation, injection	Afrezza®, Humulin®‡ R, Myxredlin®, Novolin®‡ R	Humulin®‡ R, Novolin®‡ R
Intermediate-Acting Insulins			
NPH, human insulin isophane	injection	Humulin®‡ N, Novolin®‡ N	Humulin®‡ N, Novolin®‡ N
Long-Acting Insulins			
Insulin degludec	injection	Tresiba®*	none
Insulin detemir	injection	Levemir®	Levemir®
Insulin glargine, human recombinant analog	injection	Basaglar®, Lantus®*, Lantus Solostar®*, Rezvoglar®^, Semglee®^*, Toujeo®	Lantus®
Combination Insulins (Intermediate-Acting and Rapid-Acting)			
Insulin aspart protamine and insulin aspart	injection	NovoLog® Mix 70/30*	NovoLog® Mix 70/30
Insulin lispro protamine and insulin lispro	injection	Humalog® Mix 50/50, Humalog® Mix 75/25*	Humalog® Mix
Combination Insulins (Intermediate-Acting and Short-Acting)			
NPH, human insulin isophane and insulin regular, human	injection	Humulin®‡ 70/30, Novolin®‡ 70/30	Humulin®‡ 70/30, Novolin®‡ 70/30
Combination Insulins with Non-Insulins			
Insulin degludec and Liraglutide	injection	Xultophy®	none
Insulin glargine and Lixisenatide	injection	Soliqua®	none

*Authorized generic/unbranded product is available.
‡Product is available over-the-counter.
^Interchangeable biosimilar insulin product.
PDL=Preferred Drug List

II. Evidence-Based Medicine and Current Treatment Guidelines

Current clinical guidelines are summarized in Table 2. Please note that guidelines addressing the treatment of type 1 and 2 diabetes are presented globally, addressing the role of various medication classes.

Table 2. Treatment Guidelines Using the Insulins

Clinical Guideline	Recommendation(s)
American Diabetes Association: **Standards of Care in Diabetes (2023)**[6]	Current criteria for the diagnosis of diabetes • The following are the criteria for a diagnosis of diabetes: glycosylated hemoglobin (HbA_{1c}) ≥6.5%, or a fasting plasma glucose (FPG) ≥126 mg/dL, or a two-hour plasma glucose ≥200 mg/dL during an oral glucose tolerance test or patients with classic symptoms of hyperglycemia, or classic symptoms of hyperglycemia or hyperglycemic crisis (random plasma glucose ≥200 mg/dL). Prevention or delay of type 2 diabetes • Refer adults with overweight/obesity at high risk of type 2 diabetes, as typified by the Diabetes Prevention Program (DPP), to an intensive lifestyle behavior change program to achieve and maintain a weight reduction of at least 7% of initial body weight through healthy reduced-calorie diet and ≥150 minutes/week of moderate-intensity physical activity. • A variety of eating patterns can be considered to prevent diabetes in individuals with prediabetes. • Metformin therapy for prevention of type 2 diabetes should be considered in adults at high risk of type 2 diabetes, as typified by the DPP, especially those aged 25 to 59 years with BMI ≥35 kg/m^2, higher FPG) (e.g., ≥110 mg/dL), and higher A1C (e.g., ≥6.0%), and in individuals with prior gestational diabetes mellitus (GDM). • Long-term use of metformin may be associated with biochemical vitamin B12 deficiency; consider periodic measurement of vitamin B12 levels in metformin-treated individuals, especially in those with anemia or peripheral neuropathy. Glycemic goals in adults • An A1C goal for many nonpregnant adults of <7% (53 mmol/mol) without significant hypoglycemia is appropriate. • If using ambulatory glucose profile (AGP)/glucose management indicator (GMI) to assess glycemia, a parallel goal for many nonpregnant adults is time in range (TIR) of >70% with time below range (TBR) <4% and time <54 mg/dL <1%. For those with frailty or at high risk of hypoglycemia, a target of >50% TIR with <1% TBR is recommended. • On the basis of health care provider judgment and patient preference, achievement of lower A1C levels than the goal of 7% may be acceptable and even beneficial if it can be achieved safely without significant hypoglycemia or other adverse effects of treatment. • Less stringent A1C goals (such as <8% [64 mmol/mol]) may be appropriate for patients with limited life expectancy or where the harms of treatment are greater than the benefits. HCPs should consider deintensification of therapy if appropriate to reduce the risk of hypoglycemia in patients with inappropriate stringent A1C targets. Pharmacologic therapy for type 1 diabetes • Most individuals with type 1 diabetes should be treated with multiple dose insulin injections (three to four injections per day of basal and pre-prandial insulin) or continuous subcutaneous (SC) insulin infusion therapy. • Most patients should use rapid-acting insulin analogs to reduce hypoglycemia risk. • Patients with type 1 diabetes should receive education on how to match prandial insulin doses to carbohydrate intake, premeal blood glucose, and anticipated physical activity. Pharmacologic therapy for type 2 diabetes • Healthy lifestyle behaviors, diabetes self-management education and support, avoidance of clinical inertia, and social determinants of health should be

Clinical Guideline	Recommendation(s)
	considered in the glucose-lowering management of type 2 diabetes. Pharmacologic therapy should be guided by person-centered treatment factors, including comorbidities and treatment goals. • In adults with type 2 diabetes and established/high risk of atherosclerotic cardiovascular disease, heart failure, and/or chronic kidney disease, the treatment regimen should include agents that reduce cardiorenal risk. • Pharmacologic approaches that provide adequate efficacy to achieve and maintain treatment goals should be considered, such as metformin or other agents, including combination therapy. • Weight management is an impactful component of glucose-lowering management in type 2 diabetes. The glucose-lowering treatment regimen should consider approaches that support weight management goals. • Metformin should be continued upon initiation of insulin therapy (unless contraindicated or not tolerated) for ongoing glycemic and metabolic benefits. • Early combination therapy can be considered in some individuals at treatment initiation to extend the time to treatment failure. • The early introduction of insulin should be considered if there is evidence of ongoing catabolism (weight loss), if symptoms of hyperglycemia are present, or when A1C levels (>10% [86 mmol/mol]) or blood glucose levels (≥300 mg/dL [16.7 mmol/L]) are very high. • A person-centered approach should guide the choice of pharmacologic agents. Consider the effects on cardiovascular and renal comorbidities, efficacy, hypoglycemia risk, impact on weight, cost and access, risk for side effects, and individual preferences. • Among individuals with type 2 diabetes who have established atherosclerotic cardiovascular disease or indicators of high cardiovascular risk, established kidney disease, or heart failure, a sodium–glucose cotransporter 2 inhibitor and/or glucagon-like peptide 1 receptor agonist with demonstrated cardiovascular disease benefit is recommended as part of the glucose-lowering regimen and comprehensive cardiovascular risk reduction, independent of A1C and in consideration of person-specific factors. • In adults with type 2 diabetes, a glucagon-like peptide 1 receptor agonist is preferred to insulin when possible. • If insulin is used, combination therapy with a glucagon-like peptide 1 receptor agonist is recommended for greater efficacy, durability of treatment effect, and weight and hypoglycemia benefit. • Recommendation for treatment intensification for individuals not meeting treatment goals should not be delayed. • Medication regimen and medication-taking behavior should be reevaluated at regular intervals (every three to six months) and adjusted as needed to incorporate specific factors that impact choice of treatment. • Clinicians should be aware of the potential for over-basalization with insulin therapy. Clinical signals that may prompt evaluation of over-basalization include basal dose more than ~0.5 units/kg/day, high bedtime–morning or post-preprandial glucose differential, hypoglycemia (aware or unaware), and high glycemic variability. Indication of over-basalization should prompt reevaluation to further individualize therapy.
American Diabetes Association/ European Association for the Study of Diabetes: **Management of Hyperglycemia in Type 2 Diabetes. A**	Consensus recommendations • All people with type 2 diabetes should be offered access to ongoing diabetes self-management education and support programs. • Providers and health care systems should prioritize the delivery of person-centered care. • Optimizing medication adherence should be specifically considered when selecting glucose-lowering medications.

Clinical Guideline	Recommendation(s)
consensus report by the American Diabetes Association and the European Association for the Study of Diabetes (2022)[7]	• Medical nutrition therapy focused on identifying healthy dietary habits that are feasible and sustainable is recommended in support of reaching metabolic and weight goals. • Physical activity improves glycemic control and should be an essential component of type 2 diabetes management. • Adults with type 2 diabetes should engage in physical activity regularly (>150 min/week of moderate- to vigorous-intensity aerobic activity) and be encouraged to reduce sedentary time and break up sitting time with frequent activity breaks. • Aerobic activity should be supplemented with two to three resistance, flexibility, and/or balance training sessions/week. Balance training sessions are particularly encouraged for older individuals or those with limited mobility/poor physical function. • Metabolic surgery should be considered as a treatment option in adults with type 2 diabetes who are appropriate surgical candidates with a BMI ≥40.0 kg/m^2 (BMI ≥37.5 kg/m^2 in people of Asian ancestry) or a BMI of 35.0 to 39.9 kg/m^2 (32.5 to 37.4 kg/m^2 in people of Asian ancestry) who do not achieve durable weight loss and improvement in comorbidities (including hyperglycemia) with nonsurgical methods. • In people with established CVD, a GLP-1 RA with proven benefit should be used to reduce MACE, or an SGLT2i with proven benefit should be used to reduce MACE and HF and improve kidney outcomes. • In people with CKD and an eGFR ≥20 ml/min per 1.73 m^2 and a urinary albumin/creatinine ratio >3.0 mg/mmol (>30 mg/g), an SGLT2i with proven benefit should be initiated to reduce MACE and HF and improve kidney outcomes. Indications and eGFR thresholds may vary by region. If such treatment is not tolerated or is contraindicated, a GLP-1 RA with proven cardiovascular outcome benefit could be considered to reduce MACE and should be continued until kidney replacement therapy is indicated. • In people with HF, SGLT2i should be used because they improve HF and kidney outcomes. • In individuals without established CVD but with multiple cardiovascular risk factors (such as age ≥55 years, obesity, hypertension, smoking, dyslipidemia, or albuminuria), a GLP-1 RA with proven benefit could be used to reduce MACE, or an SGLT2i with proven benefit could be used to reduce MACE and HF and improve kidney outcomes. • In people with HF, CKD, established CVD, or multiple risk factors for CVD, the decision to use a GLP-1 RA or SGLT2i with proven benefit should be independent of background use of metformin. • SGLT2i and GLP-1 RA reduce MACE, which is likely to be independent of baseline HbA1c. In people with HF, CKD, established CVD, or multiple risk factors for CVD, the decision to use a GLP-1 RA or an SGLT2i with proven benefit should be independent of baseline HbA1c. • In general, selection of medications to improve cardiovascular and kidney outcomes should not differ for older people. • In younger people with diabetes (<40 years), consider early combination therapy. • In women with reproductive potential, counseling regarding contraception and taking care to avoid exposure to medications that may adversely affect a fetus are important.
American Association of Clinical Endocrinologists/ American College of Endocrinology:	Antihyperglycemic Pharmacotherapy for Persons with Type 2 Diabetes • Individualized pharmacotherapy for persons with T2D should be prescribed based on evidence for benefit that includes glucose lowering, avoidance of hypoglycemia and weight gain, and reduction of cardio-renal risk.

Clinical Guideline	Recommendation(s)
Clinical Practice Guidelines for Developing a Diabetes Mellitus Comprehensive Care Plan (2022)[8]	• Persons with T2D and their health care professionals should use patient-centered shared decision-making to agree on therapy targets and treatments as well as a regimen for glucose monitoring (i.e., BGM, structured BGM, or CGM). • Glycemic targets include A1C, BGM, and, for those using CGM, achievement of CGM targets such as time in range (TIR), percentage in low and very low range, time above range, and glycemic variability. Nonglycemic targets include avoidance of hypoglycemia, control of BP, lipids, other CVD risk factors, and achieving and maintaining a healthy body weight. • Independent of glycemic control, targets, or treatment, if there is established or high risk for ASCVD, HF, and/or CKD, clinicians should prescribe a GLP-1 RA or an SGLT2i with proven efficacy for the specific condition(s) of the person with T2D being treated. • DM therapy should be individualized based on level of glycemia and the presence of comorbidities, complications, and access. Metformin is often the preferred initial therapy. Other agents may be appropriate as first line or in addition to metformin to reduce BG and/or to address specific comorbidities (such as ASCVD, HF, CKD, obesity, NAFLD), independent of glucose-lowering effects. • For some recently diagnosed individuals with T2D and more severe hyperglycemia (A1C ≥7.5%), unlikely to attain the A1C target with a single agent, early combination pharmacotherapy should be considered, usually to include metformin plus another agent that does not cause hypoglycemia, especially a GLP-1 RA, SGLT2i, or dipeptidyl peptidase 4 (DPP-4) inhibitor. • For newly diagnosed persons with T2D and an entry A1C >9.0% and/or ≥1.5% above target, one should initiate, along with lifestyle modifications, dual- or possibly triple-combination pharmacotherapy usually including metformin. Basal insulin along with noninsulin therapy is recommended if there are significant signs or symptoms of hyperglycemia, especially including catabolism (e.g., weight loss) or a very high A1C >10% (86 mmol/mol) or BG levels (≥300 mg/dL [16.7 mmol/L]). • Clinicians should discuss with persons with T2D the likelihood that most persons with T2D ultimately require a combination of multiple complementary antihyperglycemic agents, in addition to lifestyle interventions, to attain and maintain optimal glycemic control. • The DM care team should assess medication adherence and safety and glycemic control in persons with T2D quarterly or more frequently as needed. Subsequent visits will depend upon the metabolic targets achieved and the stability of metabolic control. • Persons with T2D who start on metformin should continue it unless intolerance or contraindications occur. When intensification of antihyperglycemic treatment is needed, other agents should be added to metformin. • Most persons with T2D who require intensification of antihyperglycemic therapy with a GLP-1 RA or insulin should initially be prescribed a GLP-1 RA. If further intensification is required, one should prescribe a basal insulin or a switch to a fixed-ratio combination of a basal insulin and a GLP-1 RA (insulin glargine U100 + lixisenatide [GlarLixi] or insulin degludec + liraglutide [IdegLira]). • Insulin should be prescribed for persons with T2D when noninsulin antihyperglycemic therapy fails to achieve target glycemic control or when a person has symptomatic hyperglycemia. • Long-acting basal insulin analogs are the recommended initial choice of insulin therapy for persons with T2D. The insulin analogs glargine (U100 or U300), degludec (U100 or U200), or detemir are preferred over intermediate-acting Neutral Protamine Hagedorn (NPH) insulin because analog insulins have demonstrated less hypoglycemia in some studies. Glargine U300 and degludec can be associated with less hypoglycemia than glargine U100 or detemir.

Clinical Guideline	Recommendation(s)
	• Many persons with T2D receiving basal insulin and not at goal A1C can have significantly improved glycemia by the addition of a GLP-1 RA or being switched to a fixed-ratio combination basal insulin–GLP-1 RA (GlarLixi or IdegLira). One of these changes should be considered before adding a meal-time insulin for postprandial glycemic control. • When control of postprandial hyperglycemia is needed and a basal insulin and a GLP-1 RA are already being used, preference should be given to rapid-acting insulins (the analogs lispro, aspart, and glulisine or the rapid-acting inhaled human insulin powder) over regular human insulin. The former have a more consistent and a more rapid onset and offset of action with less risk of hypoglycemia. • Ultra-rapid-acting insulins (faster-acting insulin aspart, lispro aabc, and [human insulin] inhalation powder) may allow a decrease in the time between insulin administration and food intake and reduce the postprandial peak of PG as compared with rapid-acting insulins. The significance of this on long-term complications is unknown. • Basal-bolus insulin regimens or continuous subcutaneous insulin infusion (CSII) (i.e., insulin pump) allow for adjustment of insulin doses according to carbohydrate intake and activity levels and are recommended for intensive insulin therapy in persons with T2D. • Premixed insulin formulations (fixed combinations of shorter- and longer-acting components) of human or analog insulin may be considered for persons with T2D who have consistent dietary and exercise patterns and in whom adherence to more intensive insulin regimens is problematic. However, these preparations have reduced dosage flexibility and may increase the risk of hypoglycemia compared with basal insulin or basal-bolus regimens. • In persons with T2D who are treated with basal-bolus insulin therapy, adding a GLP-1 RA, or switching to a fixed-ratio combination of a GLP-1 RA and a basal insulin, or adding an SGLT2i or pramlintide (less commonly used) may be able to reduce postprandial hyperglycemia, A1C, and weight. GLP-1 RAs may also allow reduction or discontinuation of bolus insulin in some individuals. <u>How should insulin therapy be used for management of persons with type 1 diabetes?</u> • Insulin must be used to treat all persons with T1D. • Physiologic insulin replacement regimens, which provide both basal and prandial (meal-related or bolus) insulin, are recommended for most persons with T1D. • Achievement of glucose targets using either MDI of insulin or CSII, is needed to prevent development of life-threatening crises, such as acute hyperglycemic crises (DKA and hyperglycemic hyperosmolar state) and catabolic state. • A multi-component self-management DM education program is recommended for persons with T1D. Ideally, this is provided by a professional with expertise (i.e., certified diabetes care and education specialist) in the topics of healthy lifestyle, insulin technique including prandial insulin dosing guided by carbohydrate counting and diet adjustments for special situations, such as physical activity and prolonged fasting. Instruction is also needed in how to deal with sick days and prevention of DKA and hypoglycemia, and other relevant issues. Due to changes in DM self-management practices and each individual's medical history, personal and cultural background, and educational needs, specific education topics may need to be repeated at regular intervals. • The ideal insulin regimen should be personalized to an individual's needs and glycemic targets, attempting to better emulate physiological insulin replacement to maintain near normoglycemia, to prevent the development and progression of DM complications, while minimizing hypoglycemia and providing flexibility for specific daily life situations/scenarios such as: exercise, sleep, acute illness, psychological stress, etc.

Clinical Guideline	Recommendation(s)

	• Insulin regimens usually should involve the use of insulin analogs for most persons with T1D and include the following approaches:
	  ○ MDI, which usually involve 1 to 2 subcutaneous injections daily of basal insulin to suppress ketogenesis and gluconeogenesis and to control glycemia between meals and overnight, and subcutaneous injections of prandial insulin or use of inhaled insulin before each meal to control meal-related glycemic excursions. CGM is the preferred method of glucose monitoring for all individuals with T1D.
	  ○ Insulin pump therapy (CSII) provides constant/continuous infusion of fast-acting insulin driven by mechanical force and delivered via a cannula inserted under the skin. CSII can improve (or enhance) glycemic control and should be an option for insulin delivery for appropriate persons with DM. Ideally, these individuals should also use CGM as stated in R13.6.a.
	  ○ Automated insulin delivery systems (AIDs), which include an insulin pump, an integrated CGM, and computer software algorithm, aim to better emulate physiological insulin replacement and achieve glycemic targets. This technology is recommended for many persons with T1D since its use has been shown to increase TIR while often reducing hypoglycemia or at least without causing increased hypoglycemia.
	  ○ Open-loop (use of a pump and sensor which do not communicate) and sensor-augmented pump (SAP) systems: (CGM communicates with pump facilitating needed adjustments to basal rate; temporary interruption of insulin delivery when glucose levels are low or forecast to be low within 30 min). Insulin pump with a CGM or an SAP is recommended to manage persons with DM treated with intensive insulin management who prefer not to use AIDs or have no access to them.
	
	How should diabetes mellitus in pregnancy be managed?
	• For women with GDM, the following treatment goals are recommended: preprandial glucose concentration ≤95 mg/dL and either a 1-h post-meal glucose ≤140 mg/dL or a 2-h post-meal glucose ≤120 mg/dL to decrease adverse fetal outcomes.
	• All women with preexisting DM (T1D, T2D, or previous GDM) need access to preconception care and counseling to ensure adequate nutrition, healthy weight, and glucose control before conception, during pregnancy, and in the postpartum period.
	• Rapid-acting insulin analogs (insulin-lispro, insulin-aspart) should be used to treat postprandial hyperglycemia in pregnant women.
	• Options for basal insulin include long-acting insulin (e.g., NPH, detemir, or glargine) or rapid-acting insulin via a CSII. Regular insulin, although not recommended as first-line therapy, is acceptable to use in managing pregnant women with DM when rapid-acting insulin analogs are not available.
	• Insulin is the preferred therapeutic choice for pregnant women with GDM or T2D, but metformin has been given a category B for pregnancy with accumulating clinical evidence of metformin's safety during the first trimester and beyond. Metformin has been shown to improve pregnancy and fetal outcomes except for increased rates of infants with SGA and later onset of obesity. The prescriber should discuss the potential risks and benefits of oral agent therapy during pregnancy as well as the need for longer-term outcome studies.

American Association of Clinical Endocrinologists/ American College of Endocrinology: **Consensus Statement**	Principles underlying the algorithm • Lifestyle modification underlies all therapy. • Maintain or achieve optimal weight. • Choice of antihyperglycemic therapy reflects glycemic targets, atherosclerotic cardiovascular disease (ASCVD), congestive heart failure (CHF), chronic kidney

Clinical Guideline	Recommendation(s)
on the Comprehensive Type 2 Diabetes Management Algorithm (2023)[9]	disease (CKD), overweight/obesity, and nonalcoholic fatty liver disease (NAFLD). • Choice of therapy includes ease of use and access. • Optimal hemoglobin A1c (A1C) is ≤6.5% or as close to normal as is safe and achievable for most patients. • Individualize all glycemic targets (A1C, glucose management indicator [GMI], time in range [TIR], fasting blood glucose [FBG], and PPG). • Get to goal as soon as possible (adjust ≤3 months). • Avoid hypoglycemia. Hypoglycemia, defined as blood glucose (BG) <70 mg/dL, is associated with an increased risk for adverse outcomes including mortality. • CGM is highly recommended to assist persons with diabetes in reaching goals safely. • Comorbidities must be managed for comprehensive care. <u>Algorithm summative information</u> • The algorithm is intended as a more concise document than the guideline, providing easily accessible, visual guidance for decision-making in the clinic setting. • In this 2023 algorithm, there continues to be an emphasis on lifestyle modification and treatment of overweight/obesity as key pillars of the management of prediabetes and DM. • The importance of appropriate management of the atherosclerotic risk factors of dyslipidemia and hypertension is highlighted. • One notable new theme is an obvious emphasis on a complication-centric approach, beyond glucose levels, to frame decisions regarding first-line pharmacologic choices for the treatment of persons with diabetes. • The algorithm is divided into discrete graphic sections that outline the principles for management of T2D and guide management of adiposity-based chronic disease (ABCD), prediabetes, and atherosclerotic risk factors of dyslipidemia and hypertension. In addition, the algorithms for antihyperglycemic agents include both complication-centric and glucose-centric approaches, and there is direction for insulin initiation and titration. Tables summarizing the benefits and risks of antihyperglycemic medications (updated) and weight-loss pharmacotherapy (new) are provided.

American Academy of Pediatrics: **Management of Newly Diagnosed Type 2 Diabetes Mellitus (T2DM) in Children and Adolescents (2013)[10]**	• Clinicians must ensure that insulin therapy is initiated for children and adolescents with T2DM who are ketotic or in diabetic ketoacidosis and in whom the distinction between types 1 and 2 diabetes mellitus is unclear and, in usual cases, should initiate insulin therapy for patients.
	  ○ Who have random venous or plasma blood glucose (BG) concentrations ≥250 mg/dL.
	  ○ Whose HbA_{1c} is >9%.
	• In all other instances, clinicians should initiate a lifestyle modification program, including nutrition and physical activity, and start metformin as first-line therapy for children and adolescents at the time of diagnosis of T2DM.
	• Monitoring of HbA_{1c} concentrations is recommended every three months and intensifying treatment is recommended if treatment goals for finger-stick BG and HbA_{1c} concentrations are not being met.
	• Advise patients to monitor finger-stick BG concentrations in patients who:
	  ○ Are taking insulin or other medications with a risk of hypoglycemia; or
	  ○ Are initiating or changing their diabetes treatment regimen; or
	  ○ Have not met treatment goals; or
	  ○ Have intercurrent illnesses.
	• Incorporate the Academy of Nutrition and Dietetics' *Pediatric Weight Management Evidence-Based Nutrition Practice Guidelines* in dietary or nutrition

Clinical Guideline	Recommendation(s)
	counseling of patients with T2DM at the time of diagnosis and as part of ongoing management. • Encourage children and adolescents with T2DM to engage in moderate-to-vigorous exercise for at least 60 minutes daily and to limit nonacademic "screen time" to less than two hours a day.
American Diabetes Association: **Type 1 Diabetes in Children and Adolescents: A Position Statement by the American Diabetes Association (2018)[11]**	<u>Blood Glucose Management: Monitoring and Treatment</u> • Most children with type 1 diabetes should be treated with intensive insulin regimens via either multiple daily injections of prandial insulin and basal insulin or continuous subcutaneous insulin infusion. • An HbA_{1c} target of <7.5% should be considered in most children and adolescents but should be individualized based on the needs and situation of the patient and family. • Children and adolescents with type 1 diabetes should have blood glucose levels monitored up to six to ten times/day including premeal, pre-bedtime, and as needed for safety (e.g., exercise, driving, illness, or the presence of symptoms of hypoglycemia). • Continuous blood glucose monitoring should be considered in all children and adolescents whether using insulin injections or an insulin pump. • In pediatric patients with type 1 diabetes automated insulin delivery systems can improve glycemic control and reduce hypoglycemia. <u>Lifestyle Management</u> • Individualized medical nutrition therapy is recommended for children and adolescents with type 1 diabetes. • Monitoring carbohydrate intake, whether by carbohydrate counting or experience-based estimation, is key to achieving optimal glycemic control. • Exercise if recommended for all children and adolescents with type 1 diabetes. The suggested goal is 60 minutes of moderate to vigorous aerobic activity daily with muscle-strengthening and bone-strengthening activities three times a week. • Children and adolescents with type 1 diabetes should be educated about prevention and management of potential hypoglycemia during and after exercise. • Strategies to prevent hypoglycemia during exercise, after exercise, and overnight following exercise include reducing prandial insulin dosing for the meal/snack preceding exercise, increasing carbohydrate intake, eating bedtime snacks, using continuous blood glucose monitoring, and/or reducing basal insulin doses. <u>Behavioral Aspects of Self-Management</u> • Children and adolescents with diabetes should be assessed for psychosocial issues and family stresses that could impact diabetes management at diagnosis and routine follow-up. • Consider including children in consent processes as early as cognitive development indicates understanding of health consequences of behavior. • Offer adolescents time by themselves with their care provider(s) starting at age 12 years, or when developmentally appropriate. <u>Complications and Comorbidities</u> • Diabetic Ketoacidosis o All individuals with type 1 diabetes should have access to an uninterrupted supply of insulin. Lack of access and insulin omissions are major causes of diabetic ketoacidosis. o Patients with type 1 diabetes should have continuous access to medical support for sick-day management. • Hypoglycemia o The recommended treatment of hypoglycemia (blood glucose <70 mg/dL) in conscious patients is 15 g of glucose, although any form of carbohydrate can

Clinical Guideline	Recommendation(s)
	be used. If hypoglycemia continues after 15 minutes, treatment should be repeated. Once blood glucose has returned to normal patients should consider consuming a meal/snack and/or reduce insulin. o All individuals with type 1 diabetes should be prescribed glucagon and families/caregivers should be educated on administration. o Treatment regimens should be reevaluated in those with hypoglycemia unawareness or one or more episodes of severe hypoglycemia. • Diabetic Kidney Disease o Annual screening for albuminuria with a random spot urine sample for albumin-to-creatinine ratio should be considered at puberty or at age >10 years, whichever is earlier, once the child has had diabetes for 5 years. o An angiotensin-converting-enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB), titrated to normalization of albumin excretion, may be considered when elevated urinary albumin-to-creatinine ratio is documented. • Retinopathy o An initial dilated and comprehensive eye examination is recommended at age 10 years or after puberty has started, whichever is earlier, once the patient has had diabetes for three to five years. o Annual routine follow-up is recommended but may be given every two years based on the advice of an eye care professional. • Neuropathy o Consider an annual comprehensive foot exam for adolescents at the start of puberty or at age 10 years, whichever is earlier, once the patient has had type 1 diabetes for 5 years. • Hypertension o Children and adolescents with type 1 diabetes should have blood pressure monitored at each visit. Elevated blood pressure should be confirmed on three separate days. o Initial treatment of high-normal blood pressure should include dietary modification and increased exercise. Pharmacologic treatment should be considered if blood pressure is not controlled after three to six months. o In patients with conformed hypertension pharmacologic treatment should be added to lifestyle modification at diagnosis. o ACE inhibitors and ARBs should be considered for initial treatment. • Dyslipidemia o A fasting lipid profile should be taken in children ≥10 years of age or older after the diagnosis of diabetes. Obtain a fasting lipid profile in children 10 years of age or older as soon as convenient after the diagnosis of diabetes o If lipids are abnormal, initial therapy should consist of optimizing glucose control and medical nutrition therapy using a Step 2 American Heart Association diet that restricts saturated fat to 7% of total calories and dietary cholesterol to 200 mg/day. o If lipids remain abnormal after six months of lifestyle intervention, consider adding a statin in children at least 10 years of age.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the insulins 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 Insulins[1-3]

Indication	Rapid-Acting Insulins			Short-Acting Insulins	Intermediate-Acting Insulins
	Insulin Aspart	Insulin Glulisine	Insulin Lispro	Insulin Regular, Human	NPH, Human Insulin Isophane
Adjunct to diet and exercise to improve glycemic control in adults and children with diabetes					
Improve glycemic control in adult patients with diabetes mellitus				✔ *	
Improve glycemic control in adults and children with diabetes mellitus	✔	✔	✔	✔	✔
Improve glycemic control in adults and pediatric patients 3 years and older with type 1 diabetes mellitus and adults with type 2 diabetes mellitus			✔ (Admelog®)		
Treatment of diabetic patients with marked insulin resistance (daily requirements more than 200 units), since a large dose may be administered subcutaneously in a reasonable volume				✔ †	

* Afrezza®. Regular insulin as used in Afrezza® is rapid-acting.
† Humulin® R (U 500)

Table 4. FDA-Approved Indications for the Insulins (Continued)[1-3]

Indication	Long-Acting Insulins			Combination Insulins (Intermediate-Acting and Rapid-Acting)		Combination Insulins (Intermediate-Acting and Short-Acting)	Combination Insulins with Non-Insulins	
	Insulin Degludec	Insulin Detemir	Insulin Glargine, Human Recombinant Analog	Insulin Aspart Protamine/ Insulin Aspart	Insulin Lispro Protamine/ Insulin Lispro	NPH, Human Insulin Isophane/ Insulin Regular, Human	Insulin Degludec/ Liraglutide	Insulin Glargine/ Lixisenatide
Improve glycemic control in adults and children with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus			✔ (Basaglar®,)					
Improve glycemic control in adult patients with diabetes mellitus				✔		✔ (Humulin® 70/30)		

Indication	Long-Acting Insulins			Combination Insulins (Intermediate-Acting and Rapid-Acting)		Combination Insulins (Intermediate-Acting and Short-Acting)	Combination Insulins with Non-Insulins	
	Insulin Degludec	Insulin Detemir	Insulin Glargine, Human Recombinant Analog	Insulin Aspart Protamine/ Insulin Aspart	Insulin Lispro Protamine/ Insulin Lispro	NPH, Human Insulin Isophane/ Insulin Regular, Human	Insulin Degludec/ Liraglutide	Insulin Glargine/ Lixisenatide
Improve glycemic control in adults and children with diabetes mellitus	✔	✔	✔ (Lantus®, Rezvoglar®, Semglee®, Toujeo®)			✔ (Novolin® 70/30)		
Treatment of patients with diabetes for the control of hyperglycemia					✔			
Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.							✔	✔

IV. Pharmacokinetics

The pharmacokinetic parameters of the insulins are listed in Table 5. For Xultophy® (insulin degludec/liraglutide) and Soliqua® (insulin glargine/lixisenatide), the pharmacokinetics of the components were not affected in a clinically relevant manner when administered as the combination products.[1-3]

Table 5. Pharmacokinetic Parameters of the Insulins[1,2]

Generic Name(s)	Onset (hours)	Peak (hours)	Duration (hours)	Half-Life (hours)	Mixing of Insulins
Rapid-Acting Insulins					
Insulin aspart	0.25	1 to 3	3 to 5	1.35	NPH
Insulin glulisine	0.2 to 0.5	Not reported	5.3	0.7	NPH
Insulin lispro	Not reported	0.5 to 1.5	3 to 4	0.43 to 0.87	May be mixed with longer-acting insulin
Short-Acting Insulins					
Insulin regular, human	0.5 to 2.5 Inh: 0.2	2 to 15 Inh: 35 to 55	8 to 22 Inh: 90 to 270	1.4 to 3.3 Inh: 120 to 206	May be mixed with longer-acting insulin
Intermediate-Acting Insulins					
NPH, human insulin isophane	0.5 to 1.5	2 to 12	24	Not reported	Insulin regular, human
Long-Acting Insulins					
Insulin degludec	1	9	Not reported	25	Insulin aspart
Insulin detemir	3 to 4	6 to 8	5.7 to 23.2	5 to 7	None
Insulin glargine, human recombinant analog	1.1	5	10.8 to 24	Not reported	None
Combination Insulins (Intermediate-Acting and Rapid-Acting)					
Insulin aspart protamine and insulin aspart	Not reported	Not reported	Not reported	Not reported	None
Insulin lispro protamine and insulin lispro	Not reported	Not reported	Not reported	Not reported	None
Combination Insulins (Intermediate-Acting and Short-Acting)					
NPH, human insulin isophane and insulin regular, human	Not reported	Not reported	Not reported	Not reported	None

Inh=inhaled human insulin

V. Drug Interactions

Major drug interactions with the insulins are listed in Table 6. There are no significant drug interactions reported with the incretin mimetics.[1-3] However, these agents slow gastric emptying and thereby have the potential to impact the absorption of concomitantly administered oral medications. Caution should be exercised when oral medications are concomitantly administered with the incretin mimetics.[1-3]

Table 6. Major Drug Interactions with the Insulins[1-3]

Drugs That May Increase the Risk of Hypoglycemia	
Drugs	Antidiabetic agents, ACE inhibitors, angiotensin II receptor blocking agents, disopyramide, fibrates, fluoxetine, monoamine oxidase inhibitors, pentoxifylline, pramlintide, propoxyphene, salicylates, somatostatin analogs (e.g., octreotide), and sulfonamide antibiotics.
Intervention	Dose reductions and increased frequency of glucose monitoring may be required when insulin is co-administered with these drugs.
Drugs That May Decrease the Blood Glucose Lowering Effect of Insulin	

Drugs	Atypical antipsychotics (e.g., olanzapine and clozapine), corticosteroids, danazol, diuretics, estrogens, glucagon, isoniazid, niacin, oral contraceptives, phenothiazines, progestogens (e.g., in oral contraceptives), protease inhibitors, somatropin, sympathomimetic agents (e.g., albuterol, epinephrine, terbutaline), and thyroid hormones.
Intervention	Dose increases and increased frequency of glucose monitoring may be required when insulin is co-administered with these drugs.
Drugs That May Increase or Decrease the Blood Glucose Lowering Effect of Insulin	
Drugs	Alcohol, beta-blockers, clonidine, and lithium salts. Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia.
Intervention	Dose adjustment and increased frequency of glucose monitoring may be required when insulin is co-administered with these drugs.
Drugs That May Blunt Signs and Symptoms of Hypoglycemia	
Drugs	Beta-blockers, clonidine, guanethidine, and reserpine.
Intervention	Increased frequency of glucose monitoring may be required when insulin is coadministered with these drugs.

VI. Adverse Drug Events

Adverse events with the insulin products are rare and are similar among the various products.[1-3]

Hypoglycemia is the most common adverse event reported with insulin therapy. Because of the differences in onset and duration of action, the timing of hypoglycemia can vary between insulin formulations. Hypoglycemia risk may be increased when patients receive excessive doses of insulin, reduce their caloric intake, increase physical activity, during illnesses, or when receiving medications that increase the hypoglycemic effects of insulin.[1-3]

Redness, swelling, and itching at the injection site may result if administration is not done properly, if the skin is sensitive to cleansing solution, or if the patient is allergic to insulin or components of the insulin formulation.[1-3]

Generalized insulin allergies are rare but may present as a skin rash over the body, shortness of breath, fast pulse, sweating, a drop in blood pressure, bronchospasm, shock, anaphylaxis, or angioedema.[1-3]

Weight gain may occur with some insulin therapies. Weight gain has been attributed to the anabolic effects of insulin and the decrease in glycosuria.[1-3]

The Afrezza® labeling includes additional warnings due to the inhalation delivery method, including cough, throat pain/irritation, and pulmonary function decline. The boxed warning for Afrezza® is listed below.[1-3]

For Xultophy® (insulin degludec/liraglutide) and Soliqua® (insulin glargine/lixisenatide), the adverse events of the components are applicable when administered as the combination products.[1-3]

Table 7. Boxed Warning for Afrezza®[2]

WARNING
WARNING: RISK OF ACUTE BRONCHOSPASM IN PATIENTS WITH CHRONIC LUNG DISEASE • Acute bronchospasm has been observed in patients with asthma and COPD using Afrezza®. • Afrezza® is contraindicated in patients with chronic lung disease such as asthma or COPD. • Before initiating Afrezza®, perform a detailed medical history, physical examination, and spirometry (FEV_1) to identify potential lung disease in all patients.

Table 8. Boxed Warning for Xultophy®[2]

WARNING
WARNING: RISK OF THYROID C-CELL TUMORS • Liraglutide, one of the components of Xultophy, causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures in both genders of rats and mice. It is unknown

WARNING

whether Xultophy causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as the human relevance of liraglutide-induced rodent thyroid C-cell tumors has not been determined.

- Xultophy is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Counsel patients regarding the potential risk for MTC with the use of Xultophy and inform them of symptoms of thyroid tumors (e.g., a mass in the neck, dysphagia, dyspnea, persistent hoarseness). Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with Xultophy.

VII. Dosing and Administration

The usual dosing regimens for the insulins are listed in Table 9. The dose of insulin is dependent upon the patient's glycemic response to food intake and exercise. Dose frequency and timing is dependent upon blood glucose levels, food consumption, time and level of exercise, as well as the insulin formulation used. Thus, an insulin regimen must be individualized to suit the specific needs and treatment goals of the patient.

Table 9. Usual Dosing Regimens for the Insulins[1-3]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Rapid-Acting Insulins			
Insulin aspart	Diabetes: Dosage must be individualized. May be administered via SC injection, CSII by external pump, and intravenously. SC injection: inject immediately (within 5 to 10 minutes) before a meal SC injection (Fiasp®): inject at the start of a meal or within 20 minutes after starting a meal CSII: approximately 50% of the total dose is usually given as meal-related boluses and the remainder is given as a basal infusion. Pre-meal boluses of should be infused immediately (within 5 to 10 minutes) before a meal IV: infuse at a concentration of 0.05 to 1.0 U/mL	Insulin aspart has not been studied in pediatric patients younger than 2 years of age or in pediatric patients with type 2 diabetes. Type 1 diabetes: Dosage must be individualized. May be administered via SC injection and as CSII by external pump. SC injection: inject immediately (within 5 to 10 minutes) before a meal SC injection (Fiasp®): inject at the start of a meal or within 20 minutes after starting a meal CSII: approximately 50% of the total dose is usually given as meal-related boluses and the remainder is given as a basal infusion. Pre-meal boluses of should be infused immediately (within 5 to 10 minutes) before a meal	Cartridge: 100 U/mL Pen: 100 U/mL Vial: 100 U/mL
Insulin glulisine	Diabetes: Dosage must be individualized. May be administered via SC injection, CSII by external pump, and intravenously.	Insulin glulisine has not been studied in pediatric patients with type 1 diabetes younger than 4 years of age and in pediatric patients with type 2 diabetes. Type 1 diabetes:	Pen: 100 U/mL Vial: 100 U/mL

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	SC injection: inject 15 minutes before a meal or within 20 minutes of starting a meal CSII: dosage must be individualized IV: infuse at a concentration of 0.05 to 1.0 U/mL	Dosage must be individualized. Approved for use in children for SC injections and for CSII by external pump, and intravenously SC injection: 0.5 to 1.0 unit/kg/day administered 15 minutes before a meal or within 20 minutes of starting a meal CSII: dosage must be individualized IV: infuse at a concentration of 0.5 to 1.0 unit/mL	
Insulin lispro	Diabetes: Dosage must be individualized. May be administered via SC injection and CSII by external pump. SC injection, CSII by external pump: 0.5 to 1 unit/kg/day; inject within 15 minutes before or immediately after a meal SC injection (Lyumjev®): inject at the start of a meal or within 20 minutes after starting a meal	Insulin lispro has not been studied in pediatric patients with type 1 diabetes younger than 3 years of age and in pediatric patients with type 2 diabetes. Diabetes: Dosage must be individualized. May be administered via SC injection and CSII by external pump. SC injection, CSII by external pump: 0.5 to 1 unit/kg/day; inject within 15 minutes before or immediately after a meal	Cartridge: 100 U/mL Pen: 100 U/mL Vial: 100 U/mL
Short-Acting Insulins			
Insulin regular, human	Diabetes: Dosage must be individualized. May be administered via SC injection, via inhalation, and intravenously. Inhalation: Initial (insulin-naïve), 4 units with each meal; dose must be individualized based on response or conversion from other formulations; for doses greater than 8 units, multiple cartridges will be needed	Diabetes: Dosage must be individualized. May be administered via SC injection, CSII by external pump, and intravenously.	Inhalation powder (Afrezza®): 4 units/cartridge 8 units/cartridge 12 units/cartridge Intravenous: 1 U/mL Pen: 100 U/mL 500 U/mL Vial: 100 U/mL 500 U/mL
Intermediate-Acting Insulins			
NPH, human insulin isophane	Diabetes:	Diabetes:	Pen: 300 U/3 mL

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Dosage must be individualized. May be administered via SC injection. SC injection: 0.5 to 1 units/kg/day; administer in 2 divided daily doses and within 60 minutes of a meal	Dosage must be individualized. May be administered via SC injection. SC injection: 0.5 to 1 units/kg/day; administer in 2 divided daily doses and within 60 minutes of a meal	Vial: 100 U/mL
Long-Acting Insulins			
Insulin degludec	Diabetes: Dosage must be individualized. May be administered via SC injection. SC injection (type 1 diabetes): administer QD SC injection (type 2 diabetes): 10 units once daily	Insulin degludec has not been studied in pediatric patients younger than 1 year of age. Diabetes: Dosage must be individualized. May be administered via SC injection. SC injection: administer QD	Pen: 300 U/3 mL 600 U/3 mL Vial: 100 U/mL
Insulin detemir	Diabetes: Dosage must be individualized. May be administered via SC injection. SC injection (type 1 diabetes): administer QD or BID SC injection (type 2 diabetes): 10 units once daily in the evening or divided into a twice daily regimen	Insulin detemir has not been studied in pediatric patients younger than 2 years of age with type 1 diabetes and pediatric patients with type 2 diabetes. Type 1 diabetes: Dosage must be individualized. May be administered via SC injection. SC injection: administer QD or BID	Pen: 300 U/3 mL Vial: 100 U/mL
Insulin glargine, human recombinant analog	Diabetes: Dosage must be individualized. May be administered via SC injection. SC injection (Lantus®, Basaglar®, Semglee®): administer QD at the same time every day; maintenance, 2 to 100 units/day For patients controlled on Lantus®, expect a higher daily dose of Toujeo®. SC injection (Toujeo®): administer QD at the same time every day; maintenance, 1 to 80 units/day	Insulin glargine, human recombinant analog has not been studied in pediatric patients younger than 6 years of age with type 1 diabetes and pediatric patients with type 2 diabetes. Type 1 diabetes: Dosage must be individualized. May be administered via SC injection. SC injection: administer QD at the same time every day; maintenance, 2 to 100 units/day	Pen: 300 U/3 mL 450 U/1.5 mL 900 U/3 mL Vial: 100 U/mL
Combination Insulins (Intermediate-Acting and Rapid-Acting)			

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Insulin aspart protamine and insulin aspart	Diabetes: Dosage must be individualized. May be administered via SC injection. SC injection: fixed ratio insulins are typically dosed on a BID basis (i.e., before breakfast and supper) with each dose intended to cover two meals or a meal and snack. May be injected within 15 minutes of meal initiation.	Safety and efficacy have not been established in pediatric patients.	Pen: 100 U (70-30)/mL Vial: 100 U (70-30)/mL
Insulin lispro protamine and insulin lispro	Diabetes Mellitus: Dosage must be individualized. May be administered via SC injection. May be injected within 15 minutes of meal initiation.	Safety and efficacy have not been established in pediatric patients.	Pen: 100 U (50-50)/mL 100 U (75-25)/mL Vial: 100 U (50-50)/mL 100 U (75-25)/mL
Combination Insulins (Intermediate-Acting and Short-Acting)			
NPH, human insulin isophane and insulin regular, human	Diabetes: Dosage must be individualized. May be administered via SC injection.	Diabetes: (Novolin only) Dosage must be individualized. May be administered via SC injection.	Pen: 100 U (70-30)/mL Vial: 100 U (70-30)/mL
Combination Insulins with Non-Insulins			
Insulin degludec and Liraglutide	Diabetes: Dosage must be individualized. Administer via SC injection QD at the same time each day. In patients naïve to basal insulin or a GLP-1 receptor agonist, the recommended starting dose is 10 units. In patients currently on basal insulin or a GLP-1 receptor agonist, discontinue therapy with basal insulin or liraglutide prior to initiation; the recommended starting dose is 16 units.	Safety and efficacy have not been established in pediatric patients.	Pen: 100 unit-3.6 mg/mL
Insulin glargine and Lixisenatide	Diabetes: Dosage must be individualized. Administer via SC injection QD within the hour prior to the first meal of the day. In patients naïve to basal insulin or a GLP-1 receptor agonist, the recommended starting dose is 15 units.	Safety and efficacy have not been established in pediatric patients.	Pen: 100 unit-33 µg/mL

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	In patients currently on 30 to 60 units of basal insulin daily with or without a GLP-1 agonist, discontinue therapy with basal insulin or GLP-1 agonist prior to initiation; the recommended starting dose is 30 units.		

BID=twice daily, CSII=Continuous Subcutaneous Insulin Infusion, IV=intravenous, QD=once daily, SC=subcutaneous

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the insulins are summarized in Table 10.

Table 10. Comparative Clinical Trials with the Insulins

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Rapid-Acting and Short-Acting Insulin: Type 1 Diabetes Mellitus				
Home et al.[12] (2006) Insulin aspart before meals and NPH insulin QD or BID vs regular insulin (REG) before meals and NPH insulin QD or BID Insulin doses were adjusted to achieve target FPG and bedtime glucose 5.0 to 8.0 mmol/L and PPG <10.0 mmol/L.	ES, MC, MN, OL, PG, RCT Patients ≥18 years of age with type 1 diabetes for at least 2 years on insulin for at least 1 year before inclusion, HbA_{1c} ≤11.0%, BMI ≤35 kg/m^2	N=753 36 months	Primary: HbA_{1c}, hypoglycemia, adverse events Secondary: Not reported	Primary: At the end of the original six month study, HbA_{1c} decreased in the insulin aspart group, with a statistically significant difference of -0.12 (95% CI, -0.22 to -0.03; P<0.02). At 30 months during the extension period, the difference of -0.16 in HbA_{1c} was maintained (95% CI, -0.32 to -0.01; P<0.035). At 30 months, mean HbA_{1c} was significantly lower in the insulin aspart group compared to the REG group after adjustment for the rate of hypoglycemic episodes and baseline HbA_{1c} (P<0.001). The RR estimate for major hypoglycemia was similar in both treatment groups at 36 months (RR, 1.0; 95% CI, 0.72 to 1.39; P value not significant). The proportion of patients reporting major hypoglycemia decreased from 16% in the first six months to 3% in the last six months in the insulin aspart group. The frequency of patients reporting major hypoglycemia also decreased in the REG group from 17 to 2%. There were no significant differences between groups in regards to major nocturnal hypoglycemia (RR, 0.89; 95% CI, 0.64 to 1.24; P value not significant). The proportion of patients experiencing adverse events during the treatment period was similar in both treatment groups (P value not reported). Secondary: Not reported
Raskin et al.[13] (2000) Insulin aspart before meals and NPH insulin QD to BID	MC, OL, RCT Type 1 diabetes patients with an HbA_{1c} ≤11.0%, baseline HbA_{1c} 7.9% in the insulin	N=882 6 months (with 6 month extension period)	Primary: Effect on eight-point blood glucose measurements and HbA_{1c} at six and 12 months	Primary: At six and 12 months, mean PPG (90 minutes postmeal) was significantly lower with insulin aspart compared to REG (P<0.05). At six months, mean pre-prandial lunch and dinner blood glucose levels were significantly lower with insulin aspart when compared to REG (P<0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs regular insulin before meals and NPH insulin QD to BID Doses of insulin were titrated to achieve FPG of 90 to 144 mg/dL, PPG ≤180 mg/dL and 2:00 AM blood glucose of 90 to 144 mg/dL.	aspart group and 7.95% in the REG group; patients were excluded if they had impaired hepatic, renal, or cardiac function; other exclusions included recurrent hypoglycemia, proliferative retinopathy, or total daily insulin requirement ≥1.4 units/kg		Secondary: Not reported	At 12 months, only pre-prandial dinner blood glucose levels were significantly lower with insulin aspart (P<0.05). At six months, HbA_{1c} was significantly lower with insulin aspart (7.78%) when compared to REG (7.93%; P=0.005). At 12 months, HbA_{1c} was significantly lower with insulin aspart (7.78%) when compared to REG (7.91%; P=0.005). Mean NPH dose increased significantly with insulin aspart compared to REG (0.314 vs 0.296 U/kg; P=0.011). Similar rates of hypoglycemia were observed in both treatment groups. Secondary: Not reported
Mathiesen et al.[14] (2007) Insulin aspart before meals and NPH insulin QD to QID vs regular insulin before meals and NPH insulin QD to QID Doses were titrated to achieve target goals FPG 4.1 to 6.1 mmol/L, PPG<7.5 mmol/L, and HbA_{1c} <6.5%.	MC, OL, PG, RCT Patients ≥18 years of age with insulin-treated type 1 diabetes for ≥12 months, either pregnant with a singleton pregnancy (gestational age ≤10 weeks) or planning to become pregnant, HbA_{1c} ≤8.0%	N=412 28 months	Primary: Major hypoglycemia during pregnancy Secondary: HbA_{1c}, self-measured eight-point plasma glucose profile, maternal adverse events, obstetric complications, diabetes complications	Primary: The rates of major maternal hypoglycemia were lower in patients taking insulin aspart than patients taking REG. There was a 28% risk reduction for major hypoglycemia (RR, 0.720; 95% CI, 0.36 to 1.46; P value not reported) and a 52% risk reduction for major nocturnal hypoglycemia (RR, 0.48; 95% CI, 0.20 to 1.14; P value not reported) for patients taking insulin aspart than patients taking REG. However, this did not reach statistical significance. Secondary: Treatment with insulin aspart was as effective as treatment with REG in regards to HbA_{1c} (mean difference, -0.04%; 95% CI, -0.18 to 0.11; P value not significant) during the second and third trimester (mean difference, -0.08%; 95% CI, -0.23 to 0.06; P value not significant). Overall eight-point plasma glucose profiles were similar between treatment groups during the second and third trimesters. PPG levels were consistently lower in the insulin aspart group following breakfast than the REG group during the first trimester (P=0.044) and the third trimester (P=0.0007).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				However, there was no difference in PPG after breakfast during the second trimester (P=0.153). Both treatments were well tolerated and the adverse event profiles were similar between both groups. The frequency and profile of obstetric complications were similar between treatments with the most frequent complications being preeclampsia, threatened preterm labor, prolonged labor, and unplanned cesarean section. Treatment groups were not different in regards to changes in vital signs, physical examinations parameters, electrocardiograms, or clinical laboratory findings (P values were not reported).
Mathieu et al.[15] (2018) ONSET 1 Mealtime faster insulin aspart (containing niacinamide) vs mealtime insulin aspart (conventional formulation) both administered with once- or twice-daily insulin detemir	DB, MC, RCT Adults with type 1 diabetes and HBA_{1c} ≤9.5%	N=675 52 weeks (initial 26 weeks + additional 26 weeks)	Primary: Change in HbA_{1c} from baseline Secondary: HBA_{1c} responders (defined as HBA_{1c} <7.0%), changes from baseline in 1-hour postprandial plasma glucose	Primary: During run-in, observed mean HbA_{1c} was reduced from 8.0% to 7.6%. During the initial 26 weeks, observed mean HbA_{1c} was reduced from baseline to 56.4 mmol/mol (7.3%) with faster aspart and to 57.6 mmol/mol (7.4%) with conventional aspart. At 52 weeks, observed mean HbA_{1c} was 58.5 mmol/mol (7.5%) with faster aspart and 59.6 mmol/mol (7.6%) with conventional aspart; estimated mean changes from baseline of −0.08% and +0.01%, respectively. The estimated treatment difference (faster aspart – conventional aspart) was −1.04 mmol/mol (95% CI, −2.05 to −0.04) or −0.10% (95% CI, −0.19 to −0.00; P=0.0424). Secondary: The percentages of participants achieving HbA_{1c} targets of 7.0% and 6.5% increased from baseline to 52 weeks with faster aspart and conventional aspart. The estimated odds of achieving HbA_{1c} targets with faster aspart were not significantly different from those with conventional aspart. Changes from baseline in 1-hour postprandial plasma glucose increment (meal test; faster aspart -1.05 mmol/L; conventional aspart -0.14 mmol/L) favored faster aspart (estimated treatment difference, -0.91 mmol/L; 95% CI, -1.40 to -0.43; P=0.0002). There was no difference in overall severe or blood glucose-confirmed hypoglycemic episodes or treatment-emergent adverse events between treatments.
Bode et al.[16] (2019)	MC, RCT	N=777	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ONSET 7 double-blind mealtime faster aspart vs mealtime insulin aspart (IAsp) vs open-label postmeal faster aspart all treated with basal insulin degludec	Pediatric patients 1 to <18 years of age with type 1 diabetes	26 weeks	Change in HbA_{1c} from baseline Secondary: Change from baseline in 1-h postprandial glucose, hypoglycemia	At week 26, mealtime and postmeal faster aspart were noninferior to IAsp regarding change from baseline in HbA_{1c} (P<0.001 for noninferiority [0.4% margin]), with a statistically significant difference in favor of mealtime faster aspart (estimated treatment difference, -0.17%; 95% CI, -0.30 to -0.03; P=0.014). Secondary: Change from baseline in 1-h postprandial glucose increment significantly favored mealtime faster aspart versus IAsp at breakfast, main evening meal, and over all meals (P<0.01 for all). No statistically significant differences in the overall rate of severe or blood glucose-confirmed hypoglycemia were observed.
Garg et al.[17] (2005) Insulin glulisine before morning and evening meals and insulin glargine QD vs insulin glulisine after morning and evening meals and insulin glargine QD vs regular insulin before morning and	MC, OL, PG, RCT Patients with type 1 diabetes on insulin therapy for >1 year, baseline HbA_{1c} 7.7% for both insulin glulisine treatment groups and 7.6% for the REG group	N=860 12 weeks	Primary: Effect on HbA_{1c}, rate of hypoglycemia, and insulin dose Secondary: Not reported	Primary: HbA_{1c} reductions for insulin glulisine administered after meals (-0.11%) did not differ significantly from REG (-0.13%; P=0.6698). HbA_{1c} reductions for insulin glulisine administered before meals (-0.26%) were significantly lower than REG (-0.13%; P=0.0234). HbA_{1c} reductions for insulin glulisine administered before meals (-0.26%) were significantly lower than insulin glulisine administered after meals (-0.11%; P=0.0062). No significant differences were observed in the rates of symptomatic hypoglycemia (all and severe cases) between pre- and postmeal insulin glulisine and REG (P>0.05). Change in total insulin dose from baseline was significantly higher in the REG group (2.35 U) compared to the premeal insulin glulisine group (0.04 U; P=0.014).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
evening meals and insulin glargine QD Prandial insulin doses were adjusted to achieve PPG of 120 to 160 mg/dL.				Secondary: Not reported
Dreyer et al.[18] (2005) Insulin glulisine before meals and insulin glargine HS vs insulin lispro before meals and insulin glargine HS Insulin doses were adjusted to achieve PPG of 120 to 160 mg/dL.	MC, OL, PG, RCT Patients with type 1 diabetes on insulin therapy for >1 year, baseline HbA_{1c} 7.6% for both treatment groups	N=672 26 weeks	Primary: Effect on HbA_{1c}, rate of hypoglycemia, effect on self-monitored blood glucose and insulin dose Secondary: Not reported	Primary: There was a comparable decrease in HbA_{1c} between the insulin glulisine and insulin lispro groups (-0.14% for both groups; P value NS). The incidences of all hypoglycemic events (nocturnal and severe) were similar between the two treatment groups. Self-monitored blood glucose levels were similar in both treatment groups in regards to pre- and postprandial, bedtime and nocturnal blood glucose levels. There was a significant increase in total insulin dose in the insulin lispro group (1.01 units) compared to the insulin glulisine group (-0.86 units; P=0.0123). There was no significant difference in change in rapid-acting insulin dose between treatment groups. Rates of hypoglycemia were similar in both treatment groups. Rates of adverse events were also similar among the two treatment groups. Secondary: Not reported
Philotheou et al.[19] (2011) Premeal insulin glulisine vs	MC, NI, OL, PG, RCT Patients 4 to 17 years of age with type 1 diabetes for ≥1 year with HbA_{1c}	N=570 (efficacy endpoints) N=572 (safety endpoints)	Primary: Change in HbA_{1c} from baseline at endpoint (study did not define "endpoint")	Primary: The adjusted mean change in HbA_{1c} from baseline to endpoint was 0.10±0.08% with insulin glulisine and 0.16±0.07% with insulin lispro. The difference between the two groups was -0.06% (95% CI, -0.24 to 0.12; P value not reported), showing non-inferiority of insulin glulisine compared to insulin lispro based on the prespecified non-inferiority margin of 0.4%.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
premeal insulin lispro All patients received NPH BID or insulin glargine QD. Rapid-acting and basal insulin doses were titrated to achieve age-specific FPG goal of 100 to 140 mg/dL (<8 years old) or 90 to 140 mg/dL (≥8 years old) and PPG goal of 120 to 180 mg/dL (<8 years old) or 100 to 160 mg/dL (≥8 years old) using blood-referenced blood glucose meters.	between 6.0 to 11.0% who were receiving insulin therapy for ≥1 year with NPH insulin or insulin glargine as basal insulin	26 weeks (plus a 24-hour follow-up period)	Secondary: Proportion of patients who reached target HbA_{1c}, change in HbA_{1c} from baseline at 12 and 26 weeks, self-monitored FPG, PPG and pre-prandial glucose, insulin doses, symptomatic hypoglycemia between 12 and 26 weeks and safety	Secondary: At baseline, 33.2 and 33.3% of patients had HbA_{1c} at goal in the insulin glulisine and insulin lispro groups, respectively. At endpoint, the percentage of patients with HbA_{1c} at goal was 38.4% with insulin glulisine and 32.0% with insulin lispro (P=0.039). Change in HbA_{1c} with insulin glulisine and insulin lispro was -0.01±0.07% and -0.03±0.06% at 12 weeks and 0.08±0.08% and 0.17±0.08% at 26 weeks, respectively (P values not reported). At endpoint, self-monitored FPG was lower in the insulin glulisine group compared to the insulin lispro group (158.0±3.8 vs 170.5±3.7 mg/dL; P=0.014). Baseline FPG, PPG and pre-prandial glucose as well as endpoint PPG and pre-prandial glucose were comparable between the two groups. Total daily insulin doses increased by 0.01±0.01 units/kg with insulin glulisine and by 0.05±0.01 units/kg with insulin lispro (P=0.0045). The monthly rate of symptomatic hypoglycemia per patient was 3.10±4.33 and 2.91±4.35 with insulin glulisine and insulin lispro, respectively (P value not reported). No difference was seen with the two groups in severe, nocturnal or severe nocturnal symptomatic hypoglycemia. The frequency and type of treatment-emergent adverse events or serious adverse events were similar between the treatment groups.
van Bon et al.[20] (2011) Insulin glulisine vs insulin aspart	MC, OL, RCT, XO Patients ≥18 years of age with type 1 diabetes treated with insulin for ≥2 years and continuous SC insulin infusion for	N=256 39 weeks (13 weeks of treatment period for each study	Primary: Unexplained hyperglycemia (>300 mg/dL) and/or perceived infusion set occlusion Secondary:	Statistical significance was defined as P <0.025 in this study. Primary: Percentage of patients with at least one unexplained hyperglycemia and/or perceived infusion set occlusion was comparable between insulin glulisine and insulin aspart (68.4 vs 62.1%; P=0.04) and between insulin glulisine and insulin lispro (68.4 vs 61.3%; P=0.03). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs insulin lispro Insulin doses were titrated to achieve PPG <180 mg/dL and pre-prandial glucose between 90 to 130 mg/dL.	≥6 months, requiring ≤90 units/day of insulin, with HbA_{1c} <8.5% and BMI<35 kg/m^2	medication)	Unexplained hyperglycemia, perceived infusion set occlusion, HbA_{1c}, proportion of patients with HbA_{1c} <7.0%, seven-point plasma glucose profiles, hypoglycemic episodes, episodes of asymptomatic ketonemia and ketoacidosis, insulin doses, time to infusion set change, infusion site reactions and serious adverse reactions	Percentage of patients reporting at least one unexplained hyperglycemia was similar when comparing insulin glulisine (61.3%) to insulin aspart (55.9%; P=0.08) and insulin lispro (56.3%; P=0.11). No significant difference was seen in the percentage of patients with at least one perceived infusion set occlusion between insulin glulisine and insulin aspart (32.8 vs 27.0%; P=0.08) and between insulin glulisine and insulin lispro (32.8 vs 27.0; P=0.06). HbA_{1c} remained stable from baseline at the end of treatment period with all three insulin groups, with no significant differences seen among groups. Similar percentage of patients achieved HbA_{1c} <7.0% in the insulin glulisine, insulin aspart and insulin lispro groups (28, 31 and 30%, respectively; P values not reported). The seven-point plasma glucose profiles were similar among all three groups at baseline. At the end of treatment, after-lunch glucose was higher with insulin glulisine compared to insulin aspart (166.1 vs 155.5 mg/dL; P=0.021), and midnight glucose was higher with insulin lispro compared to insulin glulisine (159.4 vs 148.1 mg/dL; P=0.018). The overall rate of symptomatic hypoglycemia per patient-year was higher with insulin glulisine (73.8) compared to insulin aspart (65.0; P=0.008) and insulin lispro (62.7; P<0.001). The monthly rate of significant hyperketonemia and/or hyperketonemia at risk for ketosis was higher with insulin glulisine (0.14) compared to insulin aspart (0.06; P=0.01) and insulin lispro (0.06; P=0.02). One patient was hospitalized for diabetic ketoacidosis while receiving insulin glulisine. Insulin doses remained stable throughout the study. No significant differences were seen among the three groups in time to infusion set change, frequency of infusion site reactions and serious adverse reactions. No death was reported.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Rave et al.[21] (2006) Premeal insulin glulisine (2 minutes prior to a standardized 15-minute meal) vs postmeal insulin glulisine (15 minutes postmeal) vs premeal regular insulin (30 minutes premeal) vs premeal regular insulin (2 minutes premeal)	4-way XO, OL, RCT, single-dose Patients 18 to 55 years of age with type 1 diabetes on the same insulin regimen for ≥2 months before enrollment, BMI 18 to 32 kg/m^2, HbA_{1c} <10.0%, serum C-peptide levels ≤0.9 ng/mL	N=21 4 treatment periods	Primary: Blood glucose exposure and excursion at two and six hours following a meal, mean maximum blood glucose concentration, time to reach mean maximum blood glucose concentration Secondary: Not reported	Primary: Blood glucose exposure within two hours after the start of a meal was significantly lower with insulin glulisine than with REG (279 vs 344 mg·h/dL, respectively; P value not reported). However, at six hours following a meal, blood glucose exposure was not significantly different between both groups (708 vs 770 mg·h/dL, respectively; P value not reported). When insulin glulisine was given immediately prior to a meal and REG 30 minutes prior to the meal, blood glucose control was comparable. Both two- and six-hour blood glucose exposures were well matched. However, treatment with REG resulted in time to maximum blood glucose excursion to occur 43 minutes later compared to insulin glulisine. Postmeal insulin glulisine and REG given immediately premeal produced similar effects on PPG exposure and excursion at two hours after a meal (337 vs 334 mg·h/dL, respectively) and six hours after a meal (777 vs 770 mg·h/dL, respectively; P values not reported). Insulin glulisine was absorbed more rapidly than REG and reached a mean maximum concentration that was almost twice as large as the mean maximum concentration for REG (P value was not reported). In addition, the time to reach maximum concentration for insulin glulisine was half that of REG (P value was not reported). Secondary: Not reported
Anderson et al.[22] (1997) Insulin lispro before each meal and basal insulin for 3 months vs	MC, OL, RCT, XO Patients with type 1 diabetes previously treated with REG, baseline HbA_{1c} 8.5% for both groups	N=1,008 6 months	Primary: Effect on postprandial serum glucose (one- and two-hour), HbA_{1c}, and frequency of hypoglycemia	Primary: One-hour postprandial serum glucose rise was significantly lower with insulin lispro compared to REG (12.9 vs 13.9 mmol/L; P<0.001). Two-hour postprandial serum glucose rise was significantly lower with insulin lispro compared to REG (11.2 vs 12.9 mmol/L; P<0.001). There was no difference in HbA_{1c} reduction between the two treatment groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Regular insulin (REG) before each meal and basal insulin for 3 months			Secondary: Effect on insulin dose, frequency of premeal and basal insulin injections, and weight	The rate of hypoglycemia was 12% less during treatment with insulin lispro when compared to REG (P<0.001). Secondary: A small but significant increase in total insulin dose was observed with insulin lispro when compared to REG (0.71 vs 0.69 U/kg; P<0.001). No significant difference was reported for frequency of premeal injections between the two treatment groups. Significantly less patients on REG required ≥2 basal insulin injections compared to insulin lispro (46.4 vs 44.0%; P<0.05). There were no significant differences in weight gain between the two treatment groups. There were no differences in type and frequency of adverse events between the two treatments.
Fairchild et al.[23] (2000) Insulin lispro and NPH or Lente insulin for 3 months vs regular insulin (REG) and NPH or Lente insulin for 3 months Insulin doses were titrated to achieve HbA_{1c} 6.0 to 8.0% and preprandial	OL, RCT, XO Children 5 to 10 years of age with type 1 diabetes for at least 12 months, prepubertal, on BID insulin, attending the Diabetes Clinics at the New Children's Hospital, Newcastle	N=43 6 months	Primary: HbA_{1c} Secondary: Blood glucose levels before and after meals, two-hour PPG excursions, hypoglycemic events	Primary: After three months, change in HbA_{1c} was not significantly different between patients on insulin lispro and patients on REG (mean difference, -0.19±0.63%; P value not reported). Secondary: There were no significant differences in blood glucose levels before or after meals and two-hour PPG excursions. However, the 3 AM blood glucose levels were significantly lower in patients taking REG than in patients taking insulin lispro (mean difference between treatments, -2.35 mmol/L; 95% CI, -3.98 to -0.72; P=0.01). There was no significant difference in the frequency of total hypoglycemic episodes or hypoglycemic episodes with a blood glucose <3 mmol/L between patients taking REG and patients taking insulin lispro (P value was not reported).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
blood glucose levels 4 to 10 mmol/L.				
Mortensen et al.[24] (2006) Premeal biphasic insulin aspart (BIAsp) 30 plus NPH insulin at bedtime (HS) vs premeal REG (before lunch and dinner) plus biphasic human insulin (BHI) 30 before breakfast and NPH insulin HS Insulin doses were titrated to achieve target FPG <8 mmol/L and PPG <10 mmol/L.	MN, OL, PG, RCT Adolescents 10 to 17 years of age with type 1 diabetes for at least 18 months	N=167 16 weeks	Primary: HbA_{1c}, change in PPG, body weight, hypoglycemia Secondary: Not reported	Primary: HbA_{1c} decreased by about -0.2% in both treatment arms at endpoint. There was no significant difference in the change of HbA_{1c} between groups at study endpoint (P=0.62). At 16 weeks, both the biphasic insulin aspart group and REG group had reductions in average PPG (SEM, 0.37 and 0.77, respectively; P=0.47). The increase in body weight was smaller in the biphasic insulin aspart group than the REG group. The difference between groups was significant for males (P=0.007), but not for females. The rates of hypoglycemia during the day and during the night were similar between treatment groups (P value was not reported). Secondary: Not reported
Chen et al.[25] (2006) Biphasic insulin aspart 30 (BIAsp30) TID, divided in a 30:30:40 ratio for 12 weeks; NPH could also be added at bedtime vs	OL, RCT, XO Patients ≥18 years of age with type 1 diabetes for ≥12 months, previously treated with soluble human insulin TID plus NPH at bedtime with a total daily dose <1.8 IU/kg,	N=27 24 weeks	Primary: Change in HbA_{1c} from baseline at end of each 12 week-treatment period, daily seven-point self monitoring of blood glucose Secondary: Hypoglycemia	Primary: Eleven out of 27 patients chose to take bedtime NPH while they were being treated with insulin aspart. Both the biphasic insulin aspart and the REG groups had significant improvement in HbA_{1c} levels from baseline (P<0.01). However, the biphasic insulin aspart group had a significantly greater reduction in HbA_{1c} than that of the REG group (P<0.05). Upon further analysis it was ascertained that most of the between-group difference in HbA_{1c} was driven by the patients who administered bedtime NPH in combination with their TID biphasic insulin aspart.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
REG insulin administered TID plus NPH insulin at bedtime for 12 weeks Doses were titrated to achieve FPG 5.0 to 8.0 mmol/L and PPG 5.0 to 10.0 mmol/L.	BMI <35 kg/m^2 and HbA_{1c} ≥8.0% during the last 6 months; at 12 weeks, patients were switched to the alternative insulin regimen for another 12 weeks			Both the biphasic insulin aspart and the REG groups had similar results in self monitoring of blood glucose of daytime glycemic control. However, the biphasic insulin aspart group had significantly lower blood glucose concentrations at two hours after dinner and at bedtime in comparison to the REG group (P<0.05). Secondary: The rates of hypoglycemia (events/patient-week) were similar among the biphasic insulin aspart and REG group (1.2 vs 0.7, respectively for total events and 0.2 vs 0.2, respectively for nocturnal events; P value not reported).
Garg et al.[26] (2017) SORELLA-1 SAR342434 (Admelog®; a biosimilar follow-on of insulin lispro-Humalog®) vs insulin lispro (Humalog®)	OL, MC, RCT Adult patients with type 1 diabetes treated with multiple daily injections while using basal insulin glargine (Lantus®; GLA-100)	N=507 52 weeks (26 week main study and 26 week extension)	Primary: Change in HbA_{1c} from baseline Secondary: Change from baseline FPG, and seven-point self-monitored plasma glucose profiles and postprandial plasma glucose excursions; hypoglycemia	Primary: The least squares mean change in HbA_{1c} from baseline to week 26 was similar in both treatment groups (−0.42% on SAR342434; −0.47% on insulin lispro). The least squares mean difference between SAR342434 and insulin lispro was 0.06% (95% CI, −0.084 to 0.197). Noninferiority of SAR342434 versus insulin lispro was demonstrated. During the six-month extension period, efficacy was maintained, although a small increase in HbA_{1c} occurred similarly in the two groups between week 26 and week 52. Secondary: FPG and seven-point self-monitored plasma glucose profile changes, including postprandial glucose excursions, were similar between groups. At week 52, similar changes in mean daily mealtime and basal insulin doses were observed. Hypoglycemia, treatment-emergent adverse event, and anti-insulin antibodies (incidence, prevalence) did not differ between groups.
Rapid-Acting and Short-Acting Insulin Administered By Continuous Subcutaneous Insulin Infusion (CSII): Type 1 Diabetes Mellitus				
Bode et al.[27] (2002) Insulin aspart (IAsp) administered by CSII via external pump	MC, OL, PG, RCT Patients 18 to 71 years of age with type 1 diabetes with fasting C-peptide	N=146 16 weeks	Primary: HbA_{1c}, eight-point self monitoring blood glucose, weight, hypoglycemia	Primary: After 16 weeks of treatment, the mean change in HbA_{1c} from baseline was not significantly different among the three groups (0.00%, 0.15%, and 0.18% for the IAsp, BR, and lispro groups, respectively).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs insulin lispro administered by CSII via external pump vs regular insulin (BR) administered by CSII via external pump	<0.5 ng/mL who had been treated with CSII therapy continuously for the previous 3 months		Secondary: Not reported	For the eight-point self monitoring blood glucose evaluation, postprandial values for subjects in the rapid-acting insulin analog groups were improved from baseline values and tended to be lower than those for subjects in the BR group. A few statistically significant differences were observed at week 16 between the treatment groups: dinner +90 minutes, the blood glucose value for the IAsp group was lower than those for BR and lispro groups (P=0.019); at 2:00 A.M., the blood glucose value for the BR group was lower than those for IAsp and lispro groups (P=0.002). Mean weight did not significantly increase or decrease during the study among the treatment groups. Similar numbers of subjects (≥90%) in each treatment group reported one or more minor hypoglycemic episodes. The rate of confirmed hypoglycemia was not significantly different between treatment groups. The rate of confirmed nocturnal hypoglycemia for the IAsp group was lower than that for the BR group and similar to that of the lispro group. No major nocturnal hypoglycemic episodes occurred during the study. Secondary: Not reported
Weinzimer et al.[28] (2008) Insulin aspart administered by CSII via external pump vs insulin lispro administered by CSII via external pump	MC, OL, PG, RCT Patients 3 to 18 years of age with type 1 diabetes for ≥1 year and HbA_{1c} ≤10.0% who were being treated with either insulin aspart or insulin lispro by CSII for ≥3 months	N=298 16 weeks	Primary: HbA_{1c} at week 16 Secondary: FPG, eight-point self monitoring blood glucose, weight, hypoglycemia	Primary: At study end point, the mean HbA_{1c} values were 7.9% and 8.1% (last observation carried forward) for insulin aspart and insulin lispro, respectively. The change in HbA_{1c} from baseline to week 16 was -0.15% in the insulin aspart group and -0.05% in the insulin lispro group (95% CI, -0.27 to 0.07). After 16 weeks, 59.7% of patients in the insulin aspart group and 43.8% of the patients in the insulin lispro group achieved American Diabetes Association age-specific recommendations for HbA_{1c} (P=0.040). Secondary: After 16 weeks, mean FPG were similar among the treatment groups (insulin aspart 166.5 mg/dl; lispro 180.2 mg/dl; P=0.113).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The eight-point self monitoring blood glucose profiles collected before weeks 0 and 16 showed a similar pattern for both treatment groups. No significant differences between treatment groups in mean self monitoring blood glucose values were observed at any of the eight time points at week 16. Mean body weight increased from baseline for both treatment groups during the trial, but was comparable between treatment groups (insulin aspart 1.8 kg; insulin lispro 1.6 kg; P=0.387). Rates of minor and major hypoglycemic episodes were similar between the two treatment groups. A similar percentage of patients reported at least one major hypoglycemic event during the study period (9.6 and 8.0% in the insulin aspart and insulin lispro groups, respectively). Rates of nocturnal hypoglycemic events were also similar between the treatment groups.
Colquitt et al.[29] (2003) Rapid-acting insulin analogs administered by CSII vs regular insulin administered by CSII	MA Analysis of 6 randomized trials that compared rapid-acting insulin analogs vs REG in the treatment of patients with diabetes using continuous infusions; trials less than 10 weeks in duration were excluded	N=577 Duration varied	Primary: Effect in HbA_{1c}, insulin dose, weight change, patient preference, quality of life and adverse events Secondary: Not reported	Primary: Significant improvement in HbA_{1c} of -0.26% (95% CI, -0.47 to -0.06; P=0.01) was observed with insulin lispro compared to REG. The differences in HbA_{1c} from baseline between insulin aspart, REG, or insulin lispro were not significant. No significant difference in insulin dose was reported between treatment groups. No significant difference in weight was reported between treatment groups. Two studies reported patient preference to short-acting insulin analogs. One study found no difference in satisfaction between treatment groups and one study found greater patient satisfaction towards short-acting insulin analogs. No difference in frequency of severe hypoglycemic events was reported between treatment groups. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Not reported
Rapid-Acting and Short-Acting Insulin: Type 2 Diabetes Mellitus				
McSorley et al.[30] (2002) Biphasic insulin aspart (BIAsp) 30 BID for 2 weeks vs biphasic human insulin (BHI) 30 BID for 2 weeks Patients were XO to other insulin regimen after 2 weeks of initial randomized insulin regimen.	2-period, DB, RCT, XO Patients 40 to 75 years of age with type 2 diabetes for at least 1 year, had been on BID biphasic human insulin 30 for at least 6 months	N=13 4 weeks	Primary: AUC during two hours following insulin administration at dinner and breakfast Secondary: Maximum serum insulin concentration after two injections; time to reach peak serum insulin concentrations; four-hour glucose excursion following dinner, breakfast, and lunch; glucose maximum concentration after dinner, breakfast, and lunch; time taken to reach glucose maximum concentration values	Primary: The AUC two hours following insulin administration was significantly greater for biphasic insulin aspart 30 than for biphasic human insulin 30 after dinner and breakfast (P<0.05). Secondary: Biphasic insulin aspart 30 reached a maximum concentration that was 18% higher after dinner and 35% higher after the following day's breakfast than that of biphasic human insulin 30 (P<0.05 for both values). The time taken to reach peak serum insulin concentrations was one hour earlier after breakfast and 45 minutes earlier after dinner in the biphasic insulin aspart 30 group compared to the biphasic human insulin 30 group. However, the only measure to reach statistical significance was after breakfast (P<0.05). Serum glucose excursions were significantly lower in the biphasic insulin aspart 30 group than the biphasic human insulin 30 group after dinner (P<0.05) and after breakfast (P<0.05). However, serum glucose excursion after lunch was significantly higher in the biphasic insulin aspart 30 group than the biphasic human insulin 30 group (P<0.05). Following breakfast, glucose maximum concentration was significantly lower and time to reach glucose maximum concentration was significantly earlier with biphasic insulin aspart 30 than biphasic human insulin 30 (P<0.05 for both measures). Both insulins were well-tolerated and had comparable adverse events. There were no major hypoglycemic episodes or serious adverse events reported.
Bowering et al.[31] (2017) ONSET 2	DB, MC, RCT Subjects ≥18 years of age with a BMI	N=689 26 weeks	Primary: Change in HBA_{1c} Secondary:	Primary: HBA_{1c} change was –1.38% (faster aspart) and –1.36% (conventional aspart); mean HBA_{1c} was 6.6% for both groups. Faster aspart demonstrated noninferiority versus IAsp in reducing HBA_{1c}.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Mealtime faster insulin aspart (containing niacinamide) vs mealtime insulin aspart (conventional formulation) plus insulin glargine U100 (Lantus) and metformin	≤40 kg/m^2 with type 2 diabetes and treated with basal insulin for ≥6 months and metformin for ≥3 months		Change from baseline in 2-h PPG increment, hypoglycemic episodes, change in body weight	Secondary: Estimated change from baseline in 2-h PPG increment was –3.2 mmol/L with faster aspart versus –2.9 mmol/L for conventional aspart. The estimated treatment difference was –0.36 mmol/L (95% CI, –0.81 to 0.08), which did not reach statistical significance. The difference in overall rate of severe or blood glucose-confirmed hypoglycemia was not statistically significant between treatment groups (RR, 1.09; 95% CI, 0.88 to 1.36). Body weight gain was ∼2.7 kg over 26 weeks for both treatment groups.
Lane et al.[32] (2020) ONSET 9 Fast-acting insulin aspart (faster aspart) vs insulin aspart (IAsp) both with insulin degludec with or without metformin	DB, MC, RCT Adults (≥18 years old) with type 2 diabetes for ≥10 years and had been treated with a basal-bolus insulin regimen for ≥1 year before screening with or without oral antidiabetes agents. Participants were required to have an HbA_{1c} of 7.0 to 10.0% at screening and an HbA_{1c} ≤9.0% at randomization	N=1,091 16 weeks	Primary: Change in HBA_{1c} Secondary: Change from baseline in 1-h PPG increment (meal test) and change from baseline in 1,5-anhydroglucitol 16 weeks after randomization (1,5-anhydroglucitol was used as a surrogate marker for measuring PPG excursions)	Primary: Noninferiority for the change from baseline in HBA_{1c} 16 weeks after randomization was confirmed for faster aspart versus IAsp (estimated treatment difference, -0.04%; 95% CI, -0.11 to 0.03; P<0.001). Superiority of faster aspart versus IAsp regarding change from baseline in HBA_{1c} could not be confirmed. Secondary: The observed change from baseline in 1-h PPG increment after 16 weeks was −0.43 mmol/L in the faster aspart arm and 0.08 mmol/L in the IAsp arm. Superiority of faster aspart to IAsp in terms of change from baseline in 1-h PPG increment was confirmed (estimated treatment difference, −0.40 mmol/L; 95% CI, −0.66 to −0.14; P=0.001). The observed mean change from baseline in 1,5-anhydroglucitol at 16 weeks was 1.38 µg/mL in the faster aspart arm and 0.89 µg/mL in the IAsp arm (estimated treatment difference, 0.50 µg/mL; 95% CI, 0.11 to 0.89).
Bretzel et al.[33] (2004)	MC, OL, PG, RCT Adult (≥35 years of age) type 2	N=231 12 weeks	Primary: Equivalence of the primary efficacy	Primary: Insulin aspart reduced HbA_{1c} by -0.91±1.00%, while REG reduced HbA_{1c} by -0.73±0.87% and premixed insulin reduced HbA_{1c} by -0.65±1.10%.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Insulin aspart before meals and NPH insulin QD (if needed) vs regular insulin before meals and NPH insulin QD (if needed) vs NPH/REG insulin 70/30 mix QD to BID Insulin doses were titrated to achieve blood glucose levels of 80 to 110 mg/dL.	diabetes with HbA_{1c} ≤10.0%, baseline HbA_{1c} 7.82% for insulin aspart, 7.83% for REG and 7.78% for the premixed insulin		endpoint–effect on HbA_{1c} Secondary: Not reported	Insulin aspart was found not to be statistically equivalent to REG (P=0.025) or the premixed insulin formulation (P=0.092). Significance level for P was set at 0.0083. The proportion of patients reporting an adverse event was comparable in all three treatment groups. The proportion of patients that experienced a hypoglycemic event (41% for insulin aspart and REG and 30% for premixed insulin) was not statistically different. Secondary: Not reported
Blevins et al.[34] (2020) PRONTO-T2D Ultra rapid lispro (URLi) vs lispro Treat-to-target dosing, patients could continue metformin and/or a	DB, MC, RCT Patients with type 2 diabetes on a basal-bolus insulin regimen and an HbA_{1c} between 7 and 10%	N=673 26 weeks	Primary: Change in HbA_{1c} from baseline to 26 weeks (noninferiority margin 0.4%) Secondary: 1- and 2-h PPG excursions, safety	Primary: HbA_{1c} improved for both URLi and lispro, and noninferiority was confirmed: estimated treatment difference (ETD) 0.06% (95% CI, -0.05 to 0.16). Mean change in HbA_{1c} was -0.38% for URLi and -0.43% for lispro, with an end-of-treatment HbA_{1c} of 6.92% and 6.86%, respectively. Secondary: URLi was superior to lispro in controlling 1- and 2-h PPG excursions: 1-h ETD, -0.66 mmol/L (95% CI, -1.01 to -0.30); 2-h ETD, -0.96 mmol/L (95% CI, -1.41 to -0.52). Significantly lower PPG excursions were evident from 0.5 to 4.0 h postmeal with URLi treatment. There were no significant treatment differences in rates of severe or documented hypoglycemia (<3.0 mmol/L). Incidence of overall treatment-emergent adverse events was similar between treatments.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
sodium-glucose cotransporter 2 inhibitor				
Niskanen et al.[35] (2004) Insulin aspart 30% and insulin aspart protamine 70% administered via proprietary pen for 12 weeks vs insulin lispro 25% and insulin lispro protamine 75% administered via proprietary pen for 12 weeks	MC, OL, RCT, XO Patients with type 2 diabetes previously treated with insulin with HbA_{1c} <12.0%, baseline HbA_{1c} for the whole sample size was 8.5%	N=137 24 weeks	Primary: Effect on HbA_{1c} and seven-point blood glucose levels Secondary: Patient satisfaction with the pen devices	Primary: HbA_{1c} reduction was comparable between the two treatment groups. The seven-point blood glucose profile was comparable at each time point and there was no significant difference between the two treatment groups. Secondary: Significantly more patients preferred the insulin aspart pen device compared to the insulin lispro pen device (P<0.005). The incidence of reported adverse events was similar between treatment groups.
Dailey et al.[36] (2004) Insulin glulisine before meals BID (AM and PM) and NPH insulin BID vs regular insulin before meals BID (AM and PM) and NPH insulin BID	MC, OL, PG, RCT Patients with type 2 diabetes on continuous insulin therapy for ≥6 months, baseline HbA_{1c} 7.58% for insulin glulisine and 7.52% for REG	N=876 26 weeks	Primary: Effect on HbA_{1c}, rate of hypoglycemia, effect on self-monitored blood glucose and insulin dose Secondary: Not reported	Primary: There was a small, but significantly greater decrease in HbA_{1c} observed in the insulin glulisine group compared to the REG group (-0.46 vs -0.30%; P=0.0029). No significant differences were observed in either group in the incidence of hypoglycemia. Significantly lower two-hour PPG (breakfast and dinner) was observed in the insulin glulisine group compared to the REG group (P<0.05). There was no significant difference in total daily insulin doses between the two treatment groups throughout the study. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Insulin doses were adjusted to achieve PPG 120 to 160 mg/dL.				
Rayman et al.[37] (2007) Insulin glulisine and NPH insulin BID, in addition to current oral antidiabetic agents vs Regular insulin and NPH insulin BID, in addition to current oral antidiabetic agents Insulin glulisine and regular doses were adjusted to achieve target PPG 120 to 160 mg/dL. NPH insulin was titrated to achieve FPG 90 to 120 mg/dL.	MC, MN, OL, PG, RCT Patients aged ≥18 years of age with type 2 diabetes on >6 months of continuous insulin treatment prior to study entry, HbA_{1c} 6.0 to 11.0%, ability and willingness for self monitoring of blood glucose	N=892 26 weeks	Primary: Change in HbA_{1c}, adverse events Secondary: Difference in the change of HbA_{1c} at 12 and 26 weeks between insulin glulisine and REG, self-monitored seven-point blood glucose profile, symptomatic hypoglycemia, insulin dose	Primary: HbA_{1c} decreased from baseline to study endpoint in both the insulin glulisine and REG groups. HbA_{1c} in the insulin glulisine group decreased from 7.58±0.90% to 7.25±0.95% and from 7.50±0.89% to 7.19±0.90% in the REG group (P value not reported). No difference between groups was seen in the proportion of patients achieving HbA_{1c} levels ≤7.0% (P=0.8962). There was no between-treatment difference in the frequency and type of treatment emergent adverse events observed (P value not reported). Secondary: There was no between-treatment difference in change in HbA_{1c} for insulin glulisine and REG at 12 weeks and study endpoint (P=0.3573 and P=0.5726, respectively). At study endpoint, glucose values were significantly lower two hours postbreakfast with insulin glulisine compared to REG (P<0.001). There were no noteworthy differences between both treatment groups in the frequencies and monthly rates of all symptomatic hypoglycemia. However, the frequencies and monthly rates of severe symptomatic hypoglycemia were lower in the insulin glulisine group than the REG group. Patients taking insulin glulisine also had fewer reports of nocturnal symptomatic hypoglycemia from month four to treatment end compared to patients taking REG (P=0.029). In terms of insulin doses, there was a larger increase in the short-acting dose with REG than with insulin glulisine (adjusted mean, 4.47 vs 2.95 U, respectively; P=0.0645). Overall, the total daily insulin dose increased slightly more with REG. However, the difference was not significant (P=0.1727).
Derwahl et al.[38]	OL, MC, RCT	N=505	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2018) SORELLA-2 SAR342434 (Admelog®; a biosimilar follow-on of insulin lispro-Humalog®) vs insulin lispro (Humalog®)	Adult patients with type 2 diabetes treated with multiple daily injections while using basal insulin glargine (Lantus®; GLA-100)	52 weeks (26 week main study and 26 week extension)	Change in HbA_{1c} from baseline Secondary: Change from baseline FPG, and seven-point self-monitored plasma glucose profiles and postprandial plasma glucose excursions; hypoglycemia	Least square mean change in HbA_{1c} from baseline to week 26 was similar in both treatment groups (SAR342434, -0.92% and insulin lispro, -0.85%). Noninferiority at prespecified 0.3% noninferiority margin was demonstrated (least squares mean difference of SAR342434 vs insulin lispro, -0.07%; 95% CI, -0.215 to 0.067) as was inverse noninferiority. Secondary: Similar changes in FPG, seven-point self-monitored plasma glucose profiles, including postprandial glucose excursions and mean glucose over 24 hours, and insulin dosages were observed in the two groups. Hypoglycemia, treatment-emergent adverse events, and anti-insulin antibodies (incidence and prevalence) did not differ between groups.
Rosenstock et al.[39] (2008) Basal bolus therapy (BBT) (premeal insulin lispro and insulin glargine HS) vs premeal premixed therapy (PPT) (lispro mix 50/50 TID)	MC, NI, OL, RCT Patients with type 2 diabetes	N=374 24 weeks	Primary: HbA_{1c}, percentage of patients achieving HbA_{1c} <7.0%, hypoglycemia Secondary: Not reported	Primary: HbA_{1c} was reduced significantly from baseline in both treatment groups (P<0.0001). At 24 weeks, HbA_{1c} was lower with basal bolus therapy compared to premeal premixed therapy (6.78 vs 6.95%, respectively; P=0.021). The difference between treatment groups was -0.22% (90% CI, -0.38 to -0.07; P value not reported). The percentage of patients achieving an HbA_{1c} <7.0% was 54 vs 69% in the premeal premixed therapy and basal bolus therapy groups, respectively (P=0.009). Rates of hypoglycemia were similar between both treatment groups. Secondary: Not reported
Tack et al.[40] (2008) Technosphere® Inhaled Insulin (TI) at four different doses (equivalent to 3.6, 7.3, 10.9, and 14.6 U subcutaneous	DB, MC, PC, PRO Adult patients 18 to 80 years of age with type 2 diabetes mellitus poor glycemic control (HbA_{1c} between 7 and	N=227 11 weeks	Primary: Change in HbA_{1c} of each randomized dose from baseline Secondary: PPG, safety	Primary: Mean reductions in HbA_{1c} from baseline were statistically significant for all treatment groups and increased with increasing TI doses. The greatest reduction from Technosphere powder alone was seen in the TI 14.6 U-equivalent group (0.78%). Secondary: TI treatment significantly reduced PPG excursions after a mixed meal. Over the 11-week treatment period, dose-dependent and statistically

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
regular human insulin) vs Technosphere® Powder Placebo All patients received basal insulin glargine.	12%) with a minimum of two months of treatment with a stable dose of ≥1 antihyperglycemic agent and/or basal insulin glargine therapy			significant mean reductions from baseline were seen in postprandial $AUC_{glucose}$ at 0 to 300 minutes for the 7.3, 10.9, and 14.6 U-equivalent groups (P≤0.001 for these groups). Patients randomized to the highest TI doses experienced more hypoglycemic events than those randomized to Technosphere powder alone or to the lowest two TI doses. Cough was reported by 10 subjects in the Technosphere powder alone group and by 4 to 12 subjects in the TI groups. Changes in pulmonary function parameters (FVC, FEV_1, and DL_{CO}) were minimal during the study period.
Rosenstock et al.[41] (2008) Technosphere® Inhaled Insulin vs Technosphere® Powder Placebo Each group in addition to oral antidiabetic (OAD) agents.	DB, MC, PC, PG, RCT Insulin-naive patients (18 to 80 years of age with diabetes duration of 2 to 12 years), treated with at least one OAD, were on a stable regimen for at least three months before enrollment	N=126 12 weeks	Primary: Change in HbA_{1c} from baseline to study end Secondary: PPG concentrations after the meal at baseline and after 4, 8, and 12 weeks of treatment, safety	Primary: After 12 weeks of treatment, mean HbA_{1c} decreased by −0.7% with Technosphere insulin and by −0.3% with Technosphere powder (P=0.003) from baselines of 8.0 and 7.8%, respectively. Secondary: Postprandial glucose excursions were reduced by 56% with Technosphere insulin compared with baseline, and maximal postprandial glucose levels were reduced by 43% compared with Technosphere powder. Incidences of hypoglycemia and hyperglycemia were similar for both groups, with no significant between-group differences (P=0.321 and P=0.871, respectively). Coughing episodes were similar in both groups. Pulmonary function outcomes were not considered clinically relevant.
Rosenstock et al.[42] (2010) Prandial Technosphere inhaled insulin powder plus bedtime insulin glargine vs	OL, PG, RCT Adult patients 18 to 80 years of age with type 2 diabetes mellitus poor glycemic control (HbA_{1c} between 7 and 11%) despite insulin therapy,	N=677 52 weeks	Primary: Change in HbA_{1c} from baseline to study end Secondary: Change from baseline in plasma glucose concentrations, proportion of	Primary: Mean changes in HbA_{1c} from baseline to week 52 were similar across all analysis populations with all upper 95% CIs <0.4, showing that inhaled insulin is non-inferior to biaspart insulin. Secondary: Mean fasting plasma glucose values at week 52 were 7.8 mmol/L for inhaled insulin plus insulin glargine and 8.7 mmol/L for biaspart insulin. The between-group difference was −1.0 mmol/L (SD 0.3, 95% CI −1.6 to −0.3, P=0.0029).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
twice daily premixed biaspart insulin (70% insulin aspart protamine suspension and 30% insulin aspart of rDNA origin).	with or without oral antidiabetes drugs		patients achieving HbA_{1c} ≤7%, change in FPG, weight, safety	The proportion of patients with HbA_{1c} of 7.0% or less at week 52 was similar between patients on inhaled insulin and insulin glargine (22%) and those on biaspart insulin (27%, P=0.2793). Mean weight gain was significantly lower with inhaled insulin plus insulin glargine 0.9 kg (SD 0.3; 95% CI 0.3 to 1.5) than with biaspart insulin 2.5 kg (0.3, 1.9 to 3.0), with a treatment difference of −1.6 kg (SD 0.4; 95% CI −2.4 to −0.7; P=0.0002). In the safety population, adverse events occurred in 272 patients (84%) on inhaled insulin plus insulin glargine and 296 (89%) of those on biaspart insulin, with hypoglycemia being the most frequent adverse event, occurring in 31% of inhaled insulin patients and 49% of biaspart insulin patients. 103 patients (32%) treated with inhaled insulin plus insulin glargine reported cough compared with 14 (4%) receiving biaspart insulin.
Raskin et al.[43] (2012) Prandial inhaled Technosphere Insulin (TI) vs standard antidiabetes treatment (usual care) Control group of non-diabetic patients also included with no intervention	MC, OL, RCT Patients 18 to 80 years of age with type 1 or type 2 diabetes for at least two years and HbA_{1c} ≥6.6% and ≤12.0%	N=1699 2 years	Primary: Change from baseline in pre-bronchodilator FEV_1 at month 24 between the diabetes treatment groups Secondary: Treatment group difference in the incidence of FEV_1 findings (≥15% decline) and change from baseline in FVC, TLC, DL_{CO} and HbA_{1c}	Primary: Over two years, small declines from baseline in FEV_1 were observed in all groups, with the smallest change in those without diabetes. The adjusted mean treatment group difference in change in FEV_1 from baseline to month 24 was 0.037 (95% CI, 0.014 to 0.060). The upper limit of the 95% CI for the treatment group difference in FEV_1 change at month 24 was less than the pre-specified non-inferiority margin of 100 mL (50 mL/year), demonstrating non-inferiority with TI over usual care. Secondary: At month 24, the adjusted treatment group difference in mean FVC was small (0.034 l [standard error of the mean 0.0135]). TLC and DL_{CO} treatment group differences were not statistically significant. In all, 42 of 730 (5.75%) patients receiving TI and 27 of 824 (3.28%) receiving usual care had protocol-predefined FEV_1 findings (≥15% decrease from baseline) at last measurement. Treatment group difference (usual care—TI) in the percentage of patients with FEV_1 decline of ≥15% from baseline was −2.48% (95% CI, −4.5578 to 0.3956). Lower bound of 95% CI did not exceed −5%, thereby demonstrating that TI was non-inferior to usual care.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Mean (standard deviation) change in HbA_{1c} from baseline to month 24 was comparable between treatment groups. More treatment-emergent adverse events (TEAE) were reported in patients receiving TI (n=729 [79.0%]) than in patients receiving usual care (n=674 [71.0%]; The most common TEAE in both treatment groups was hypoglycemia. Cough, the second most common TEAE, was more frequent with TI than with usual care.
Rapid-Acting and Short-Acting Insulin: Type 1 and Type 2 Diabetes Mellitus				
Vignati et al.[44] (1997) Insulin lispro and NPH insulin BID before meals for 2 months vs regular insulin and NPH insulin BID before meals for 2 months Doses of both regimens were adjusted to achieve 2-hour postprandial serum glucose ≤160.2 mg/dL and fasting serum glucose ≤140.0 mg/dL.	MC, OL, RCT, XO Patients with type 1 diabetes and type 2 diabetes previously treated with REG and NPH, baseline HbA_{1c} 8.0% for both groups in patients with type 1 diabetes and 8.1% for both groups in patients with type 2 diabetes	N=707 4 months	Primary: Effect on HbA_{1c}, pre-prandial glucose levels, PPG levels and frequency of hypoglycemia, and insulin dose Secondary: Not reported	Primary: There was no significant difference in HbA_{1c} reduction between the two treatment groups (P>0.648). Pre-prandial glucose levels did not differ significantly between the two treatment groups for any meal (P≥0.066) or at bedtime (P>0.404). PPG was significantly lower with insulin lispro compared to REG for the morning meal (8.6 vs 9.8 mmol/L; P<0.001) and the evening meal (8.6 vs 9.6 mmol/L; P<0.005) for type 1 diabetics. No significant difference was noted in the noon meal. PPG was significantly lower with insulin lispro compared to REG in the morning meal only in type 2 diabetics (9.5 vs 10.4 mmol/L; P<0.001). There was no significant difference in hypoglycemic events between the two treatment groups (P=0.677 for type 1 diabetics and P=0.419 for type 2 diabetics). Endpoint insulin dose was significantly higher with insulin lispro compared to regular human insulin in type 1 diabetics albeit the difference was small (0.63 vs 0.60 U/kg; P=0.015). There were no significant differences in insulin doses in type 2 diabetics. Secondary: Not reported
Anderson et al.[45] (1997)	MC, OL, RCT	N=631	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Insulin lispro before meals and basal insulin vs regular insulin before meals and basal insulin	Patients with type 1 diabetes and type 2 diabetes previously treated with REG, baseline HbA_{1c} 8.2% for both groups in patients with type 1 diabetes and baseline HbA_{1c} 8.9% for REG and 8.7% for insulin aspart	12 months	Effect on HbA_{1c}, postprandial rise in serum glucose, frequency of hypoglycemia, and insulin dose Secondary: Not reported	HbA_{1c} was significantly lower with insulin lispro compared to REG in type 1 diabetics (8.1 vs 8.3%; P<0.05). There was no difference in HbA_{1c} between treatment groups for type 2 diabetics. Postprandial (two-hour) serum glucose rise was significantly reduced with insulin lispro compared to REG in type 1 diabetics (64%; P=0.007) and type 2 diabetics (48%; P=0.004). There was no difference in rates of hypoglycemia between the two treatment groups. There was a small, but significant reduction in premeal insulin dose in the insulin lispro group (-0.03 U/kg; P=0.004) but a small and significant increase in the basal insulin dose (0.05 U/kg; P<0.001) in type 1 diabetics. There were no dose changes in the REG group. For type 2 diabetics, the daily dose increase of insulin was comparable between the treatment groups. Secondary: Not reported
Plank et al.[46] (2005) Short-acting insulin analogs (insulin lispro and/or insulin aspart) vs regular insulin	MA Analysis of 42 randomized trials that compared short-acting insulin analogs vs REG in the treatment of type 1 diabetes and type 2 diabetes patients	N=7,933 Duration varied	Primary: Effect on HbA_{1c} and number of hypoglycemic episodes Secondary: Quality of life, pregnancy outcomes, and adverse events	Primary: A small but significant difference in HbA_{1c} was observed with short-acting insulin analogs compared to REG in type 1 diabetes (-0.12%; 95% CI, -0.17 to -0.07). No significant differences in HbA_{1c} were observed with short-acting insulin analogs compared to REG in patients with type 2 diabetes (-0.02%; 95% CI, -0.10 to 0.07). No significant differences in hypoglycemic rates were observed with short-acting insulin analogs compared to REG in type 1 diabetic patients (-0.05 episodes/patient/month; 95% CI, -0.22 to 0.11). No significant differences in hypoglycemic rates were observed with short-acting insulin analogs compared to REG in patients with type 2 diabetes (-0.04 episodes/patient/month; 95% CI, -0.12 to 0.04).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Quality of life reported in type 1 diabetes favored short-acting insulin analogs in four studies and found no difference in three studies. No significant difference in quality of life was reported in studies with type 2 diabetics (two studies total). There were no significant differences in maternal or fetal outcomes between the two insulin groups. Comparable incidence and type of adverse events were reported for both insulin groups.
Siebenhofer et al.[47] (2006) Rapid-acting insulin analogs (insulin lispro, insulin aspart, insulin glulisine) vs regular insulin	MA Analysis of 49 randomized trials that compared rapid-acting insulin analogs to REG in patients with type 1 diabetes and type 2 diabetes	N=8,274 Duration varied	Primary: HbA_{1c}, hypoglycemia Secondary: Adverse events	Primary: In patients with type 1 diabetes, the WMD in HbA_{1c} was estimated to be -0.1% (95% CI, -0.2 to -0.1; P=0.01) in favor of insulin analogs compared to REG. In the subgroup analyses, results were divided into patients taking continuous SC insulin injections and patients taking conventional intensified insulin therapy. In patients taking continuous SC insulin therapy compared to REG, the WMD in HbA_{1c} was -0.2 (95% CI, -0.3 to -0.1; P value not reported) and in patients taking intensified insulin therapy compared to REG, the WMD was -0.1% (95% CI, -0.1 to 0.0; P value not reported). In patients with type 2 diabetes, the WMD of HbA_{1c} was estimated to be 0.0% (95% CI, -0.1 to 0.0). None of the studies evaluating differences in HbA_{1c} between insulin analogs and REG showed significant differences (P values not reported). In children, adolescents, pregnant patients with type 1 diabetes, there were no significant reductions in HbA_{1c} (P values were not reported). The WMD in overall hypoglycemia in patients with type 1 diabetes was -0.2 (95% CI, -1.1 to 0.7; P value not reported) for insulin analogs compared to REG. In patients with type 2 diabetes, the WMD was -0.2 (95% CI, -0.5 to 0.1; P=0.8). There were also no significant differences in overall hypoglycemia in pre-pubertal children. There were no statistically significant differences in these three groups. However, in the event rate of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				overall hypoglycemia in adolescents per patient per 30 days was significantly reduced with insulin analogs compared to REG (P=0.02). The event rate in pregnant women was significantly higher with insulin analogs compared to REG (P<0.05). Secondary: Overall, frequency and type of adverse events were comparable for the two treatment groups (P values not reported).
Intermediate-Acting and Long-Acting Insulins: Type 1 Diabetes Mellitus				
Thalange et al.[48] (2015) Insulin degludec (IDeg) once-daily vs insulin detemir (IDet) once- or twice-daily both with prandial insulin aspart	MC, NI, OL, PG, RCT Children 1 to 17 years of age with type 1 diabetes who had been receiving insulin treatment (any regimen) for at least three months, without concomitant oral anti-diabetic drugs and with HbA_{1c} levels of ≤11%	N=350 26 weeks (followed by 26-week extension; n=280)	Primary: Change in HbA_{1c} after 26 weeks Secondary: FPG, safety	Primary: Non-inferiority of IDeg to IDet with respect to change in HbA_{1c} from baseline to week 26 was confirmed (estimated treatment difference, IDeg–IDet: 0.15%-points; 95% CI, -0.03 to 0.32). Secondary: At 52 weeks, HbA_{1c} was 7.9% (IDeg) vs 7.8% (IDet), change in mean FPG was −1.29 mmol/L (IDeg) vs 1.10 mmol/L (IDet) (estimated treatment difference, −1.62 mmol/L; P=0.0090), and mean basal insulin dose was 0.38 U/kg (IDeg) vs 0.55 U/kg (IDet). The majority of IDet treated patients (64%) required twice-daily administration to achieve glycemic targets. Hypoglycemia rates did not differ significantly between IDeg and IDet, but confirmed and severe hypoglycemia rates were numerically higher with IDeg (not significant) although nocturnal hypoglycemia rates were numerically lower (not significant). Rates of hyperglycemia with ketosis were significantly lower for IDeg vs IDet (0.7 vs 1.1 patient-years of exposure; P=0.0066). Both treatments were well tolerated with comparable rates of adverse events.
Davies et al.[49] (2015) Insulin degludec (IDeg) vs insulin detemir (IDet)	ES, OL, PG, RCT Patients with type 1 diabetes mellitus currently treated with any basal–bolus insulin regimen for ≥12 months prior to screening and with	N=370 1 year	Primary: Adverse events, hypoglycemia, immunogenicity, insulin dose and body weight Secondary: Not reported	Primary: After one year, IDeg provided a 33% lower rate of nocturnal hypoglycemia compared with IDet (estimated rate ratio [IDeg : IDet] 0.67; 95% CI, 0.51 to 0.88; P<0.05). IDeg improved HbA_{1c} after one year of treatment, similarly to IDet, but IDeg also provided a significantly greater reduction in fasting plasma glucose compared with IDet (estimated difference [IDeg − IDet], −1.11 mmol/l; 95% CI, −1.83 to −0.40; P<0.05). The rate of severe adverse events was 23 and 35 events per 100 patient-years of exposure in the IDeg and IDet treatment groups, respectively. Immunogenicity of IDeg, assayed by IDeg-specific antibodies and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
both with prandial insulin aspart	$HbA_{1c} \leq 10.0\%$ and BMI ≤ 35.0 kg/m^2			antibodies cross-reacting between IDeg and human insulin, was low throughout treatment. Body weight increased from baseline in both treatment arms, but the increase was greater in the IDeg compared with the IDet treatment arm (estimated difference, 1.07 kg; 95% CI, 0.47 to 1.67; P<0.05). Secondary: Not reported
Heller et al.[50] (2012) BEGIN: Basal-Bolus Type 1 study Insulin degludec QD (FlexPen®) plus insulin aspart with meals vs Insulin glargine QD (SoloStar®) plus insulin aspart with meals	MC, NI, OL, PG, RCT Patients ≥18 years of age with type 1 diabetes for at least one year with at least one year of prior basal-bolus insulin therapy, $HbA_{1c} \leq 10\%$, BMI ≤ 35 kg/m^2	N=629 52 weeks	Primary: Reduction in HbA_{1c} from base line at week 52 Secondary: Proportion of patients that achieved HbA_{1c} <7%, overall rate of hypoglycemia, rate of nocturnal hypoglycemia (week 16 to end)	Primary: After 52 weeks of treatment, HbA_{1c} was reduced by 0.40% (SE 0.03) in the insulin degludec group and 0.39% (SE 0.07) in the insulin glargine group, with an ETD of -0.01% (95% CI, -0.14 to 0.11; P<0.0001), thus showing non-inferiority of insulin degludec compared to basal-bolus therapy with insulin glargine plus insulin aspart. Secondary: There was no significant difference in the proportion of participants that achieved a target HbA_{1c} of <7% (40% and 43% for the degludec and glargine groups respectively; P=0.48). The number of confirmed episodes of hypoglycemia were similar in both the insulin degludec and insulin glargine groups (42.54 and 40.18 episodes per patient-year exposure, respectively) with a rate ratio of 1.07 (95% CI, 0.89 to 1.28; P=0.48). The number of confirmed episodes of nocturnal hypoglycemia from week 16 to 52 was significantly reduced in the insulin degludec group compared with the insulin glargine group (3.91 compared with 5.22 episodes per patient-year exposure, respectively) with a rate ratio of 0.73 (95% CI, 0.56 to 0.96; P=0.024).
Bode et al.[51] (2013) BEGIN: Basal-Bolus Type 1 study Insulin degludec QD (FlexPen®) plus	ES of a MC, NI, OL, PG, RCT (Heller et al) Patients ≥18 years of age with type 1 diabetes for at least	N=629 104 weeks	Primary: Reduction in HbA_{1c} from base line at week 104 Secondary:	Primary: After 104 weeks, the observed mean HbA_{1c} was reduced by 0.27%-points and 0.24% (full analysis set) and by 0.31% and 0.24% (extension trial set) with insulin degludec and insulin glargine, respectively. ETD was -0.04% (full analysis set) was not statistically significant (95% CI, -0.17 to 0.09, P value not reported)

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
insulin aspart with meals vs Insulin glargine QD (SoloStar®) plus insulin aspart with meals	one year with at least one year of prior basal-bolus insulin therapy, HbA_{1c} ≤10%, BMI ≤35 kg/m^2		Overall rate of hypoglycemia, rate of nocturnal hypoglycemia	Secondary: The rate of overall hypoglycemia was similar in both groups (P value not reported). The rate of nocturnal hypoglycemia was significantly lower with insulin degludec compared with insulin glargine (3.9 compared with 5.3 episodes per patient-year of exposure, respectively) with an estimated rate ratio of 0.75 (95% CI, 0.59 to 0.95; P=0.02).
Mathieu et al.[52] (2013) BEGIN: Flex Type 1 study Insulin degludec (FlexPen®) QD (forced- flex dosing) + insulin aspart with meals vs Insulin degludec (FlexPen®) QD (same-time dosing) + insulin aspart with meals vs Insulin glargine (SoloStar®) QD (same-time dosing) plus insulin aspart with meals	MC, NI, OL, PG, RCT Patients ≥18 years of age with type 1 diabetes current basal-bolus insulin therapy, HbA_{1c} ≤10%, BMI ≤35 kg/m^2	N=493 26 weeks	Primary: Change in HbA_{1c} from baseline to week 26 Secondary: FPG and SMPG profiles, overall hypoglycemia, nocturnal hypoglycemia	Primary: The mean decrease from baseline in HbA_{1c} was -0.40% in the degludec (forced-flex) group, -0.41% in the degludec (same-time) group, and -0.58% in the glargine (same-time) group. The ETD between the degludec (forced-flex) group and the glargine (same-time) group was 0.17% (95% CI, 0.04 to 0.30; no P value reported). ETD between the two degludec groups (forced-flex vs same-time) was 0.01% (95% CI, -0.13 to 0.14). The ETD between the degludec (same-time) and glargine (same-time) groups was not reported. Secondary: Laboratory-measured FPG decreased from baseline to week 26 by -1.28, -2.54, and -1.33 mmol/L in the degludec (forced-flex), degludec (same-time) and glargine (same time) groups, respectively. There was no significant difference in FPG when degludec (forced-flex) was compared with glargine (no P value reported). However, there was a significant difference in FPG in favor of degludec (same-time) when compared to degludec (forced-flex) with an ETD of 0.95 mmol/L (95% CI, 0.15 to 1.75; P=0.021). After 26 weeks, observed 9-point SMPG means appeared similar among groups. There was a significant difference in favor of insulin degludec (forced-flex) compared with the glargine group only at the “before lunch” time. The ETD was 0.85 mmol/L (95% CI, 0.12 to 1.57; P=0.022). The proportion of participants who attained prebreakfast SMPG target less than 5.0 mmol/L at week 26 was 11.3% (degludec forced-flex), 23.8% (degludec same-time), and 18.4% (glargine same-time).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Overall, confirmed and severe hypoglycemia rates were similar across groups at week 26 (no P values reported). There rates of nocturnal hypoglycemia were generally lower with insulin degludec forced-flex dosing (no P value reported).
Pieber et al.[53] (2007) Insulin detemir BID (AM and HS) and insulin aspart before meals vs insulin glargine at bedtime and insulin aspart before meals Insulin doses were titrated to achieve a target of ≤7.3 mmol/L for pre-breakfast and pre-evening meal plasma glucose for insulin detemir and pre-breakfast plasma glucose for insulin glargine.	OL, PG, RCT Men and women ≥18 years of age with type 1 diabetes for at least 1 year who had a BMI ≤35 kg/m^2 and HbA_{1c} 7.5 to 12.0%	N=322 26 weeks	Primary: Change in HbA_{1c}, change in FPG, hypoglycemia Secondary: Not reported	Primary: At 26 weeks, both groups had comparable changes in HbA_{1c} (between-treatment difference, -0.03; 95% CI, -0.25 to 0.19; P value not reported). However, insulin glargine resulted in significantly lower home measured FPG than insulin detemir (7.0 vs 7.7 mmol/L, respectively; P<0.001). The overall risk of hypoglycemia was comparable in both treatment groups (RR, 0.96; 95% CI, 0.68 to 1.35; P=0.811). However, insulin detemir resulted in lower rates of nocturnal hypoglycemia (episodes/subject-year) than with insulin glargine (4.3 vs 6.6, respectively; P<0.05). Secondary: Not reported
Heller et al.[54] (2009) Insulin detemir PM or BID (AM and PM) and insulin aspart before meals	MC, NI, OL, PG, RCT Patients ≥18 years of age with type 1 diabetes for ≥1 year who were receiving basal-bolus insulin	N=443 52 weeks	Primary: HbA_{1c} at 52 weeks Secondary: Proportion of patients achieving HbA_{1c} ≤7.0% with	Primary: Change in HbA_{1c} from baseline at 52 weeks was -0.53 and -0.54% with insulin detemir and insulin glargine, respectively (mean difference, 0.01%; 95% CI, -0.13 to 0.16), confirming non-inferiority. Patients receiving twice-daily insulin detemir experienced greater HbA_{1c} reduction (-0.58%) compared to those receiving once-daily insulin detemir (-0.49%; P value not reported).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs insulin glargine PM and insulin aspart before meals Basal insulin doses were titrated to achieve PG ≤108 mg/dL. Prandial insulin doses were titrated to achieve PPG ≤162 mg/dL.	regimen for ≥3 months with HbA_{1c} ≤11.0%		or without major hypoglycemia in the last month of treatment, FPG, within-patient variation in self-monitored pre-breakfast and pre-dinner blood glucose, 10-point self-monitored plasma glucose profiles and safety	Secondary: Similar percentage of patients achieved HbA_{1c} ≤7.0% with insulin detemir compared to insulin glargine (33.0 vs 30.4%; P value not significant). The HbA_{1c} goal was achieved without major hypoglycemia during the last month of treatment in 31.9 and 28.9% of patients in the insulin detemir and insulin glargine groups, respectively (P value NS). No significant differences were observed between the two groups with regard to changes in FPG, within-patient variation in self-monitored pre-breakfast and pre-dinner blood glucose and 10-point self-monitored plasma glucose profiles. During the study, 91.6% of patients in the insulin detemir group and 88.2% in the insulin glargine group met the criteria to switch from once- to twice-daily dosing. At the end of the study, 65.8 and 4.8% of patients in the insulin detemir and insulin glargine groups, respectively, were receiving BID dosing. The total basal insulin dose at the end of the study was 0.40 units/kg and 0.33 units/kg with insulin detemir and insulin glargine, respectively. There were no significant differences between the two groups with regard to weight gain and incidence of hypoglycemia. Adverse events were reported in 92.6 and 89.6% of patients in the insulin detemir and insulin glargine groups, respectively. Twelve and one serious adverse events were probably or possibly related to insulin detemir and insulin glargine, respectively. Injection site reactions were reported more frequently with insulin detemir compared to insulin glargine (8.0 vs 1.4%; P value not reported).
Vague et al.[55] (2003) Insulin detemir BID and insulin aspart before meals vs	MC, OL, PG, RCT Adult type 1 diabetes patients on a basal-bolus insulin regimen for ≥2 months; baseline HbA_{1c}	N=448 26 weeks	Primary: Effect on HbA_{1c}, FPG, variability in fasting self monitoring of blood glucose, weight gain, and	Primary: After six months, both insulin detemir and NPH reduced HbA_{1c} -0.55% (P value NS). After six months, FPG with insulin detemir (9.19 mmol/L) was comparable to NPH (9.94 mmol/L; P=0.097).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
NPH insulin BID and insulin aspart before meals Basal insulin doses were adjusted to achieve FBG 72 to 126 mg/dL and PPG <180 mg/dL.	8.18% for participants in the insulin detemir group and 8.11% for those randomized into the NPH group		frequency of hypoglycemia Secondary: Not reported	There was significantly less day-to-day fluctuation of fasting self monitoring of blood glucose profiles with insulin detemir when compared to NPH (P<0.001). Body weight change from baseline was significantly lower with insulin detemir (-0.2 kg) compared to NPH (0.7 kg; P<0.001). The RR of hypoglycemia was 22% lower with insulin detemir compared to NPH (P<0.05). The RR of nocturnal hypoglycemia was 34% lower with insulin detemir compared to NPH (P<0.005). Secondary: Not reported
Hermansen et al.[56] (2004) Insulin detemir BID and insulin aspart before meals vs NPH insulin BID and insulin aspart before meals	OL, RCT Adult type 1 diabetes patients on a basal-bolus insulin regimen for ≥6 months, baseline HbA_{1c} 8.48% for participants in the insulin detemir group and 8.29% for those randomized into the NPH group	N=595 18 weeks	Primary: Effect on HbA_{1c}, FPG, self monitoring of blood glucose profile, weight gain, and frequency of hypoglycemia Secondary: Not reported	Primary: After 18 weeks, HbA_{1c} was significantly lower in the insulin detemir group (7.88%) compared to the NPH group (8.11%; P<0.001). After 18 weeks, there was no significant difference in FPG with insulin detemir (7.58 mmol/L) compared to NPH (8.10 mmol/L; P>0.05). There was significantly less day-to-day fluctuation of self monitoring of blood glucose profiles with insulin detemir when compared to NPH (P<0.05). Body weight change from baseline was significantly lower with insulin detemir (-0.95 kg) compared to NPH (0.07 kg; P<0.001). The risk of hypoglycemia was 21% lower with insulin detemir compared to NPH (P=0.036). The risk of nocturnal hypoglycemia was 55% lower with insulin detemir compared to NPH (P<0.001). Secondary: Not reported
Home et al.[57] (2004)	MC, OL, PG, RCT Men and women >18 years of age	N=409 16 weeks	Primary: Change in HbA_{1c}, change in FPG from baseline	Primary: At 16 weeks, there was no significant difference in HbA_{1c} between all treatment groups (P=0.082). Insulin detemir every 12 hours had a reduction in HbA_{1c} of -0.85%. When dosed every morning and at

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Insulin detemir every morning (QAM) and at bedtime plus premeal insulin aspart vs insulin detemir every 12 hours (Q12H) plus premeal insulin aspart vs NPH insulin BID plus premeal insulin aspart Doses were titrated to achieve target FPG goals 4.0 to 7.0 mmol/L and PPG goals ≤10 mmol/L.	with type 1 diabetes for >1 year already on mealtime plus basal insulin for >2 months, with a basal dose <100 IU/day, HbA_{1c} ≤12.0%, BMI ≤35.5 kg/m^2		Secondary: 10-point self monitoring of blood glucose, frequency of hypoglycemia, weight gain	bedtime, HbA_{1c} was reduced by -0.82%, whereas, NPH only reduced HbA_{1c} by -0.65%. In combination, both detemir groups resulted in significantly greater reductions in HbA_{1c} than NPH (difference, -0.18%; 95% CI, -0.34 to -0.02; P=0.027). FPG levels were statistically significantly lower in both the detemir every 12 hours (P=0.004) and detemir every morning and at bedtime group (P<0.001) than the NPH group. Differences between the detemir groups did not result in statistical significance. Secondary: Overall 10-point self monitoring of blood glucose profiles were comparable between the three treatment groups (P>0.05). The overall risk of hypoglycemia was significantly lower with insulin detemir every 12 hours (25%; P=0.046) and insulin detemir every morning and at bedtime (32%; P=0.002) compared to NPH. There were no significant differences in risk of nocturnal hypoglycemia between insulin detemir every 12 hours and NPH. However, when dosed every morning and at bedtime, insulin detemir had a significantly lower risk of nocturnal hypoglycemia than NPH (53%; P<0.001). Mean weight change was significantly decreased with insulin detemir every 12 hours (-0.8 kg; P=0.006) and insulin detemir every morning and at bedtime (-0.6 kg; P=0.040) when compared to NPH. However, there was no significant difference in weight change between the insulin detemir groups (P>0.05).
Russell-Jones et al.[58] (2004) Insulin detemir HS and regular insulin before meals vs	MC, OL, PG, RCT Men and women ≥18 years of age with type 1 diabetes for ≥1 year already on basal or premixed insulin QD in the	N=749 6 months	Primary: Change in HbA_{1c} from baseline, change in FPG and fasting self monitoring of blood glucose, nine-point self monitoring of	Primary: Mean HbA_{1c} value decreased by -0.06% with insulin detemir while HbA_{1c} increased by 0.06% with NPH. However, the baseline-adjusted mean HbA_{1c} values did not significantly differ between groups (-0.12%; 95% CI, -0.25 to 0.02; P=0.083). Both FPG and fasting self monitoring of blood glucose decreased similarly in the insulin detemir group and were slightly decreased with

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
NPH insulin HS and regular insulin before meals Doses were titrated to achieve target FPG goal 72 to 126 mg/dL and PPG goal of 180 mg/dL.	evening (5 PM to 11 PM) and REG before meals for ≥2 months and HbA_{1c} ≤12.0%		blood glucose profile, 24-hour continuous blood glucose monitoring, hypoglycemia, body weight Secondary: Not reported	NPH. Both endpoints resulted in significant reductions with insulin detemir in comparison to NPH (P=0.001 and P<0.001, respectively). Nine-point self monitoring of blood glucose profiles demonstrated significantly lower glucose values before breakfast with insulin detemir when compared to NPH (P<0.001). In study participants that underwent 24-hour continuous blood glucose monitoring, insulin detemir had significantly less blood glucose fluctuations for mean levels nocturnally and over 24 hours (P<0.05). Overall rates of hypoglycemia were comparable between groups. However, the RR of nocturnal hypoglycemia was 26% lower with insulin detemir compared to NPH (P=0.003). There was also a 30% risk reduction of minor hypoglycemic episodes during the night with insulin detemir (P=0.003). Body weight gain was significantly lower with insulin detemir compared to NPH (-0.54 kg; P=0.024). Secondary: Not reported
Standl et al.[59] (2004) Insulin detemir BID and regular insulin before meals vs NPH insulin BID and regular insulin before meals Basal insulin doses were adjusted to	ES, MC, OL, PG, RCT Adult patients with type 1 diabetes on a basal-bolus insulin regimen for ≥2 months, baseline HbA_{1c} 7.72% for participants taking insulin detemir and 7.66% for those randomized into the NPH group	N=421 (n=289 in the 6 month extension trial) 12 months (6-month treatment period and 6-month extension trial)	Primary: Effect on HbA_{1c}, FPG, nine-point self monitoring of blood glucose profile, weight gain, and frequency of hypoglycemia Secondary: Not reported	Primary: After 12 months, HbA_{1c} was comparable between the insulin detemir group (7.88%) and the NPH group (7.78%; P=0.288). After 12 months, there was no significant difference in FPG with insulin detemir (10.1 mmol/L) compared to NPH (9.84 mmol/L; P=0.665). Mean nine-point self monitoring of blood glucose profiles showed significantly lower blood glucose 90-minutes after lunch and dinner (P<0.05). There were no significant differences at other times in the profile. After 12 months, body weight change from baseline was significantly lower with insulin detemir (-1.44 kg) compared to NPH (0.3 kg; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
achieve FPG 4.0 to 7.0 mmol/L (72 to 126 mg/dL) and PPG <10 mmol/L (180 mg/dL).				There was no significant difference in the overall risk of hypoglycemia between insulin detemir and NPH (P=0.139). There was no significant difference in the risk of nocturnal hypoglycemia between insulin detemir and NPH (P=0.067). Secondary: Not reported
De Leeuw et al.[60] (2005) Insulin detemir BID and insulin aspart before meals vs NPH insulin BID and insulin aspart before meals Basal insulin doses were adjusted to achieve FBG 72 to 126 mg/dL and PPG <180 mg/dL.	ES, MC, OL, PG, RCT Adult type 1 diabetes patients on a basal-bolus insulin regimen for ≥2 months, baseline HbA_{1c} 8.18% for participants in the insulin detemir group and 8.03% for those randomized into the NPH group	N=316 12 months (6-month treatment period and 6-month extension period)	Primary: Effect on HbA_{1c}, FPG, nine-point self monitoring of blood glucose, frequency of hypoglycemia, and weight gain Secondary: Not reported	Primary: Similar reductions in mean HbA_{1c} values were observed in both treatment groups. After 12 months, insulin detemir reduced HbA_{1c} -0.64% and NPH reduced HbA_{1c} -0.56% (P value was not reported). After 12 months, FPG with insulin detemir (10.7 mmol/L) was comparable to NPH (10.8 mmol/L; P value not reported). Nine-point self monitoring of blood glucose profiles were comparable between insulin detemir when compared to NPH (value not reported; P<0.24). There were no significant differences in overall rates of hypoglycemia between treatment groups. The RR of nocturnal hypoglycemia was 32% lower with insulin detemir when compared to NPH (P=0.016). After 12 months, body weight gain was significantly lower with insulin detemir compared to NPH (-1.34 kg; P<0.001). Secondary: Not reported
Pieber et al.[61] (2005) Insulin detemir BID (AM and PM) and insulin aspart before meals	MC, OL, PG, RCT Adult type 1 diabetes patients on a basal-bolus insulin regimen for ≥2 months; baseline HbA_{1c}	N=400 16 weeks	Primary: Effect on HbA_{1c} and FPG Secondary: Variability in fasting self monitoring of	Primary: HbA_{1c} was significantly reduced in all three groups. Insulin detemir dosed in the morning and at dinner reduced HbA_{1c} -0.43%. When dosed in the morning and at bedtime, HbA_{1c} was reduced -0.49%. NPH reduced HbA_{1c} -0.39%. There was no significant difference between the groups (P=0.64). FPG reductions were significantly greater with insulin detemir dosed in the morning and dinner (-0.17 mmol/L; P<0.001) and insulin detemir

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs insulin detemir BID (AM and HS) and insulin aspart before meals vs NPH insulin BID (AM and HS) and insulin aspart before meals Basal insulin doses were adjusted to achieve FBG 72 to 126 mg/dL and PPG <180 mg/dL.	8.01% for participants taking insulin detemir every morning and at dinner, 8.13% for those taking insulin detemir every morning and at bedtime, and 8.08% for those randomized into the NPH group		blood glucose, 10-point self monitoring of blood glucose, 24-hour glucose profile, frequency of hypoglycemia, and weight gain	dosed in the morning and bedtime (-1.48 mmol/L; P<0.006) when compared to NPH (0.49 mmol/L). There was no significant difference in FPG between the insulin detemir groups (P=0.15). Secondary: Within-person variation in fasting self monitoring of blood glucose was significantly lower with either insulin detemir treatments compared to NPH (P<0.001). There was no significant difference in fasting self monitoring of blood glucose between the insulin detemir groups (P=0.48). Overall 10-point self monitoring of blood glucose profiles were comparable between the three groups (P=0.103). Twenty four-hour glucose profiles demonstrated lower glucose fluctuations with both insulin detemir treatments compared to NPH (P=0.049). Overall and nocturnal rates of hypoglycemia were comparable between all groups. Mean weight changes were significantly different with detemir dosed in the morning and dinner (-0.6 kg; P<0.001) and insulin detemir dosed in the morning and bedtime (0.1 kg; P=0.050) when compared to NPH (0.7 kg).
Kølendorf et al.[62] (2006) Insulin detemir BID and insulin aspart before meals for 16 weeks vs NPH insulin BID and insulin aspart	OL, RCT, XO Adult type 1 diabetes patients on a basal-bolus insulin regimen for >4 months, baseline HbA_{1c} 7.9% for participants receiving insulin detemir first and	N=130 32 weeks	Primary: Incidence of self-recorded hypoglycemia Secondary: Incidence of severe hypoglycemic episodes, effect on HbA_{1c} and self monitoring plasma glucose	Primary: The RR of hypoglycemia was 18% lower with insulin detemir compared to NPH (P=0.001). The RR of nocturnal hypoglycemia was 50% lower with insulin detemir compared to NPH (P<0.0001). Secondary: There were 19 severe hypoglycemic episodes with insulin detemir and 33 episodes with NPH; however, due to the low number of episodes an analysis could not be conducted. HbA_{1c} was reduced by approximately -0.3% in both treatment arms (P value was not reported).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
before meals for 16 weeks	7.9% for those receiving NPH first			There was significantly less day-to-day fluctuation of self-monitored plasma glucose profiles with insulin detemir when compared to NPH (P<0.001).
Robertson et al.[63] (2007) Insulin detemir HS or BID (AM and HS) and insulin aspart before meals vs NPH insulin QD or BID and insulin aspart before meals Insulin aspart doses were titrated to achieve PPG 121 to 182 mg/dL.	OL, PG, RCT Children 6 to 17 years of age with type 1 diabetes, treated with insulin for at least 12 months (total daily dose ≤2 U/kg), and HbA_{1c} ≤12.0%	N=347 26 weeks	Primary: HbA_{1c} and eight-point plasma glucose profiles assessed at 18 and 26 weeks, self-measured FPG on four days after 18 and 26 weeks Secondary: Hypoglycemia	Primary: HbA_{1c} at 26 weeks decreased by approximately -0.8% in both the insulin detemir and NPH groups (8.0 vs 7.9%, respectively; 95% CI, -0.1 to 0.3; P value not reported). The mean eight-point plasma glucose profiles after 26 weeks were assumed parallel and did not have a statistically significant difference between insulin detemir and NPH (P=0.302). Plasma glucose levels were lower with insulin detemir than NPH at all time points except at 03.00 hour. However, the analysis of self-measured nocturnal plasma glucose at 03.00 hour did not show a statistical difference between treatments (P=0.194). Mean self-measured FPG after 26 weeks was lower with insulin detemir than with NPH (P=0.022). Within-subject FPG variation also showed lower FPG levels with insulin detemir than NPH (P<0.001). Secondary: The study determined that the risk of having nocturnal hypoglycemia was 26% lower with insulin detemir (P=0.041). However, the risks of 24-hour and diurnal hypoglycemia were similar in both groups (P=0.351 and P=0.492, respectively). Also, the risks of having severe episodes, confirmed episodes or symptoms of hypoglycemia were similar in both groups (P=0.799, P=0.275, and P=0.425, respectively).
Bartley et al.[64] (2008) Insulin detemir PM or BID and insulin aspart before meals vs	OL, PG, RCT Patients ≥18 years of age with type 1 diabetes, HbA_{1c} ≤11.0%, BMI ≤35.0 kg/m^2, and receiving a basal-bolus insulin regimen ≥3 months	N=497 24 months	Primary: Change in baseline HbA_{1c} Secondary: Change in baseline FPG, proportion of patients achieving HbA_{1c} ≤7.0% without	Primary: Insulin detemir resulted in significantly greater decreases in HbA_{1c} compared to NPH (final HbA_{1c}, 7.36 vs 7.50%; decrease, -0.94 vs -0.72%; difference, -0.22%; 95% CI, -0.41 to -0.03). Secondary: Insulin detemir significantly decreased FPG compared to NPH (final FPG, 8.35 vs 9.43 mmol/L; P=0.019).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
NPH insulin PM or BID and insulin aspart before meals Insulin doses were titrated to achieve plasma glucose target ≤6.0 mmol/l before breakfast and dinner.			hypoglycemia, incidence in hypoglycemia, change in baseline body weight, safety	Significantly more patients receiving insulin detemir achieved HbA_{1c} ≤7.0% without hypoglycemia compared to patients receiving NPH (22 vs 13%; P=0.019). The risk of major and nocturnal hypoglycemia was significantly lower with insulin detemir (P<0.001). Specifically, insulin detemir was associated with a 69 and 49% lower risk of major and nocturnal hypoglycemia. Insulin detemir resulted in significantly less weight gain compared to NPH (1.7 vs 2.7 kg; P=0.024). The overall safety prolife was similar between the two treatments. Four deaths were reported with insulin detemir (cardiorespiratory arrest in relation to status epilepticus, sudden death, bronchopneumonia, and MI following surgery). All events were judged to not be related to insulin detemir. Withdrawals due to adverse events were more common with insulin detemir.
Blevins et al.[65] (2015) ELEMENT 1 LY2963016 insulin glargine (Basaglar®; biosimilar to Lantus®) vs insulin glargine (Lantus®)	OL, MC, RCT Patients with type 1 diabetes (HbA_{1c} ≤11%) being treated with basal (once-daily) and bolus insulin	N=535 52 weeks	Primary: Change in HbA_{1c} from baseline to 24 weeks Secondary: Proportion of patients reaching HbA_{1c} <7%, daily mean blood glucose, insulin dose, hypoglycemia, weight change	Primary: Both treatment groups had similar and significant (P<0.001) within-group decreases in mean HbA_{1c} values from baseline. LY2963016 met the non-inferiority criteria compared with Lantus® for change in HbA_{1c} from baseline to 24 weeks (−0.35 vs −0.46%; least-squares mean difference, 0.108%; 95% CI, −0.002 to 0.219; P>0.05). Secondary: There were no significant (P>0.05) treatment differences in other efficacy measures, including proportion of patients reaching HbA_{1c} <7%, daily mean blood glucose, and insulin dose at 24 and 52 weeks. At 52 weeks, similar findings were observed between LY2963016 and Lantus® for safety outcomes, including adverse events, allergic reactions, hypoglycemia, weight change and insulin antibodies.
Ratner et al.[66] (2000) Insulin glargine HS	PG, RCT Type 1 diabetes patients, baseline	N=534 28 weeks	Primary: Effect on HbA_{1c}, FPG, and incidence of hypoglycemia	Primary: Reduction in HbA_{1c} was similar with NPH (-0.21%) and insulin glargine (-0.16%; P=0.4408).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs NPH insulin HS or BID (AM and HS) Doses of both insulins were titrated to achieve preprandial blood glucose 4.4 to 6.7 mmol/L.	HbA_{1c} 7.7% in both groups		Secondary: Not reported	Reduction in FPG was similar with NPH (-0.94 mmol/L) and insulin glargine (-1.12 mmol/L; P=0.3546). After the one month titration phase, significantly less patients on insulin glargine reported symptomatic hypoglycemia (39.9 vs 49.2%; P=0.0219) or nocturnal hypoglycemia (18.2 vs 27.1%; P=0.0116). Overall incidence of all symptomatic hypoglycemia was similar between treatment groups throughout the study. Secondary: Not reported
Tan et al.[67] (2004) Analysis was on data 6 months prior to initiating insulin glargine therapy and data 6 months after initiating insulin glargine therapy. Patients were divided into those taking insulin glargine only and those taking insulin glargine plus NPH insulin in the AM.	RETRO Patients ≤18 years of age with type 1 diabetes when initiating insulin glargine therapy between June 1, 2001 and June 30, 2002, not using continuous SC insulin infusion or inhaled insulin before starting insulin glargine therapy	N=71 12 months	Primary: Change in HbA_{1c}, blood glucose concentrations, hypoglycemia (number of self-reported symptomatic hypoglycemia and number of blood glucose readings <50 mg/dL) Secondary: Not reported	Primary: There was no difference in HbA_{1c} between baseline and six months after initiating insulin glargine therapy (8.9±1.6% and 8.9±1.5%, respectively). In the divided groups, there was no statistical difference in the change in HbA_{1c} between patients taking insulin glargine only vs patients taking insulin glargine plus NPH (P value not reported). Mean blood glucose concentrations decreased slightly after initiating insulin glargine in all subjects. Patients taking insulin glargine plus NPH had slight improvements in average blood glucose levels, whereas patients taking insulin glargine only had a slight deterioration and a slight rise in average blood glucose levels. All changes were not statistically significant (P values not reported). There was a decrease in self-reported episodes of symptomatic hypoglycemia after initiating insulin glargine therapy. However, there was no difference between baseline and after starting insulin glargine therapy in the frequency of blood glucose values <50 mg/dL (P value not reported). Secondary: Not reported
Ashwell et al.[68] (2006)	MC, RCT, 2-way, XO	N=56 32 weeks	Primary: HbA_{1c} at treatment endpoints	Primary: At 16 weeks, HbA_{1c} was lower with insulin glargine compared to NPH (between treatment difference, -0.5; 95% CI, -0.7 to -0.3; P<0.001).

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Insulin glargine HS and insulin lispro before meals for 16 weeks vs NPH insulin QD or BID and regular insulin before meals for 16 weeks Doses were adjusted to achieve target pre-breakfast, preprandial, and postprandial levels of 4.0 to 6.5 mmol/L, in the absence of hypoglycemia.	Patients aged 18 to 65 years of age with type 1 diabetes, no previous experience with insulin glargine, previously on a multiple insulin injection regimen for at least 1 year, random C-peptide ≤0.10 nmol/L, HbA_{1c} 7.0 to 9.5%		Secondary: Prebreakfast self monitoring of blood glucose concentration, 24-hour eight-point self monitoring of blood glucose levels, 24-hour inpatient plasma glucose levels, monthly rate of hypoglycemia	Secondary: Prebreakfast self monitoring of blood glucose concentration was lower in the insulin glargine group than the NPH group (between treatment difference, -1.5; 95% CI, -2.6 to -0.5; P<0.005). Self monitoring of blood glucose concentrations were lower before and after breakfast with insulin glargine compared to NPH. The 24-hour eight-point self monitoring of blood glucose concentrations was also lower with insulin glargine (between treatment difference, -1.9; 95% CI, -3.1 to -0.8; P=0.001). During the inpatient assessment, 24-hour eight-point self monitoring of blood glucose levels were lower at all points with insulin glargine compared to NPH (P=0.037 for plasma glucose AUC; P=0.002 for PPG AUC; P=0.038 for plasma glucose before breakfast). Seventy-two percent of patients taking insulin glargine reported nocturnal hypoglycemia compared to 83% of patients taking NPH. This resulted in a -44% reduction in the monthly rate of nocturnal hypoglycemia with insulin glargine compared to NPH (P<0.001).
Herwig et al.[69] (2007) Insulin glargine QD and regular insulin or insulin lispro before meals vs NPH insulin QD to TID and regular insulin or insulin lispro before meals Doses of insulin glargine were	OL Pediatric patients with type 1 diabetes for >1 year duration	N=142 20±10 months	Primary: HbA_{1c}, hypoglycemia Secondary: Not reported	Primary: HbA_{1c} significantly increased from 7.3±1.0% to 7.6±1.1% (P=0.003) and from 7.7±1.6% to 8.3±1.5% (P=0.0001) in both the insulin glargine and NPH groups. The incidence of symptomatic hypoglycemia was comparable between both groups; however, the overall incidence of severe hypoglycemia was significantly lower in the insulin glargine group (P=0.002). Secondary: Not reported

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titrated to achieve target FBG 4.4 to 7.8 mmol/L and doses of NPH insulin were titrated to achieve target FBG 4.4 to 8.9 mmol/L.				
Kudva et al.[70] (2007) Insulin glargine and insulin aspart before meals vs ultralente insulin and insulin aspart before meals	RCT, XO Patients with median age of 43 years with type 1 diabetes	N=22 16 weeks	Primary: Hypoglycemia Secondary: Not reported	Primary: Measures of glycemic variation did not differ significantly between insulin glargine and ultralente insulin. In the insulin glargine group, the standard deviation of blood glucose showed a tendency to be lower and the standard deviation of nocturnal blood glucose concentrations was significantly lower. However, glucose concentrations were significantly lower during the one hour before and three hours after lunch with ultralente insulin. Secondary: Not reported
Chatterjee et al.[71] (2007) Insulin glargine QD and insulin aspart before meals for 16 weeks vs NPH insulin BID and insulin aspart before meals for 16 weeks	OL, RCT, XO Patients 18 to 75 years of age with type 1 diabetes for at least 6 months on either BID or multiple dose insulin injections, BMI <45 kg/m^2, HbA_{1c} 6.0 to 11.0%	N=60 36 weeks	Primary: Change in HbA_{1c} Secondary: Frequency of overall hypoglycemic episodes, change in FPG, body weight, lipid profile	Primary: At 36 weeks, treatment with insulin glargine resulted in lower HbA_{1c} levels compared to NPH (between-treatment difference, -0.19±0.09; 95% CI, -0.36 to 0.01; P=0.04). At the end of the second treatment period, those patients switching from glargine to NPH experienced an increase in HbA_{1c} of 0.16%, whereas those who switched from NPH to glargine experienced a reduction of -0.1%. Secondary: Both groups had similar mean incidences of overall hypoglycemic episodes (between-treatment difference, 1.21; 95% CI, 0.56 to 2.64; P=0.63). The OR for the incidence of hypoglycemia compared in both groups was 1.2 (95% CI, 0.55 to 2.59; P value not reported). FPG was also lower with insulin glargine vs NPH (between-treatment difference, -3.00; 95% CI, -4.80 to -1.20; P<0.01).

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				There was no significant difference in change in body weight between both groups (mean difference, -0.24; 95% CI, -0.87 to 0.39; P=0.45). Similarly, there was no difference in TC or TG levels between groups (P value not reported).
Manini et al.[72] (2007) Insulin glargine vs intensive insulin treatment (NPH)	RCT Patients with a mean age of 46 years with type 1 diabetes for at least 1 year duration and suboptimal glucose control under intensive insulin treatment	N=47 8 months	Primary: Change in HbA_{1c}, health-related quality of life Secondary: Not reported	Primary: Insulin glargine resulted in a mean HbA_{1c} decrease of -0.7% from baseline (P<0.0001). Insulin glargine also resulted in improved health-related quality of life scores using a Well-being Enquiry for Diabetics questionnaire. The results showed improvements in discomfort (P=0.020), impact (P=0.0002), and total score (P=0.0005). The questionnaire score changes were also associated with a lower perceived risk of hypoglycemia and fewer daily-life associated issues with insulin glargine. Secondary: Not reported
Rosenstock et al.[73] (2000) Insulin glargine HS (containing 30 µg/mL zinc chloride) vs insulin glargine HS (containing 80 µg/mL zinc chloride) vs NPH insulin HS or BID	DB, MC, PG, RCT Patients with type 1 diabetes on basal-bolus multiple daily insulin regimen for at least 2 months, 18 to 70 years of age, had BMI 18 to 28 kg/m^2, HbA_{1c} <10.0%, postprandial serum C-peptide <0.2 pmol/mL	N=256 4 weeks	Primary: FPG at study end point calculated as the mean of three FPG values on days 27, 28 and 29 Secondary: Change from baseline in overnight plasma glucose, mean FPG, blood glucose profile, nocturnal blood glucose, stability of FPG, $HbA_{1c,}$ safety and adverse events	Primary: Adjusted mean FPG at end point was 9.2 mmol/L for the pooled insulin glargine groups and 11.3 mmol/L for the NPH group (P=0.001). Secondary: The adjusted mean overnight plasma glucose levels after 5 AM were 7.8 mmol/L for insulin glargine 30, 7.3 mmol/L for insulin glargine 80, and 10.7 mmol/L for NPH (P values not reported). At the end of the study, the mean standard deviations for FPG were 7.6±2.3 and 7.5±1.9 mmol/L for the insulin glargine 30 and insulin glargine 80 groups, respectively, and 9.0±2.4 mmol/L for the NPH group (P<0.001). Blood glucose profile determined from seven self monitoring of blood glucose values during the day was not different among the treatment group (P value not reported). Nocturnal blood glucose measured by self monitoring of blood glucose at 3 AM was higher in the insulin glargine group than in the NPH group (P value not reported).

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				Stability of FPG was significantly lower in patients receiving insulin glargine 30 compared to patients receiving NPH (P<0.05). The mean standard deviation for HbA_{1c} levels were -0.40±0.48 and -0.40±-0.49 in the insulin glargine 30 and insulin glargine 80 groups, respectively, and -0.40±0.48 in the NPH group (P value not reported). Fewer patients receiving NPH (93.2%) reported a hypoglycemic episode than patients receiving insulin glargine (97.6 and 100% for insulin glargine 30 and insulin glargine 80, respectively; P=0.03). All events were considered mild and none resulted in discontinuation from study treatment. Insulin glargine was as safe as NPH with no differences between treatments with regard to the incidence of adverse effects, including the most frequent event, injection site reactions.
Rossetti et al.[74] (2003) Insulin glargine PM and insulin lispro before meals vs insulin glargine HS and insulin lispro before meals vs NPH insulin QD and insulin lispro before meals Glycemic targets were blood glucose	RCT Patients with type 1 diabetes and fasting plasma C-peptide ≤0.15 nmol/L on intensified treatment with multiple daily combinations of lispro and NPH at each meal and NPH at bedtime	N=51 12 weeks	Primary: HbA_{1c} level Secondary: Blood glucose profile from home blood glucose monitoring, hypoglycemia	Primary: In patients taking NPH, HbA_{1c} increased slightly from baseline, but was not statistically significant. However, HbA_{1c} decreased both with the dinnertime as well as the bedtime dose of insulin glargine (P<0.04). There was no significant difference in the change of HbA_{1c} in both insulin glargine groups (P value NS). Secondary: Patients taking insulin glargine had lower blood glucose concentrations in the fasting state, after breakfast, before lunch, and after lunch (P<0.05). The before-dinner blood glucose with NPH and insulin glargine at dinnertime was similar (P value NS), but was lower with insulin glargine at bedtime (P<0.05). The after-dinner blood glucose was lower with insulin glargine at dinner-time and bedtime than with NPH (P<0.05). However, the bedtime blood glucose was not different with all three treatment groups (P value NS). The frequency of mild hypoglycemia was lower in patients taking insulin glargine than in patients taking NPH (P<0.005). There was no difference between the insulin glargine at dinnertime and insulin glargine at bedtime groups (P value NS). Patients taking insulin glargine had a lower frequency

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6.4 to 7.2 mmol/L in the fasting state, before meals, and at bedtime and blood glucose at 8.0 to 9.2 mmol/L 90 minutes after meals.				of nocturnal hypoglycemic episodes than patients taking NPH (P<0.05). There were no differences between both insulin glargine groups (P value NS).
Home et al.[75] (2015) EDITION 4 Insulin glargine U-300 QAM vs Insulin glargine U-300 QPM vs insulin glargine U-100 QAM vs insulin glargine U-100 QPM Mealtime insulin was continued and dose adjustments of basal insulin were made weekly.	MC, PG, RCT Patients ≥18 years of age with a diagnosis of type 1 diabetes for at least one year, use of any mealtime insulin analog for ≥3 months	N=549 6 months	Primary: HbA_{1c} change from baseline to month six Secondary: Percentage of participants attaining HbA_{1c} <7.0%, self-measured plasma glucose, hypoglycemia	Primary: The change in HbA_{1c} (primary end point; baseline 8.1%) was equivalent in the two treatment groups (difference, 0.04%; 95% CI, -0.10 to 0.19), and Gla-300 was thus noninferior. Similar results with wider 95% CIs were found for morning and evening injection times and for prebreakfast self-measured plasma glucose overall. Secondary: A similar percentage of participants in each overall group achieved HbA_{1c} <7.0% at month 6, 16.8% for Gla-300 and 15.0% for Gla-100. No relevant differences were observed in the change from baseline to month six in preinjection or within-participant variability of preinjection self-measured plasma glucose and the average of the 8-point self-measured plasma glucose estimations. Over six months, 255 people (93%) in the Gla-300 group had one or more confirmed (≤70 mg/dL) or severe hypoglycemic events compared with 257 (94%) in the Gla-100 group. For nocturnal hypoglycemia, this was 188 (69%) and 193 (70%) of study participants.
Pesić et al.[76] (2007)	RCT	N=48	Primary:	Primary:

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Insulin glargine QD and insulin aspart before meals vs NPH insulin HS and insulin aspart before meals vs NPH insulin BID and insulin aspart before meals	Patients with type 1 diabetes on long-term conventional insulin therapy	12 weeks	Change in FPG, change in HbA_{1c} Secondary: Frequency of hypoglycemia	FPG was lower in the glargine group in comparison to the NPH BID group (7.30 vs 7.47 mmol/L, respectively), but this difference was not significant. FPG levels for the NPH-at-bedtime group were reported as significantly higher compared to either of the other two groups (8.44 mmol/L; P<0.05). At 12 weeks, HbA_{1c} decreased in both the NPH BID (from 7.80±0.83% to 7.01±0.63%) and insulin glargine groups (from 7.72±0.86% to 6.87±0.50%). However, there was no change in HbA_{1c} in the NPH-at-bedtime group. Secondary: A lower frequency of mild hypoglycemic episodes was observed in the insulin glargine group compared to both NPH groups (P<0.05).
Dundar et al.[77] (2009) NPH QD vs insulin detemir QD vs insulin glargine QD All patients received NPH insulin for ≥6 months before transitioning to either insulin detemir or insulin	RETRO, XO Pediatric and adolescent patients with a mean age of 12.7±3.4 years, with type 1 diabetes for 5.4±3.0 years who were receiving NPH insulin daily and insulin aspart three times daily for ≥6 months	N=34 12 months (6 months of NPH, followed by 6 months of insulin detemir or insulin glargine)	Primary: Mean total daily insulin dose, mean FPG, numbers of severe and nocturnal hypoglycemia, mean HbA_{1c}, BMI SDS and safety Secondary: Not reported	Primary: Total daily insulin doses were similar among all three insulin groups (P>0.05 for all comparisons). No significant difference was seen in mean FPG between NPH and both long-acting insulins combined (P>0.05). Incidence of severe hypoglycemia with NPH was similar compared to insulin detemir and insulin glargine (P>0.05). Eight episodes of nocturnal hypoglycemia was reported in four patients during NPH treatment compared to three episodes reported in three patients in both long-acting insulin groups combined (P>0.05). Mean HbA_{1c} was significantly lower with insulin glargine and insulin detemir compared to NPH (P<0.05 for both). No significant difference was seen between insulin glargine and insulin detemir. The increase in BMI SDS was significantly lower with insulin detemir compared to the increase seen with NPH and insulin glargine (P<0.05 for both). No difference was noted between NPH and insulin glargine.

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glargine at a dose that was 40 to 45% of total daily NPH insulin dose, in addition to insulin aspart TID at the same doses.				No adverse events were reported during treatment with insulin glargine and insulin detemir. Secondary: Not reported
Chase et al.[78] (2008) Insulin glargine AM and insulin lispro before meals vs NPH or Lente insulin BID (AM and PM) and insulin lispro before meals Basal insulin doses were titrated to achieve FPG 70 to 100 mg/dL.	AC, OL, PG, RCT Patients 9 to 17 years of age with type 1 diabetes with HbA_{1c} ≥7.0 to ≤9.5%, and receiving any daily insulin regimen consisting of ≥2 injections or a continuous infusion	N=175 24 weeks	Primary: Change in baseline HbA_{1c} Secondary: Incidence of hypoglycemia, safety	Primary: There was no difference in the decrease in HbA_{1c} with insulin glargine (-0.25%) and NHP (0.05%; P=0.1725). However, it was reported that the decrease in HbA_{1c} was significantly greater with insulin glargine in patients with higher baseline HbA_{1c}. Secondary: The incidence of hypoglycemia was significantly higher with insulin glargine (P=0.0298). There was no difference in the incidence of severe hypoglycemia between the two treatments. Both treatments were well tolerated and there was no difference in the rate of overall adverse events between them (P=0.1944). Metabolism and nutrition disorders (e.g., hypoglycemia, hyperglycemia, etc) were the most commonly reported treatment-emergent adverse events, and these occurred with comparable frequency between the two treatments (11.8 vs 5.6%; P=0.1803). Significantly more serious adverse events were reported with insulin glargine (P=0.0164).
Ahern et al.[79] (2002) Insulin pump therapy containing basal insulin The total patient population was stratified based on age: 1 to 6 years, 7 to	PRO Patients ≤18 years of age with type 1 diabetes, followed in children's diabetes clinic for at least 1 year prior to start of pump therapy, previously on a 2 to 3	N=161 Average of 32±9 months	Primary: HbA_{1c}, diabetes-related adverse events Secondary: Not reported	Primary: Patients in all three groups had good diabetes control prior to study start. However, HbA_{1c} levels fell by 0.6 to 0.7% in all three groups by 12 months. These levels were significantly lower than prepump levels (P≤0.02). Within each age group, the incidence of severe hypoglycemic events during pump therapy was lower than during prior injection therapy. The differences did not achieve statistical significance.

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11 years, and 12 to 18 years. Patients were started on daily dose of insulin therapy prior to study start. The total daily dose was divided as 50% premeal bolus doses and 50% as basal replacement, given as a single hourly rate over the first 24 hours.	injection/day regimen			When all three groups were combined, there was a significantly lower incidence of severe hypoglycemic events during the first 12 months of pump therapy than during the 12 months prior to pump therapy (P<0.05). Secondary: Not reported
Intermediate-Acting and Long-Acting Insulins: Type 2 Diabetes Mellitus				
Zinman et al.[80] (2012) BEGIN: Once Long study Insulin degludec (FlexPen®) QD vs insulin glargine (SoloSTAR®) QD Patients in both treatment arms were also treated with metformin. Patients could also continue treatment with a	MC, NI, OL, PG, RCT Patients ≥18 years of age with a diagnosis of type 2 diabetes for ≥6 months, HbA_{1c} of 7% to 10%, BMI≤40 kg/m^2, treated with oral antidiabetic agents for at least three months prior to screening, and insulin treatment-naïve	N=990 52 weeks	Primary: Change in HbA_{1c} from baseline to week 52 Secondary: Change from baseline in FPG and SMBG, patients with A_{1c} <7%, function health status, and safety	Primary: Mean HbA_{1c} decreased by 1.06% in the insulin degludec group and 1.19% in the insulin glargine group with an ETD of 0.09% (95% CI, -0.04 to 0.22; no P value reported). Secondary: FPG decreased from baseline to the end of the trial in both groups, with the most pronounced decline occurring during the first 12 weeks. Mean FPG levels decreased by 3.8 to 5.9 mmol/L in the degludec group and 3.3 to 6.4 mmol/L in the glargine group. There was a significant reduction in FPG in favor of the degludec group (ETD of -0.43 mmol/L [95% CI, -0.74 to -0.13; P=0.05]). The 9-point SMBG profiles appeared similar at baseline and decreased in both groups at the end of the trial Patients that achieved HbA_{1C} levels of <7% at the end of the trial were similar between groups, with 52% of patients in the degludec group and 54% of patients in the glargine group (P=0.40). There was also a similar

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DDP-4 inhibitor, but only 2% of evaluated patients utilized a DDP-4 inhibitor.				proportion of participants who achieved HbA_{1C} levels of <7% without confirmed hypoglycemia (degludec 42%; glargine 46%; P=0.34) and without nocturnal confirmed hypoglycemia (degludec 53%; glargine 54%; P=0.68) in the last 12 weeks of treatment. Rates of overall confirmed hypoglycemic episodes were similar (P=0.106) between treatment groups. The rate of nocturnal confirmed hypoglycemic episodes was significantly lower with degludec compared to glargine with an ERR of 0.64 (95% CI, 0.42 to 0.98; P=0.038). In specific analyses of the maintenance period (weeks 16 to 52), overall confirmed hypoglycemia rates were similar between treatments (P=0.067), and as with the overall rate, the rate of nocturnal confirmed hypoglycemia was significantly lower with degludec (P=0.004).
Rodbard et al.[81] (2013) BEGIN Once Long Study Insulin degludec (FlexPen®) QD vs insulin glargine (SoloSTAR®) QD Patients in both treatment arms were also treated with metformin. Patients could also continue treatment with a DDP-4 inhibitor, but only 2% of evaluated patients utilized a DDP-4 inhibitor.	ES of a MC, NI, OL, PG, RCT (Zinman et al) Patients ≥18 years of age with a diagnosis of type 2 diabetes for ≥6 months, HbA_{1c} of 7% to 10%, BMI≤40 kg/m^2, treated with oral antidiabetic agents for at least three months prior to screening, and insulin treatment-naïve	N=808 104 weeks	Primary: Change in HbA_{1c} from baseline to week 104 Secondary: Change from baseline in FPG and SMBG, patients with A_{1c} <7%, and safety	Primary: In the extension trial set, after 104 weeks of treatment, the observed mean (SD) HbA_{1c} decreased from 65 ± 9 mmol/mol (8.1 ± 0.8%) at baseline to 53 ± 10 mmol/mol (7.0 ± 0.9%) with degludec and from 66 ± 9 mmol/mol (8.2 ± 0.8%) at baseline to 52 ± 9 mmol/mol (6.9 ± 0.8%) with glargine. There was no statistical difference between treatments with an ETD of 0.07% (95% CI, −0.07 to 0.22; P=0.339). Secondary: Overall confirmed hypoglycemia rates were similar between degludec and glargine when considering the entire trial period (1.72 and 2.05 episodes/patient-year; estimated rate ratio of 0.84; 95% CI, 0.68 to 1.04; P=0.115) and maintenance period (1.80 and 2.21 episodes/patient-year; estimated rate ratio of 0.80; 95% CI, 0.63 to 1.01; P=0.063) Nocturnal confirmed hypoglycemia was significantly lower with degludec at end of trial compared with glargine (0.27 vs 0.46 episodes/patient-year; estimated rate ratio of 0.57 [95% CI, 0.40 to 0.81; P=0.002]) and significantly lower in the maintenance period (0.28 vs 0.53 episodes/patient-year; estimated rate ratio of 0.47 [95% CI, 0.32 to 0.69); P<0.001]). The rate of severe hypoglycemia was significantly lower with degludec than glargine when considering the entire trial period for the safety

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				analysis set (0.006 vs 0.021 episodes/patient-year; estimated rate ratio of 0.31 [95% CI, 0.11 to 0.85; P=0.023]). The observed mean reduction in laboratory-measured fasting plasma glucose was significantly greater with degludec (4.17 mmol/L) than with glargine (3.56 mmol/l) with an ETD of −0.36 mmol/L (95% CI, −0.67 to −0.05; P=0.021). Similar results were seen in the extension trial set. The 9-point self-monitored blood glucose profiles were similar at baseline and at end of treatment for both treatments in both the full and extension trial sets. There were no significant differences in prandial increments.
Philis-Tsimikas et al.[82] (2013) Insulin degludec (FlexPen®) QD vs sitagliptin 100 mg QD All patients received the active treatment in addition with one or two other oral antidiabetic agents in any combination (metformin, sulphonylureas, glinides, or pioglitazone)	AC, MC, PG, OL, RCT Patients ≥18 years of age with a diagnosis of type 2 diabetes for ≥6 months, inulin-naïve, HbA_{1c} 7.5 to 11%, BMI ≤40 kg/m^2, treated with one or two oral antidiabetic agents (metformin, sulphonylureas or glinides or pioglitazone) with an unchanged dose for at least three months	N=458 26 weeks	Primary: Change in HbA_{1c} from baseline to week 26 Secondary: Change from baseline to week 26 in FPG, patients with HgA_{1c} <7%, patients with HgA_{1c} <7% and no hypoglycemic episodes, mean SMPG, prandial glucose, responders with HgA_{1c} <6.5%, HRQoL score	Primary: Insulin degludec provided a statistically significant reduction in HbA_{1c} when compared to sitagliptin. After 26 weeks of treatment, mean HbA_{1c} was 7.2% in the insulin degludec group and 7.7% in the sitagliptin group. The ETD was -0.43% (95% CI, -0.61 to -0.24; no P value reported). Secondary: After 26 weeks, the observed mean FPG was 6.2 mmol/L (111.7 mg/dL) with insulin degludec and 8.5 mmol/L (153.2 mg/dL) with sitagliptin. The estimated mean change from baseline was −3.41 mmol/L (−61.4 mg/dL) with insulin degludec and −1.24 mmol/L (−22.3 mg/dL) with sitagliptin (ETD, −2.17 mmol/L; 95% CI, −2.59 to –1.74; no P value reported). Treatment with in insulin degludec showed a higher proportion of subjects achieving HbA_{1c} <7.0% at end of trial with 41% in the insulin degludec group and 28% in the sitagliptin group (OR, 1.60; 95% CI, 1.04 to 2.47; no P value reported). The proportion of subjects achieving HbA_{1c} <7.0% without hypoglycemia at end of trial was 25% in the insulin degludec group and 23% in the sitagliptin (OR, 0.92; 95% CI, 0.55 to 1.53; no P value reported). The observed proportion of subjects achieving HbA_{1c} ≤6.5% at end of trial was 28.0% with insulin degludec and 14.9% with sitagliptin (OR, 1.98; 95% CI, 1.17 to 3.33; no P value reported).

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				At all time-points in the 9-point profile, the estimated mean SMPG value was lower for insulin degludec compared to sitagliptin after 26 weeks of treatment. The estimated mean of the overall 9-point profile was lower with insulin degludec than with sitagliptin (ETD −1.31 mmol/l; 95% CI, −1.69 to −0.94; No P value reported). The prandial glucose increment, defined as the difference in SMPG values 90 min before and after a meal, was seen to be higher with insulin degludec compared to sitagliptin across 'all meals' and at breakfast after 26 weeks; the ETD was 0.35 mmol/L (95% CI, 0.05 to 0.65; no P value reported) for 'all meals' and 0.54 mmol/L (95% CI, 0.07 to 1.02; no P value reported) for breakfast. The change in nocturnal prandial glucose was greater with insulin degludec than with sitagliptin from bedtime to breakfast; with an ETD of -0.94 mmol/L (95% CI, −1.43 to −0.46; no P value reported). The patient-reported outcome results appeared to be similar between the two treatment groups for the DPM, SF-36 v2 and Hypoglycemic Episode—Interview Questionnaire, with only marginal changes over time. The rate of confirmed hypoglycemic episodes was higher with insulin degludec compared with sitagliptin (3.07 vs 1.26 episodes per patient-year; no P value reported). There was no difference between treatment groups in the rate of nocturnal confirmed hypoglycemic episodes with 0.52 and 0.30 episodes per patient-year for insulin degludec and sitagliptin groups, respectively. Only one episode of severe hypoglycemia occurred during the study (insulin degludec group) with a rate of 0.01 episodes per patient-year. Patients treated with a sulphonylurea or pioglitazone had an increased rate of hypoglycemic episodes than those that did not for both groups. Patients in the insulin degludec arm who received a sulphonylurea or pioglitazone had a hypoglycemic episode rate of 3.43 compared with a rate of 1.71 in patients who did not. In the sitagliptin group, patients who were also

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				treated with a sulphonylurea or pioglitazone had a rate of 1.92 whereas patients treated without had a rate of 0.00.
Meneghini et al.[83] (2013) Insulin degludec (FlexPen®) QD (forced- flex dosing) vs Insulin degludec (FlexPen®) QD (same-time dosing) vs insulin glargine (SoloSTAR®) QD (same-time dosing) Patients continued oral antidiabetic agents currently prescribed	MC, NI, OL, PG, RCT Patients ≥18 years of age with a diagnosis of type 2 diabetes for ≥6 months, BMI of ≤40 kg/m^2, and previously treated with either oral antidiabetic drugs (baseline HbA_{1c} = 7.0 to 11.0%) or, any basal insulin ± oral antidiabetic agents (baseline HbA_{1c} = 7.0 to 10.0%)	N=687 26 weeks	Primary: Change in HgA_{1c} from baseline to week 26 Secondary: Patients with HgA_{1c} <7%, change from baseline in FPG and SMPG, safety	Primary: Mean HbA_{1c} changes from baseline to week 26 were similar between treatment groups. Observed mean decreases were -1.28% (degludec forced-flex), -1.07% (degludec same-time), and -1.26% (glargine same-time). ETD between degludec (forced-flex) and glargine groups was 0.04% (95% CI, -0.12 to 0.20). ETD between degludec (forced-flex) and degludec (same-time) groups not significant (-0.13%; 95% CI, -0.29 to 0.03). Secondary: After 26 weeks of treatment, similar proportions of participants had achieved an HbA_{1c} of <7.0% with degludec (forced-flex) and glargine (same-time) groups (38.9% vs 43.9%, P=0.34); likewise, no statistically significant difference in HbA_{1c} was found between the degludec (forced-flex) and degludec (same-time) groups (38.9% vs 40.8%, P=0.99). Mean laboratory-measured FPG values decreased in all treatment groups. At the end of the trial, the observed mean FPG concentration was 5.8 mmol/L for both degludec groups and 6.2 mmol/L for the glargine group. Insulin degludec (forced-flex) was associated with a significantly greater reduction in FPG than glargine (same-time) after 26 weeks of treatment (ETD, –0.42 mmol/L; 95% CI, –0.82 to –0.02; P=0.04). There was no significant difference between the degludec groups (ETD, –0.05 mmol/L; 95% CI, –0.45 to 0.35; P value not reported). After 26 weeks, mean 9-point SMPG profiles were similar for the three treatment groups and decreased compared with corresponding mean profiles at baseline. A similar proportion of participants (44 to 51%) reported confirmed hypoglycemia in the three treatment groups. There were no significant differences found between the insulin degludec (forced-flex) and insulin glargine (same-time) groups with respect to the rates of overall confirmed hypoglycemia and nocturnal confirmed hypoglycemia. There was no

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				significant difference in hypoglycemia rates when both degludec groups were compared.
Garber et al.[84] (2012) BEGIN Basal-Bolus Type 2 study Insulin degludec (FlexPen®) QD + insulin aspart at meal time vs insulin glargine (SoloSTAR®) QD + insulin aspart at meal time Patients may also be treated with metformin, pioglitazone or both	MC, NI, OL, PG, RCT Patients ≥18 years of age with a diagnosis of diabetes type 2 for ≥6 months, HbA_{1c} of 7 to 10%, BMI ≤40 mg/m^2, treated with any insulin-containing regimen for at least three months (with or without oral agents)	N=1,006 52 weeks	Primary: Change in HbA_{1c} from baseline to 52 weeks Secondary: FPG, SMPG, prandial plasma glucose increment, HRQoL, safety	Primary: The estimated mean change from baseline in HbA_{1c} was −1.10% with insulin degludec and −1.18% with insulin glargine with an ETD of 0.08% (95% CI, −0.05 to 0.21). Secondary: Concentrations of FPG decreased by 2.3 mmol/L with insulin degludec and 2.0 mmol/L with insulin glargine (ETD −0.29 mmol/L; 95% CI, −0·65 to 0·06; P=0.1075). The 9-point SMPG profiles seemed similar for the two treatment groups at baseline and decreased in both groups by week 52 (no P values reported). After 52 weeks, mean prandial increments were similar between treatment groups for all meals (no P values reported). The HRQoL questionnaire showed a significant difference between treatment groups in favor of insulin degludec compared with insulin glargine for the SF-36 domain of bodily pain (P=0.0320). No other results for HRQoL SF-36 domains provided in the primary publication. Rates of overall, nocturnal, and diurnal confirmed hypoglycemia were significantly lower in patients treated with insulin degludec than with insulin glargine. Rates of overall confirmed hypoglycemia were 11.09 episodes per patient-year exposure with insulin degludec and 13.63 with insulin glargine; the estimated rate ratio was 0.82 (95% CI, 0.69 to 0.99; P=0.0359) in favor of insulin degludec. Too few severe hypoglycemic events occurred for differences between groups to be assessed. The proportions of participants with confirmed hypoglycemic events were similar with insulin degludec (609 [81%] of 753 participants) and insulin glargine (206 [82%] of 251 participants). The rate of nocturnal confirmed hypoglycemia was 1.39 episodes per patient-year exposure for insulin degludec and 1.84 for insulin glargine. The rate ratio for nocturnal confirmed hypoglycemic episodes was 0.75 (95% CI, 0.58 to 0.99; P=0.0399) in favor of insulin degludec.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Hollander et al.[85] (2015) BEGIN Basal-Bolus Type 2 study Insulin degludec (FlexPen®) QD + insulin aspart at meal time vs insulin glargine (SoloSTAR®) QD + insulin aspart at meal time Patients may also be treated with metformin, pioglitazone or both	ES of a MC, NI, OL, PG, RCT (Garber et al) Patients ≥18 years of age with a diagnosis of diabetes type 2 for ≥6 months, HbA_{1c} of 7 to 10%, BMI ≤40 mg/m^2, treated with any insulin-containing regimen for at least three months (with or without oral agents)	N=1,006 78 weeks	Primary: Change in HbA_{1c} from baseline to 52 weeks Secondary: FPG, SMPG, prandial plasma glucose increment, HRQoL, safety	Primary: In the extension trial population, the mean HbA_{1c} value decreased from 8.2% at baseline to 7.2% after 78 weeks of treatment with insulin degludec and from 8.3% to 7.1% with insulin glargine (ETD of 0.14%; 95% CI, −0.01 to 0.30; P value not reported). In the full analysis set population, the mean HbA1c value decreased from 8.3% at baseline to 7.3% with insulin degludec and from 8.4% to 7.2% with insulin glargine (ETD 0.16%; 95% CI, 0.02 to 0.30; P=0.022). The FPG level decreased by 2.4 mmol/L (43 mg/dL) after 78 weeks of treatment with insulin degludec and by 2.2 mmol/L (40 mg/dL) after treatment with insulin glargine in the extension trial set population (ETD was −0.19 mmol/L; 95% CI, −0.59 to 0.21; P value not reported). Similar results were obtained in the full analysis set population. The ERR of overall confirmed hypoglycemia in the extension trial set for comparing the insulin degludec groups compared to the insulin glargine group was 0.76 (95% CI, 0.62 to 0.94; P=0.011). In the full analysis set population, the rates of overall confirmed hypoglycemia were not significantly different between the insulin degludec and insulin glargine groups (ERR, 0.85; 95% CI, 0.70 to 1.02; P value not reported). The ERR of nocturnal confirmed hypoglycemia in the extension trial set for comparing the insulin degludec groups compared to the insulin glargine group was 0.69 (95% CI, 0.51 to 0.93; P=0.016). Lower rates of nocturnal hypoglycemia were also observed with insulin degludec in the full analysis set (ERR, 0.76; 95% CI, 0.58 to 1.00; P=0.047). The estimated rates of severe hypoglycemia were low and not significantly different between insulin degludec and insulin glargine in both the extension trial set (ERR, 0.66; 95% CI 0.31 to 1.37; P value not reported) and the full analysis set populations (ERR, 0.83; 95% CI 0.43 to 1.61; P value not reported).
Gough et al.[86] (2013)	MC, NI, OL, PG, RCT	N=457 26 weeks	Primary: Change in HbA_{1c} from baseline to 26 weeks	Primary: Change in HbA_{1c} from baseline, improved with both insulin degludec 200 units/mL and insulin glargine after 26 weeks of treatment. Mean HbA_{1c}

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Insulin degludec 200 units/mL (FlexTouch®) QD vs insulin glargine (SoloSTAR®) QD Patients were continued on metformin. If DPP-4 inhibitors were labeled for use in combination with insulin, patients continued their DPP-4 inhibitor, otherwise it was also discontinued	Patients ≥18 years of age, diagnosis of type 2 diabetes for ≥6 months, HbA_{1c} 7 to 10%, BMI ≤45 kg/m^2, previous treatment with metformin with or without additional oral antidiabetic drugs for ≥3 months		Secondary: Number of treatment-emergent confirmed hypoglycemic episodes, change from baseline in FPG, SMBG frequency of patients reaching A_{1c} <7%	decreased by 1.3 ± 1.01% (14.3 ± 11.0 mmol/mol, mean ± SD) for both treatment groups, with an ETD of 0.04 (95% CI, −0.11 to 0.19). Secondary: There was no significant difference in the proportion of participants that achieved the HbA_{1c} target of <7% between insulin degludec 200 units/mL with 52% and insulin glargine with 56% (OR, 0.85; 95% CI, 0.56 to 1.30). Insulin degludec 200 units/mL resulted in a statistically significantly greater FPG reduction than insulin glargine after 26 weeks of treatment. The ETD between groups was -0.42 (95% CI, −0.78 to −0.06; no P value reported). Overall, the 9-point SMBG profiles decreased in both treatment groups and were similar after 26 weeks. No subjects in either of the treatment groups reported episodes of severe hypoglycemia. The proportion of patients that experienced a confirmed episode of hypoglycemia was 28.5% for insulin degludec and 30.7% for insulin glargine. Event rates were 1.22 and 1.42 episodes/patient-year, respectively (ERR, 0.86; 95% CI, 0.58 to 1.28; P=0.46). A total of 6.1% and 8.8% of participants in the insulin degludec 200 units/mL and insulin glargine experienced nocturnal confirmed hypoglycemic episodes with rates of 0.18 and 0.28 episodes/patient-year, respectively (ERR, 0.64, 95% CI, 0.30 to 1.37, P=0.25).
Sullivan et al.[87] (2019) DELIVER Naïve D Insulin glargine 300 units/mL (Gla-300) vs insulin degludec (IDeg)	Cohort, OS, RETRO Insulin-naïve adults with type 2 diabetes on oral antihyperglycemic drugs and/or a glucagon-like peptide-1 receptor agonist (GLP-1 RA)	N=1,276 6 months	Primary: HbA_{1c} reduction, HbA_{1c} target attainment, hypoglycemia Secondary: Not reported	Primary: Mean HbA_{1c} decreased significantly from baseline to follow-up in both groups; and these reductions were comparable in the Gla-300 and IDeg cohorts (−1.67% vs –1.58%, respectively; P=0.51). Patients in both cohorts were also similarly likely to attain the HbA_{1c} targets <7%: 23.8% and 27.4%; P=0.20; <8%: 55.0% and 57.1%; P=0.63). Overall and inpatient/emergency department-associated hypoglycemia incidences and event rates were similar in both cohorts using fixed six-month or variable on-treatment follow-up. Secondary: Not reported
Meneghini et al.[88]	OL, OS	N=1,832	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2007) Insulin detemir±oral antidiabetic drug transferred from 3 groups of patients: oral antidiabetic drug only, NPH±oral antidiabetic drug, insulin glargine±oral antidiabetic drug	Subgroup of patients with type 2 diabetes from the German cohort of PREDICTIVE study	12 weeks	Incidence of severe adverse drug reactions (severe adverse drug reactions) (major hypoglycemic events) Secondary: Hypoglycemic events, weight changes, HbA_{1c}, FPG	No severe adverse drug reactions were reported during the 12 week follow-up. Reports of adverse drug reactions occurred in 0.3% of patients, including one report of drug intolerance, two diabetes-related reports, one report of headache, and one report of skin allergy (P values were not reported). Secondary: The percentage of patients experiencing hypoglycemia and the frequency of hypoglycemic episodes were lower in the insulin detemir group during the four weeks preceding the follow-up visit compared to baseline. The total, daytime, and nocturnal hypoglycemic events at baseline decreased from 3.3, 2.0, and 1.3 events/patient-year, respectively, to -2.7, -1.6, and -1.2, respectively (P<0.0001). The percentage of patients experiencing these events decreased from 7.2, 5.5, and 3.7%, respectively, to 2.0, 1.6, and 0.5% at follow-up (P values not reported). There were overall reductions in body weight following the transition to insulin detemir (P<0.0001). All three groups of patients had weight reduction after initiating insulin detemir (P<0.0001 in the oral antidiabetic drug only group, P<0.0099 in the NPH±oral antidiabetic drug group, and P<0.0001 in the insulin glargine±oral antidiabetic drug group). A reduction of -1.1±0.03% in mean HbA_{1c} was observed at study endpoint (P<0.0001). Patients that were in the oral antidiabetic drug only group had a reduction of -1.29±0.03% (P<0.0001) from baseline, which was a slightly greater reduction than in the NPH±oral antidiabetic drug and insulin glargine±oral antidiabetic drug groups (-0.60±0.09% and -0.59±0.06%, respectively; P<0.0001 for both). There was a significant reduction in mean FPG overall (P<0.0001). However, patients transitioning from the oral antidiabetic drug only group tended to have a greater reduction in FPG from baseline than those transitioning from the other two treatment regimens (P<0.0001).
Hollander et al.[89] (2008)	MC, NI, OL, PG, RCT	N=319 52 weeks	Primary: HbA_{1c} at 52 weeks	Primary: Mean HbA_{1c} at 52 weeks was 7.19% with insulin detemir and 7.03% with insulin glargine (mean difference, 0.17; 95% CI, -0.07 to 0.40), meeting the prespecified non-inferiority margin.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Insulin detemir PM or BID (AM and PM) and insulin aspart before meals vs insulin glargine PM and insulin aspart before meals Basal insulin doses were titrated to achieve pre-breakfast and pre-dinner PG ≤108 mg/dL. Prandial insulin doses were titrated to achieve PPG ≤162 mg/dL. Insulin secretagogues and α-glucosidase inhibitors were discontinued. United States patients on TZDs were allowed to continue treatment.	Patients ≥18 years of age with type 2 diabetes for ≥1 year who were receiving oral diabetic medications or insulin with or without oral diabetes medications for >4 months with HbA_{1c} 7.0 to 11.0% and BMI ≤40 kg/m^2		Secondary: Change in body weight, proportion of patients achieving HbA_{1c} ≤7.0% with or without major hypoglycemia in the last three months of treatment, FPG, within-patient variation in self-monitored pre-breakfast and pre-dinner blood glucose, 10-point self-monitored plasma glucose profiles and safety	Secondary: Patients receiving insulin detemir experienced significantly less weight gain compared to those receiving insulin glargine (2.8 vs 3.8 kg; P<0.05). Similar percentage of patients achieved HbA_{1c} ≤7.0% with insulin detemir compared to insulin glargine (36.2 vs 36.7%; P value NS). The HbA_{1c} goal was achieved without symptomatic hypoglycemia in 17.1 and 21.4% of patients in the insulin detemir and insulin glargine groups, respectively (P value NS). No significant differences were observed between the two groups with regard to FPG at the end of study, changes in FPG, within-patient variation in self-monitored pre-breakfast and pre-dinner blood glucose and 10-point self-monitored plasma glucose profiles. Episodes of major hypoglycemia were reported in 4.7 and 5.7% of patients in the insulin detemir and insulin glargine groups, respectively (P=0.588). Incidence of nocturnal and symptomatic hypoglycemia was also comparable between the two groups (P>0.05 for both). Severe treatment-emergent adverse events were reported in 13.6 and 19.0% of patients in the insulin detemir and insulin glargine groups.
Raskin et al.[90] (2009) Insulin detemir PM or BID (AM and PM)	MC, NI, OL, PG, RCT Patients ≥18 years of age with type 2 diabetes who	N=385 26 weeks	Primary: HbA_{1c} at 26 weeks Secondary:	Primary: The least squared mean change in HbA_{1c} from baseline at 26 weeks was -1.08% with insulin detemir and -1.28% with insulin glargine (difference, 0.207; 95% CI, 0.0149 to 0.3995; P=0.035), showing non-inferiority.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
and insulin aspart before meals (IDet) vs insulin glargine PM and insulin aspart before meals (IGla) Basal insulin doses were titrated to achieve pre-breakfast PG ≤108 mg/dL. Treatment with insulin secretagogues and α-glucosidase inhibitors were discontinued. Treatment with TZDs and metformin was continued.	previously received any oral diabetes medication or insulin with or without oral diabetes medications with HbA_{1c} 7.0 to 11.0% and BMI ≤40 kg/m^2		FPG, body weight, safety	When last observation carried forward analysis was used, the least squared mean change in HbA_{1c} was -0.94 and -1.25% with insulin detemir and insulin glargine, respectively. The difference between the two groups (0.307; 95% CI, 0.1023 to 0.5109; P=0.004) was inconclusive regarding possible inferiority of insulin detemir since the 95% CI included 0.4, the prespecified inferiority margin. Secondary: No significant differences were seen in change in FPG from baseline at 26 weeks between the two treatment groups. Patients in the insulin detemir group experienced less weight gain compared to those in the insulin glargine group (1.20±3.96 vs 2.70±3.94 kg; P=0.001). Rates of overall, nocturnal and major hypoglycemic events were comparable between the two groups. Sixty-six percent of patients in the insulin detemir group and 71% in the insulin glargine group reported treatment-emergent adverse events.
Rosenstock et al.[91] (2008) Insulin detemir PM or BID (AM and HS) vs insulin glargine HS Basal insulin doses were titrated to	MC, NI, OL, PG, RCT Insulin-naïve type 2 diabetics ≥18 years of age, receiving oral antidiabetic agents, with HbA_{1c} 7.5 to 10.0%, and BMI ≤40.0 kg/m^2	N=582 52 weeks	Primary: Change in baseline HbA_{1c} Secondary: Change in baseline plasma glucose and body weight, proportion of patients achieving HbA_{1c} ≤7.0% without hypoglycemia,	Primary: Decreases in HbA_{1c} were -1.5% with both treatments and were comparable after 52 weeks at 7.2 and 7.1% (difference, 0.05%; 95% CI, -0.11 to 0.21), thereby meeting the criteria for non-inferiority for insulin detemir vs insulin glargine. Secondary: Within-patient variation of self-monitored plasma glucose pre-breakfast and -dinner did not differ significantly between the two treatments. The overall shape of the 10-point self-monitored plasma glucose profile during the last week of treatment was similar between the two treatments (P value NS).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
achieve FPG ≤6 mmol/L. Existing oral antidiabetic drug therapy was continued.			incidence of hypoglycemia, safety	Weight gain was significantly less with insulin detemir compared to insulin glargine (3.0 vs 3.9 kg; P=0.01). With both treatments, 52% of patients achieved HbA_{1c} ≤7.0%, with 33 and 35% of patients receiving insulin detemir and insulin glargine doing so without hypoglycemia (P value not reported). The risk of hypoglycemia of any type was comparable between the two treatments. The overall rate was low at 5.8 vs 6.2 episodes per patient-year with insulin detemir vs insulin glargine (RR, 0.94; 95% CI, 0.71 to 1.25), while the rate of nocturnal hypoglycemia was 1.3 episodes per patient-year with both treatments. Serious adverse events were less frequent with insulin detemir (42 patients with 47 events vs 53 patients with 73 events; P value not reported). One death was reported with insulin detemir (cause and/or reason unknown). Adverse events recorded as serious tended to be of a wide-ranging disparate nature, with no clear pattern of between-treatment differences. The only differences in adverse events were injection-site disorders (4.5 vs 1.4%), allergic reactions (3 vs 1 patients), and skin disorders including pruritus and rash (6 vs 1 patients).
King[92] (2009) Insulin detemir SC QD vs insulin glargine SC QD Once the patient achieved 2 consecutive days at goal, the insulin treatment was	DB, RCT, XO Type 2 diabetics receiving oral antidiabetic agents	N=36 24 hours	Primary: 24-hour glycemic control, time to basal glycemic control, insulin dose Secondary: Not reported	Primary: Glucose profiles for each hour were similar between the two treatments. Glucose values for each five minute interval for insulin detemir during the basal period, the period 12 hours after injection, and overall 24-hour period were similar to insulin glargine. The AUC for the self-monitored glucose levels over 24 hours was 293.2 and 3,114.5 mg.h/dL (point ratio, 0.941; 90% CI, 0.885 to 1.001); therefore, the two treatments were considered bioequivalent for 24-hour glucose. Target basal glycemic control was achieved in all patients in 3.8 and 3.5 days with insulin detemir and insulin glargine (*P*=0.360).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
switched to the other agent.				The dose of insulin detemir was similar to that of insulin glargine (26.3 and 22.6 units/day; *P*=0.837). Approximately one percent of all glucose values during the basal period were <70 mg/dL. Secondary: Not reported
Meneghini et al.[93] (2013) Insulin detemir vs insulin glargine Treat-to-target with weekly titrations	OL, RCT Insulin-naïve adults with type 2 diabetes on a stable dose of metformin ≥1500 mg with an HbA_{1c} of 7 to 9%	N=457 26 weeks	Primary: Change in HbA_{1c} from baseline Secondary: Proportion of subjects achieving HbA_{1c} levels ≤7 or ≤6.5% at 26 weeks, and the proportions achieving this without symptomatic hypoglycemia during the last month of treatment; safety	Primary: The observed mean HbA_{1c} reductions with detemir and glargine from baseline were 0.48% and 0.74% to end-of-study values of 7.48% and 7.13%, respectively. The estimated between-treatment difference (detemir–glargine) was 0.30% (95% CI, 0.14 to 0.46%) in the full analysis set and 0.35% (95% CI, 0.19 to 0.51%) in the per protocol analysis set. As the upper 95% CI values exceeded 0.4%, non-inferiority for detemir could not be confirmed. Secondary: The proportions of patients reaching $HbA_{1c} \leq 7\%$ at 26 weeks were 38% (80/209) and 53% (107/204) (P=0.026) in the detemir and glargine groups, respectively; whereas for patients reaching $HbA_{1c} \leq 7\%$ without hypoglycemia in the last four weeks, there was no significant difference between the treatments (32 and 38%, respectively; P=0.438). $HbA_{1c} \leq 6.5\%$ was attained by 11 and 21% in the detemir and glargine groups, respectively (P=0.011), 8.6% and 15.2% without hypoglycemia (P=0.073). The overall rate of hypoglycemia was low, with fewer than five episodes per subject-year in either treatment arm; the only two major events reported occurred with glargine. There was a significantly lower (27%) rate of all hypoglycemic episodes with detemir versus glargine, with no difference in the rate of nocturnal hypoglycemia Weight decreased slightly with detemir and increased slightly with glargine. Observed mean weight change was −0.49 kg with detemir and +1.0 kg with glargine, with a statistically significant estimated treatment difference of −1.5 kg (95% CI, −2.17 to −0.89 kg) in favor of detemir.
Liebl et al.[94] (2009)	MC, RCT	N=719 26 weeks	Primary: Change in baseline HbA_{1c}	Primary: Insulin detemir plus insulin aspart significantly decreased HbA_{1c} compared to biphasic aspart 30 (-1.56 vs -1.23%; treatment difference,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Insulin detemir PM and insulin aspart before meals vs biphasic insulin aspart 30 (consisting of 30% insulin aspart and 70% protamine-crystallized insulin aspart) BID Insulin detemir doses were titrated to achieve pre-breakfast PG 72 to 126 mg/dL and insulin aspart doses were titrated to achieve PPG ≤180 mg/dL. Biphasic insulin aspart doses were titrated to achieve pre-breakfast and pre-dinner plasma glucose 72 to 126 mg/dL. All oral antidiabetic drugs were discontinued to compare two insulin regimens.	Adult type 2 diabetics ≥6 months, BMI ≤40 kg/m^2, currently receiving 1 or 2 oral antidiabetic agents, with or without concomitant QD intermediate- or long-acting insulin, and HbA_{1c} ≥7.0 to ≤12.0%		Secondary: Proportion of patients achieving HbA_{1c} ≤7.0%; change in baseline FPG and body weight, self-monitored glucose prolife, incidence of hypoglycemia	0.234%; 95% CI, 0.398 to -0.070; P=0.0052). Final HbA_{1c} values were 6.96 and 7.17%. Secondary: After 26 weeks, 60 and 50% of patients achieved HbA_{1c} ≤7.0% with insulin detemir plus insulin aspart and biphasic aspart 30 (P value not reported). Patients previously receiving basal insulin had significantly greater decrease with insulin detemir plus insulin aspart (-1.21 vs -0.75%; P=0.0129), whereas insulin-naïve patients had similar decreases (-1.69 vs -1.42%; P=0.106). There was no difference in the decrease of FPG between the two treatments (-52.3 vs -51.8 mg/dL; P=0.345). There was no difference in the amount of weight gain between the two treatments (4.1 vs 4.0 kg; P value not reported). Daily glucose profiles indicate that both treatments decrease glucose levels throughout the day. PPG was significantly lower with insulin detemir plus insulin aspart compared to biphasic aspart 30 (after breakfast; P=0.012, after lunch; P<0.001, and after dinner; P<0.001). A total of five and zero patients experienced major hypoglycemia with insulin detemir plus insulin aspart compared to biphasic aspart 30 (P value not reported). The rate of minor hypoglycemia was 31 vs 28%; P=0.837). The rate of nocturnal minor hypoglycemia was similar between the two treatments (7.4 vs 7.3%; P=0.666).
Haak et al.[95]	MC, OL, PG, RCT	N=505	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2005) Insulin detemir HS and insulin aspart before meals vs NPH insulin HS and insulin aspart before meals Insulin doses were adjusted to achieve an FBG goal 4.0 to 7.0 mmol/L, PPG goal <10 mmol/L, and nocturnal goal of 4 to 7 mmol/L.	Patients aged ≥35 years of age with type 2 diabetes for ≥12 months, HbA_{1c} ≤12.0% and who had received insulin treatment for ≥2 months	26 weeks	Change in HbA_{1c} and FPG from baseline, nine-point self monitoring of blood glucose profile, hypoglycemia, weight gain Secondary: Not reported	At 26 weeks, significant HbA_{1c} reductions were observed with both the insulin detemir group (-0.2%; P=0.004) and the NPH group (-0.4%; P=0.0001). There was no significant difference in HbA_{1c} reduction between the two groups (P value not reported). At 26 weeks, both the insulin detemir group and NPH group had significant reductions in FPG from baseline (P=0.027 and P=0.026, respectively). However, differences between groups were NS (P=0.66). There were no significant differences in mean nine-point self monitoring of blood glucose profiles between the two groups (P=0.58). There was no significant difference in both nocturnal and total hypoglycemia between insulin detemir and NPH (P=0.95 and P=0.48, respectively). At 26 weeks, body weight changes from baseline were significantly lower with insulin detemir compared to NPH (1.0 vs 1.8 kg, respectively; P=0.017). Secondary: Not reported
Fajardo Montañana et al.[96] (2008) Insulin detemir HS and insulin aspart before meals vs NPH insulin HS and insulin aspart before meals	RCT, OL, PG, MC Patients ≥18 years of age with type 2 diabetes, HbA_{1c} 7.5 to 11.0%, BMI 25 to 40 kg/m^2, who were receiving two daily doses of insulin (at least one of them a premix) for ≥3 months; patients could also be receiving treatment with metformin;	N=277 26 weeks	Primary: Weight changes after 26 weeks Secondary: HbA_{1c} and FPG, proportion of patients achieving HbA_{1c} ≤7.0% without hypoglycemia during the last four weeks of treatment,	Primary: Mean weight gain at week 26 in the ITT population was significantly lower with insulin detemir (0.4 kg) than with NPH insulin (1.9 kg; P≤0.0001). In the PP analysis, there were similar changes in weight (0.4 kg with insulin detemir and 2.0 kg with NPH insulin; P≤0.0001). BMI increased less with insulin detemir (0.2 kg/m^2) than with NPH insulin (0.8 kg/m^2; P≤0.0001). Overall, 46.4% of insulin detemir patients showed no change or weight loss compared with 22.6% of NPH insulin patients. Secondary: At week 26, HbA_{1c} decreased from 8.9 to 7.8% in the insulin detemir group and from 8.8 to 7.8% in the NPH group (P=NS).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Basal insulin doses were titrated to achieve pre-breakfast PG ≤6.1 mmol/L. Insulin aspart doses were titrated to achieve PPG ≤10.0 mmol/L. Metformin therapy could be continued.	patients on other oral antidiabetic drugs were excluded		intra-subject variability in FPG, hypoglycemia	FPG decreased from 10.8 to 8.8 mmol/L in the insulin detemir group and from 10.1 to 8.9 mmol/L in the NPH insulin group (P=NS). The proportion of patients achieving an HbA_{1c} ≤7.0% without hypoglycemia during the last four weeks of treatment was 27% in both treatment groups (P=NS). Intra-subject variability of self-measured FPG at 26 weeks was lower with insulin detemir than with NPH insulin (P<0.0001). Patients in the insulin detemir group experienced significantly less hypoglycemia than patients in the NPH insulin group. Hypoglycemia was reported by 34.7% of patients treated with insulin detemir and by 65.3% of patients receiving NPH insulin. Nocturnal hypoglycemia was reported in 30.1% of insulin detemir patients and 69.9% of NPH insulin patients (RR 0.62 for all hypoglycemic events and 0.43 for nocturnal events; P<0.0001 for both).
Philis-Tsimikas et al.[97] (2006) Insulin detemir PM vs insulin detemir AM vs NPH insulin PM Insulin doses titrated to achieve a pre-breakfast and pre-dinner FPG ≤108 mg/dL.	MC, OL, PG, RCT Men and women ≥18 years of age, had a BMI ≤40 kg/m^2, type 2 diabetes for ≥12 months, insulin naïve, HbA_{1c} 7.5 to 11.0% following at least 3 months of treatment with ≥1 oral antidiabetic drug	N=498 20 weeks	Primary: Change in HbA_{1c} from baseline Secondary: Change in FPG, nine-point self monitoring of blood glucose profile, hypoglycemia	Primary: Both insulin detemir groups had similar reductions in HbA_{1c} compared to that of the NPH group. At 20 weeks, both evening and morning insulin detemir was found to be as effective as evening NPH (mean difference, 0.10%; 95% CI, -0.08 to 0.29 and 0.13%; 95% CI, -0.07 to 0.32, respectively). Equivalence was found between both insulin detemir groups (estimated difference, -0.03%; 95% CI, -0.21 to 0.15; P value not reported). Secondary: At 20 weeks, evening insulin detemir had changes in FPG similar to those with evening NPH (mean difference, -0.46 mmol/L; 95% CI, -1.05 to 0.13). However, morning insulin detemir had significantly higher FPG than both evening NPH and evening insulin detemir (mean difference, 0.88 mmol/L; 95% CI, 0.31 to 1.5; P=0.003 and 1.33 mmol/L; 95% CI, 0.85 to 1.80; P<0.001, respectively). Prebreakfast self monitoring of blood glucose was higher in the morning insulin detemir group in comparison to both evening groups (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Existing oral antidiabetic drug therapy was continued.				However, predinner self monitoring of blood glucose was lower in the morning insulin detemir group than that of the evening detemir and evening NPH groups (P=0.005 and P<0.001, respectively). Both evening groups resulted in similar self monitoring of blood glucose profiles. When compared to evening NPH, evening insulin detemir resulted in a significant risk reduction in the rate of hypoglycemic episodes over 24 hours and confirmed nocturnal episodes (P=0.0019 and P=0.031, respectively). On the other hand, when comparing morning and evening detemir, the rates of hypoglycemia were statistically similar. In comparison to evening NPH, morning insulin detemir did have a significant risk reduction of 87% for confirmed nocturnal hypoglycemia (P<0.001).
Montanana et al.[98] (2008) Insulin detemir SC QD vs NPH SC BID All patients received insulin aspart at main meals. Concomitant treatment with metformin was allowed.	PG, RCT Type 2 diabetics ≥18 years of age with HbA_{1c} 7.5 to 11.0%, BMI 25 to 40 kg/m^2, and receiving 2 daily doses of insulin (≥1 premix) ≥3 months	N=271 26 weeks	Primary: Change in baseline body weight Secondary: Change in baseline HbA_{1c} and FPG; proportion of patients achieving HbA_{1c} ≤7.0% without hypoglycemia, incidence of hypoglycemia, safety	Primary: Insulin detemir (0.4kg) resulted in significantly less weight gain compared to NPH (1.9 kg; difference, 1.5 kg; *P*<0.0001). Increases in BMI were significantly less with insulin detemir compared to NPH (difference, 0.6 kg/m^2; *P*<0.0001). Secondary: There was no difference in the decrease in HbA_{1c} between the insulin detemir (8.9 to 7.8%) and NPH (8.8 to 7.8%) (*P* value not reported). There was no difference in the decrease in FPG between insulin detemir (10.0 to 8.8 mmol/L) and NPH (10.1 to 8.9 mmol/L) (*P* value not reported). The proportion of patients achieving HbA_{1c} ≤7.0% without hypoglycemia during the last four weeks of treatment was 27% with both treatments. The incidence of hypoglycemia was significantly lower with insulin detemir compared to NPH (RR, 0.62 (all events) and 0.43 (nocturnal); *P*<0.0001 for both). Both treatments were well tolerated with no major safety concerns noted and a similar incidence of adverse events with both treatments.
Hermansen et al.[99]	MC, OL, PG, RCT	N=476	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2006) Insulin detemir BID vs NPH insulin BID Basal insulin doses were adjusted to achieve pre-breakfast FBG of 108 mg/dL. Existing oral antidiabetic drug therapy was continued.	Adult type 2 diabetes patients with no history of insulin use, baseline HbA_{1c} 8.61% for participants taking insulin detemir and 8.51% for those randomized into the NPH group	26 weeks	Effect on HbA_{1c} Secondary: FPG, proportion of participants achieving an $HbA_{1c} \leq 7.0\%$, proportion of participants achieving an $HbA_{1c} \leq 7.0\%$ without hypoglycemia, 10-point self monitoring of blood glucose, frequency of hypoglycemia, and weight gain	After 26 weeks, HbA_{1c} reductions in the insulin detemir group (-1.8%; P=0.004) did not differ significantly from reductions observed in the NPH group (-1.9%; P=NS). Secondary: After 26 weeks, the difference in mean FPG reductions between insulin detemir and NPH was not significant (0.32 mmol/L; P>0.05). The proportion of patients achieving an $HbA_{1c} \leq 7.0\%$ was 70% in those taking insulin detemir and 74% with those taking NPH. The difference between treatment groups was not significant. The proportion of patients achieving an $HbA_{1c} \leq 7.0\%$ without hypoglycemia was significantly higher in those taking insulin detemir (26%) compared to those taking NPH (16%; P=0.008). There was significantly less day-to-day fluctuation of fasting self monitoring of blood glucose profiles with insulin detemir when compared to NPH (P=0.021). There were no significant differences in mean 10-point self monitoring of blood glucose profiles between the two treatment groups (P=0.19). There was a 47% lower risk of overall hypoglycemia with insulin detemir compared to NPH (P<0.001). There was a 55% lower risk of nocturnal hypoglycemia with insulin detemir compared to NPH (P<0.001). After 26 weeks, body weight change from baseline was significantly lower with insulin detemir (1.2 kg) compared to NPH (2.8 kg; P<0.001).
Rosenstock et al.[100] (2015) ELEMENT 2 LY2963016 insulin glargine (Basaglar®; biosimilar to Lantus®)	OL, MC, RCT Patients with type 2 diabetes who were insulin-naïve (HbA_{1c} ≥7 and ≤11.0%) or previously on insulin glargine (HbA_{1c}	N=535 24 weeks	Primary: Change in HbA_{1c} from baseline to 24 weeks Secondary: Proportion of patients reaching	Primary: Both treatment groups had similar and significant (P<0.001) within-group decreases in mean HbA_{1c} values from baseline. LY2963016 met non-inferiority criteria compared with Lantus® for change in HbA_{1c} from baseline (-1.29 vs -1.34%, respectively; least-squares mean difference, 0.052%; 95% CI, -0.070 to 0.175; P>0.05). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs insulin glargine (Lantus®)	≤11%) and treated with ≥2 oral antihyperglycemic medications		HbA_{1c} <7%, daily mean blood glucose, insulin dose, hypoglycemia, weight change	There were no treatment differences (P>0.05) in fasting plasma glucose, proportion of patients reaching HbA_{1c} <7% or insulin dose at 24 weeks. Adverse events, allergic reactions, weight change, hypoglycemia and insulin antibodies were similar between treatment groups. Similar findings were observed in patients who were insulin-naïve or previously treated with insulin glargine at baseline.
Riddle et al.[101] EDITION 1 (2014) Insulin glargine U-300 via modified SoloSTAR® pen QPM vs insulin glargine U-100 via SoloSTAR® pen QPM Dose adjustment weekly, but no more often than every three days. Metformin was continued at prior dosage throughout the study.	MC, OL, PG Patients ≥18 years of age with a diagnosis of T2DM, HbA_{1c} 7.0 to 10.0%, and use of basal insulin therapy (≥42 units/day) with or without metformin for at least one year	N=804 6 months	Primary: HbA_{1c} change from baseline at month six Secondary: FPG change from baseline, percentage of participants attaining HbA_{1c} <7.0% and ≤6.5% or FPG ≤6.7 and <5.6 mmol/L, changes of basal and total daily insulin doses and of body weight, changes in SMPG profiles, hypoglycemic events, including percentage of participants with one or more confirmed or nocturnal hypoglycemic event from week nine to month six,	Primary: Mean HbA_{1c} decreased similarly in the two treatment groups with a final HbA_{1c} of 7.25% (SD 0.85) in the U-300 group compared to 7.28% (0.92) in the U-100 group. The LS mean change was 0.83% for both groups; difference 0.00% (95% CI, 0.11 to 0.11). Because the upper CI limit was below the 0.4% threshold, U-300 met the non-inferiority criterion. Secondary: Similar reductions to HbA_{1c} were observed for FPG in both treatment groups (from 8.72 mmol/L [SD 2.83] to 7.24 mmol/L [2.57] with U-300 and 8.90 mmol/L [2.94] to 7.21 mmol/L [2.40] with U-100). The percentages of participants attaining target HbA_{1c} levels were similar with U-300 and U-100 (39.6 and 40.9% for HbA_{1c} <7.0%, 21.0 and 21.6% for HbA_{1c} ≤6.5%, 46.3 and 44.9% for FPG ≤6.7, and 26.5 and 23.2% for FPG <5.6 mmol/L, respectively). Daily basal insulin dosage increased for both U-300 and U-100 at the end of the six month study. The dose increase was higher with U-300 than with U-100; LS mean difference was 0.09 units/kg/day (95% CI, 0.062 to 0.124). Mealtime insulin doses increased slightly in the first two weeks but were unchanged from baseline and alike in the two groups thereafter. Body weight increased by 0.9 kg in both treatment groups. The SMPG profiles declined in both treatment groups. No significant differences between changes in means at individual time points were demonstrated. The reduction of preinjection SMPG (combination of pre- and post-dinner measurements) from baseline to month six was similar between treatments. There was also no between-treatment difference in the change of day-to-day variability of preinjection SMPG during treatment.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			and other adverse events	The proportion of participants with one or more confirmed or severe nocturnal hypoglycemic events between the start of week nine and month six was 36% (146/404) on U-300, compared with 46% (184/400) on U-100. Analysis of this prespecified main measure of hypoglycemia demonstrated superiority of U-300 over U-100 with a significantly lower relative risk (RR 0.79; 95% CI, 0.67 to 0.93; P=0.0045). The percentage of participants reporting severe hypoglycemia at any time was similar for the two groups with 5.0% for U-300 compared with 5.7% for U-100 (RR 0.87; 95% CI, 0.48 to 1.55). The most common adverse events were infections, gastrointestinal events, or musculoskeletal complaints; these were equally distributed between the groups.
Yki-Järvinen et al.[102] EDITION 2 (2014) Insulin glargine U-300 via modified SoloSTAR® pen QPM vs insulin glargine U-100 via SoloSTAR® pen QPM Insulin dose adjustment weekly. Other oral antidiabetic agents were continued.	MC, OL, PG, RCT Patients ≥18 years of age with a diagnosis of T2DM, HbA_{1c} 7.0 to 10.0%, use of basal insulin therapy (≥42 units/day)	N=808 6 months	Primary: HbA_{1c} change from baseline at month six or last visit on treatment without rescue therapy Secondary: FPG change from baseline, percentage of participants attaining HbA_{1c} <7.0% and ≤6.5% or FPG ≤6.7 and <5.6 mmol/L, changes of basal and total daily insulin doses and of body weight, changes in SMPG profiles, hypoglycemic	Primary: Mean HbA_{1c} decreased similarly in the two treatment groups with a final HbA_{1c} at six months of 7.57% for U-300 and 7.56% for U-100, representing a mean treatment difference of -0.01% (95% CI, -0.14 to 0.12). Because the upper CI limit was below the 0.4% threshold, U-300 met the non-inferiority criterion. Secondary: Similar reductions in FPG from baseline (-1.14 and -1.06), percentage of participants attaining HbA_{1c} <7.0% (30.6% and 30.4%) and ≤6.5% (14.5% and 14.8%), were observed in the U-300 and U-100 groups respectively. Numerically, percentage of participants attaining a FPG ≤6.7 mmol/L (48.7% and 54.1%) and <5.6 mmol/L (29.4% and 33.6%) were higher for the U-300 group than U-100 group, the difference was not statistically significant. Overall, glucose measurements of the 8-point profile showed a comparable decrease in SMPG for both the U-300 and U-100 groups. However, the mean prebreakfast SMPG was lower with U-100 than with U-300 during the first eight weeks, and a more gradual decrease in prebreakfast SMPG was observed with U-300 than with U-100. At month six, a similar average prebreakfast SMPG was reached in both groups (119 mg/dL for U-300 and 113 mg/dL for U-100). Comparable results were observed between U-300

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			events, including percentage of participants with one or more confirmed or nocturnal hypoglycemic event from week nine to month six, and other adverse events	and U-100 for change in preinjection SMPG and variability in preinjection SMPG. The daily basal insulin dose increased from baseline to month six in both groups, mainly during the first 12 weeks. There was a significant difference in insulin dose between treatment groups at month six, with a LS mean difference of 11 units/day (95% CI, 8 to 14), with those in the U-300 group requiring 10% more basal insulin (units/kg/day) than those receiving U-100. Overall, 123 participants (30.5%) in the U-300 group experienced 379 nocturnal hypoglycemic events, and 169 participants (41.6%) in the U-100 group experienced 766 nocturnal hypoglycemic events. A significantly lower percentage of participants reported at least one nocturnal or severe hypoglycemic event from week nine to month six with U-300 (21.6%) compared with U-100 (27.9%). Analysis of this prespecified main secondary end point demonstrated superiority of U-300 over U-100 (RR 0.77; 95% CI, 0.61 to 0.99, P=0.038). The risk of nocturnal confirmed or severe hypoglycemia was also reduced with U-300 compared with U-100 during the six-month study period (RR, 0.71; 95% CI, 0.58 to 0.86). During the six-month treatment period, 288 participants (71.5%) treated with U-300 and 322 participants (79.3%) treated with U-100 reported one or more hypoglycemic events. In total, 2,750 hypoglycemic events were reported in the U-300 group and 3,675 in the U-100 group. The most common adverse events in the U-300 and U-100 groups were infections, nervous system disorders, gastrointestinal events and musculoskeletal complaints. These were equally distributed between the treatment groups.
Bolli et al.[103] EDITION 3 (2015) Insulin glargine U-300 via TactiPen® injector QPM	MC, OL, PG, RCT Patients ≥18 years of age with a diagnosis of T2DM for at least one year, use of oral	N=873 6 months	Primary: HbA_{1c} change from baseline at month six Secondary:	Primary: The mean decrease in HbA_{1c} was equivalent in the two treatment groups. At month six, the LS mean difference in change of HbA_{1c} was 0.04% (95% CI, −0.09 to 0.17) meeting the non-inferiority criterion. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs insulin glargine U-100 via SoloSTAR® pen QPM Insulin dose adjustment weekly.	glucose-lowering drugs in the last six months, and insulin naïve		FPG change from baseline, percentage of participants attaining HbA_{1c} <7.0% and ≤6.5% or FPG ≤6.7 and <5.6 mmol/L, changes of basal and total daily insulin doses and of body weight, changes in SMPG profiles, hypoglycemic events, including percentage of participants with one or more confirmed or nocturnal hypoglycemic event from week nine to month six, and other adverse events	The proportion of participants reaching target HbA_{1c} or laboratory-measured FPG at month six was much the same in the two treatment groups. Similar results in both the U-300 and U-100 groups were observed for change in pre-injection SMPG and variability in pre-injection SMPG. FPG from baseline to month six was somewhat greater in the U-100 group than in the U-300 group (LS mean difference, 0.39; 95% CI, 0.10 to 0.68). Over the 24-hour period, the eight-point SMPG profiles showed a similar decrease from baseline to month six with both U-300 and U-100 (LS mean difference, 0.18; 95% CI, −0.07 to 0.42). The pre-breakfast SMPG decreased more gradually with U-300 than with U-100. The basal insulin dose increased throughout the six-month treatment period in both treatment groups, but more so with U-300; mean increase was 0.62 (0.29) U/kg/day U-300, and to 0.53 (0.24) U/kg/day with U-100 (no P value reported). Between the start of week nine and month six, the percentage of participants experiencing at least one nocturnal confirmed or severe hypoglycemic event was 16% with U-300 and 17% with U-100 (RR, 0.89; 95% CI, 0.66 to 1.20). The percentage of participants who experienced ≥1 confirmed or severe hypoglycemic event was lower with U-300 (201/435, 46%) than with U-100 (230/438, 53%) over the six-month study period (RR, 0.88; 95% CI, 0.77 to 1.01). Weight gain during the treatment period was lower with U-300 (LS mean increase, 0.49; 95% CI, 0.14 to 0.83 kg) than with U-100 (LS mean increase 0.71; 95% CI, 0.36 to 1.06 kg; P value was non-significant).
Ritzel et al.[104] (2015) Insulin glargine U-300 via pen injector QPM vs	MA of EDITION 1, 2, and 3 Patients ≥18 years of age with a diagnosis of T2DM	N=2496 6 months	Primary: Change in HbA_{1c} from baseline, proportion of participants with HbA_{1c} <7.0, change in average pre-injection	Primary: The mean decrease in HbA_{1c} was similar in the two treatment groups. The proportion of participants who reached target HbA_{1c} after 6 months of treatment was similar in both treatment groups: 449 participants (36.2%) on U-300 and 438 participants (35.5%) on U-100. Laboratory-measured FPG decreased similarly in both groups. There was also no between-treatment difference in the variability of pre-injection SMPG at month six.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
insulin glargine U-100 via SoloSTAR® pen QPM Insulin dose adjustment weekly.			SMPG from baseline, and change in laboratory-measured FPG from baseline Secondary: Safety and tolerability	Secondary: The annualized rate (events per participant-year) of confirmed (≤70 mg/dl) or severe hypoglycemia at any time of day over the six-month study period was 15.22 with U-300 and 17.73 with U-100 (rate ratio, 0.86; 95% CI, 0.77 to 0.97; P=0.0116), corresponding to a relative difference of 14% in favor of U-300. No between-treatment differences in safety profile were identified, with similar rates of adverse events reported across all three studies.
Strojek et al.[105] (2009) Insulin glargine QD vs biphasic aspart 30 QD Insulin doses were titrated to achieve a FPG of 5.0 to 6.1 m mol/L. All patients also received metformin and glimepiride.	MC, NI, OL, PG, RCT Patients ≥18 years of age with type 2 diabetes who were insulin-naïve and receiving oral diabetes medications for ≥6 months, with HbA_{1c} >7.0 and ≤11.0%, BMI ≤40 kg/m^2	N=433 26 weeks	Primary: HbA_{1c} at 26 weeks Secondary: Proportion of patients achieving HbA_{1c} ≤6.5 and <7.0% without hypoglycemia after 26 weeks, HbA_{1c} reduction by >1% from baseline, nine-point self-measured plasma glucose profiles, PPG increments, Diab-MedSat and safety	Primary: HbA_{1c} at 26 weeks was 7.1 and 7.3% with biphasic aspart and insulin glargine, respectively (difference, -0.16%, 95% CI, -0.30 to -0.02; *P*=0.029), demonstrating non-inferiority. Secondary: In both treatment groups, 25% of patients achieved HbA_{1c} ≤6.5%. In the biphasic aspart group, 44.9% of patients achieved HbA_{1c} <7.0%, and 19.4% of patients achieved this value without hypoglycemia. The corresponding results with insulin glargine were 44.9 and 20.0%, respectively (*P* values not reported). In the biphasic aspart and insulin glargine groups, 60 and 57% of patients, respectively, achieved HbA_{1c} reduction by >1% (*P* value not reported). Biphasic aspart was associated with lower post-dinner and bedtime plasma glucose compared to insulin glargine on the nine-point self-measured plasma glucose profiles (*P*<0.05). No significant differences were observed at other time points. PPG increments were comparable between the two groups. No significant difference was seen between biphasic aspart and insulin glargine in treatment satisfaction as measured by Diab-MedSat questionnaire (score difference, -0.11; 95% CI, -2.36 to 2.14; *P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Fifty-eight and 51% of patients in the biphasic aspart and insulin glargine groups, respectively, reported at least one hypoglycemic event (RR, 1.41; 95% CI, 1.03 to 1.93; *P*=0.034). The risk of nocturnal hypoglycemia was also higher with biphasic aspart compared to insulin glargine (RR, 2.41; 95% CI, 1.34 to 4.34; *P*=0.003). No significant differences were seen in daytime hypoglycemia. Treatment-emergent adverse events were reported in 51 and 48% of patients in the biphasic aspart and insulin glargine groups, respectively. Less than 1% of patients reported serious adverse events that are possibly or probably related to study medications. One treatment-emergent death was reported in the insulin glargine group and was considered not related to the study medication. No significant differences were seen in cardiovascular risk markers, waist circumference or body weight.
Bretzel et al.[106] (2008) APOLLO Insulin glargine QD vs pre meal insulin lispro Insulin glargine doses were titrated to achieve FPG <5.5 mmol/L. Insulin lispro doses were titrated to achieve pre-prandial glucose <5.5 mmol/L and PPG <7.5 mmol/L.	MC, NI, OL, PG, RCT Patients 18 to 75 years of age with type 2 diabetes for ≥1 year, HbA_{1c} 7.5 to 10.5%, BMI ≤35 kg/m^2, FPG ≥6.7 mmol/L and receiving oral diabetes medications for ≥6 months with no dose change in the past 3 months	N=418 (intent-to-treat) N=377 (per-protocol) 44 weeks	Primary: Change in HbA_{1c} from baseline at 44 weeks Secondary: Proportion of patients with HbA_{1c} ≤6.5 or ≤7.0%, change in FPG, proportion of patients with FPG ≤5.5 mmol/L, changes in nocturnal blood glucose and eight-point blood glucose profiles, percentage of patients with nocturnal, severe	Per-protocol population was used in all efficacy endpoint analyses for non-inferiority testing. Intent-to-treat population was used subsequently for superiority testing. Primary: The adjusted mean change in HbA_{1c} was -1.71 and -1.87% with insulin glargine and insulin lispro, respectively, which met the predefined 0.4% limit for non-inferiority between the two groups. Intent-to-treat analysis failed to show superiority (-1.69 vs -1.82%; *P*=0.0908). Secondary: Thirty percent and 38% of patients reached HbA_{1c} ≤6.5% and 57 and 69% of patients reached HbA_{1c} ≤7.0% in the insulin glargine and insulin lispro groups, respectively (*P* values not reported). Change in FPG from baseline at 44 weeks was -4.3±2.3 and -1.8±2.3 mmol/L with insulin glargine and insulin lispro (*P*<0.0001). Significantly more patients in the glargine group achieved FPG ≤5.5 mmol/L compared to the insulin lispro group (38 vs 6%; *P* value not reported [per-protocol]; 35 vs 5%; *P*<0.001 [intent-to-treat]).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
The dose of oral diabetes medications remained stable throughout the entire study. Patients who were treated with a sulfonylurea were converted to equivalent dose of glimepiride during the screening phase.			and symptomatic hypoglycemia	Decrease in nocturnal glucose was significantly greater with insulin glargine compared to insulin lispro (-3.3 vs -2.6 mmol/L; *P*=0.0041 [per-protocol]; -3.3 vs -2.7 mmol/L; *P*=0.0017 [intent-to-treat]). A greater reduction was seen with insulin lispro compared to insulin glargine in PPG after breakfast, lunch, dinner and bedtime (*P*<0.05 for all). The rate of nocturnal hypoglycemia per patient was similar between insulin glargine and insulin lispro (0.42 vs 0.27; *P*=0.0709). The rates of severe and symptomatic hypoglycemia are significantly lower with insulin glargine compared to insulin lispro (0.02 vs 0.06; *P*=0.0989; 3.46 vs 11.02; *P*<0.0001, respectively).
Buse et al.[107] (2009) DURABLE Insulin glargine SC QD vs biphasic lispro 25 SC BID	MC, OL, PG, RCT Type 2 diabetics 30 to 80 years of age with HbA_{1c} >7.0%, receiving ≥2 oral antidiabetic agents for 90 days, and BMI <45 kg/m^2	N=1,045 24 weeks	Primary: HbA_{1c} at trial end Secondary: Change in baseline HbA_{1c}, body weight, and insulin dose; proportion of patients achieving HbA_{1c} <7.0 and ≤6.5%; seven-point self-monitored glucose profiles; incidence of hypoglycemia; safety	Primary: Biphasic lispro 25 achieved a significantly lower final HbA_{1c} compared to insulin glargine (7.3 vs 7.2%; P=0.005). Secondary: Biphasic lispro 25 had significantly greater decreases in HbA_{1c} compared to insulin glargine (-1.7 vs -1.8%; P=0.005). Biphasic lispro 25 was associated with significantly more weight gain compared to insulin glargine (2.5 vs 3.6 kg; P<0.0001). After 24 weeks, the total daily insulin dose was significantly higher with biphasic lispro 25 compared to insulin glargine (0.40 vs 0.47 units/kg; P<0.001). The proportion of patients achieving HbA_{1c} <7.0% was significantly greater with biphasic lispro 25 compared to insulin glargine (40.3 vs 47.5%; P<0.001). There was no difference between the two treatments in the proportions of patients achieving HbA_{1c} ≤6.5% (22.2 vs 24.6%; P=0.174).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Biphasic lispro 25 had a significantly higher rate of overall hypoglycemia (23.1 vs 28.0 episodes per patient-year; P=0.007), but a significantly lower rate of nocturnal hypoglycemia compared to insulin glargine (11.4 vs 8.9 episodes per patient year P=0.009). The rate of severe hypoglycemia was similar between the two treatments (0.03 vs 0.10 episodes per patient year; P=0.167). Overall, 4.3 and 6.2% of patients receiving insulin glargine and biphasic lispro 25 experienced at least one serious adverse event (P=0.051); the rate of cardiovascular-related serious adverse events was similar between the two treatments (26 vs 29%; P=0.716). There were six and 15 adverse events leading to discontinuation with insulin glargine and biphasic lispro 25 (P=0.077). One and five deaths occurred with insulin glargine and biphasic lispro 25 (P=0.218).
Yki-Järvinen et al.[108] (2000) Insulin glargine HS vs NPH insulin HS Initial doses were titrated to achieve FPG target ≤120 mg/dL. Existing oral antidiabetic drug therapy was continued.	RCT Patients 40 to 80 years of age with type 2 diabetes for at least 3 years, BMI <40 kg/m^2, HbA_{1c} 7.5 to 12.0%, previous oral therapy with either sulfonylureas alone or combined with acarbose, metformin, or metformin alone for at least 1 year, negative history of ketoacidosis, women of childbearing potential were required to be on contraceptive protection,	N=426 52 weeks	Primary: HbA_{1c} Secondary: FPG, 24-hour blood glucose profile, incidence of hypoglycemia, and serum C-peptide concentrations	Primary: The HbA_{1c} in the insulin glargine group decreased to 8.34±0.09% at end point from baseline (P<0.001) and 8.24±0.09% in the NPH group (P<0.001). Secondary: In the group of patients that achieved target FPG ≤120 mg/dL, HbA_{1c} decreased to 7.75±0.14% and 7.60±0.12% in the insulin glargine and NPH groups, respectively. However, there was no difference between groups (P values not reported). At study end point, blood glucose concentrations were significantly lower in the insulin glargine group than the NPH group before and after dinner. However, in the group of patients that achieved target FPG, blood glucose at 3 AM was significantly lower in patients taking NPH than those taking insulin glargine (P=0.0012). In the entire group of patients, the percentage of patients experiencing at least one symptomatic hypoglycemic episode was lower in the insulin glargine group than the NPH group. In the group of patients achieving target FPG, the percentage of patients experiencing symptomatic hypoglycemia was 33.0% and 50.7% in the insulin glargine and NPH groups, respectively (P=0.027).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	willingness to perform self monitoring of blood glucose			Serum C-peptide concentrations decreased similarly from baseline in both treatment groups (P<0.001).
Riddle et al.[109] (2003) Insulin glargine HS vs NPH insulin HS Insulin doses were titrated to achieve target FPG ≤100 mg/dL. Existing oral antidiabetic drug therapy was continued.	CS, MC, OL, PG, RCT Patients 30 to 70 years of age with type 2 diabetes for ≥2 years, treated with stable doses of 1 or 2 oral antidiabetic drug for ≥3 months, BMI 26 to 40 kg/m^2, HbA_{1c} 7.5 to 10.0%, FPG ≥140 mg/dL at screening	N=764 24 weeks	Primary: Percentage of patients achieving an HbA_{1c} ≤7.0% without a single instance of symptomatic nocturnal hypoglycemia confirmed by plasma-referenced glucose ≤72 mg/dL Secondary: Changes from baseline in HbA_{1c}, FPG, and weight; percentage of patients achieving an HbA_{1c} ≤7.0% or FPG ≤100 mg/dL independent of the occurrence of hypoglycemia; percentage of patients achieving FPG ≤100 mg/dL without confirmed hypoglycemia; overall rates of	Primary: The percentage of patients reaching a target HbA_{1c} ≤7.0% without a single instance of symptomatic nocturnal hypoglycemia was achieved by more patients taking insulin glargine than patients taking NPH (32.2 vs 26.7%, respectively; P<0.05). Secondary: Mean HbA_{1c} at end point was 6.96% with insulin glargine and 6.97% with NPH (between-treatment difference, -0.03%; 95% CI, -0.13 to 0.08; P=NS). Both groups also achieved comparable decreases in FPG at end point (between-treatment difference, -3.6 mg/dL; 95% CI, -8.82 to 1.62; P=NS). Weight increased similarly from baseline to end point in both groups (between-treatment difference, 0.2 kg; 95% CI, -0.24 to 0.68; P=NS). The HbA_{1c} ≤7.0% target was reached by 58.0% of patients on insulin glargine and 57.3% of patients in the NPH group. The goal FPG ≤100 mg/dL was achieved by 36.2% of patients on insulin glargine and 34.4% of patients on NPH. This target was achieved without hypoglycemia more often by patients taking insulin glargine. FPG ≤100 mg/dL without documented nocturnal hypoglycemia was achieved by 22.1% of patients taking insulin glargine compared to 15.9% of patients taking NPH (P<0.03). The rates of hypoglycemia (events/patient-year) with insulin glargine vs NPH were 13.9 vs 17.7, respectively for all symptomatic events (P<0.02) and 9.2 vs 12.9, respectively, for all confirmed events (P<0.005).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			symptomatic hypoglycemia	
Rosenstock et al.[110] (2009) Insulin glargine HS vs NPH insulin BID Insulin doses were titrated to achieve FPG ≤120 mg/dL during the first 3 years of the study, then FPG ≤100 mg/dL during the last 2 years of the study. Oral antidiabetic drug and/or prandial insulin could be continued or modified during the trial, and regular insulin could be added with meals at the investigator's discretion.	MC, OL, PG, RCT Patients 30 to 70 years of age with type 2 diabetes with HbA_{1c} 6.0 to 12.0% who were treated with oral antidiabetic drugs or insulin (alone or in combination) for ≥1 year	N=1,017 5 years	Primary: Percentage of patients with three or more step progression in Early Treatment Diabetic Retinopathy Study score after five years of treatment with either insulin glargine or NPH insulin Secondary: HbA_{1c}, FPG, and hypoglycemia	Primary: In the ITT analysis, 12.5% of patients in the insulin glargine group experienced a ≥3 step progression in Early Treatment Diabetic Retinopathy Study score after five years compared to 14.6% of patients receiving NPH insulin (difference, −2.10%; 95% CI, −6.29 to 2.09). In the PP analysis, 14.2 and 15.7% of patients experienced a ≥3 step progression in Early Treatment Diabetic Retinopathy Study score after five years, respectively (difference, -1.98%; 95% CI, -7.02 to 3.06). Secondary: After five years, the mean FPG in the insulin glargine group was 7.8 and 7.7 mmol/L in the NPH insulin group (ITT population). The proportion of patients achieving FPG ≤5.6 mmol/L was 28.5% with insulin glargine and 24.3% with NPH insulin. After five years, the mean HbA_{1c} (last observation carried forward) improved from a baseline of 8.4 and 8.3 to 7.8 and 7.6% for patients in the insulin glargine and NPH insulin groups, respectively (difference, 0.21%; P=0.0053). Weight gain was 3.7 kg with insulin glargine compared to 4.8 kg with NPH insulin (ITT; P=0.0505). The use of NPH insulin was associated with a greater incidence of severe hypoglycemia than insulin glargine (11.1 vs 7.6%, respectively; P=0.0439). However, there was no significant difference in symptomatic hypoglycemia (P=0.1366) or nocturnal hypoglycemia (P=0.2248) between the treatment groups.
Aschner et al.[111] (2015) GALAPAGOS Insulin glargine (± glulisine)	MC, OL, RCT Insulin-naïve type 2 diabetes patients ≥35 years of age failing	N=923 24 weeks	Primary: Percentage of patients reaching HbA_{1c} < 7% at study end without any documented	Primary: A similar percentage of patients treated with glargine (± glulisine) (33.2%) or premix (31.4%) achieved HbA_{1c} <7% with no documented symptomatic hypoglycemia over the 24-week treatment period. The glargine (± glulisine) strategy did not show superiority compared with a premix strategy on the primary endpoint (difference in success rate = 1.8%;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs premixed insulin (insulin aspart 30% and protamine-crystallized insulin aspart (70%) continuing metformin ± insulin secretagogue	oral agents (HbA_{1c} 7.0 to 10.5%)		symptomatic hypoglycemia (blood glucose ≤3.1 mmol/L) Secondary: Changes in HbA_{1c}, percentage of patients who achieved HbA_{1c} <7% and <6.5%, weight, insulin dose, hypoglycemia, adverse events	P=0.56). The primary endpoint was met by 43.8% of those treated with glargine alone, 19.3% treated with glargine + glulisine, and 37.7% and 27.9% of those treated with once-daily and twice-daily premix, respectively. Secondary: Mean HbA_{1c} values were the same at baseline in both groups (8.7%), decreased throughout the study, and were 7.2% with glargine (± glulisine) and 7.0% with premix at study end. The least squares (LS) mean change (standard error) from baseline to study end was –1.48 (0.04) % and –1.64 (0.04) % with glargine (± glulisine) and premix, respectively. The LS mean difference between groups was 0.16% (95% CI, 0.04 to 0.27) in favor of premix (P=0.008). The LS mean change from baseline in FPG was greater with glargine (± glulisine) (–3.0 mmol/l) than with premix (–2.6 mmol/l), with an LS mean difference of –0.3 mmol/l (95% CI, –0.5 to –0.2; P<0.001). A similar percentage of patients treated with glargine (± glulisine) or premix experienced at least one treatment-emergent adverse event (34.6 vs 35.7%). Mean body weight gain was similar for glargine (± glulisine) and premix More patients using premix achieved target (52.6 vs 43.2%, P=0.005); symptomatic hypoglycemia was less with glargine (1.17 vs 2.93 events/patient–year).
Fritsche et al.[112] (2003) Insulin glargine AM and glimepiride 3 mg QD vs insulin glargine HS and glimepiride 3 mg QD vs	MC, OL, PG, RCT Patients with type 2 diabetes <75 years of age, previously on oral therapy with any sulfonylurea as monotherapy or in combination with metformin or acarbose, BMI <35 kg/m^2, FPG ≥120 mg/dL, HbA_{1c} 7.5 to 10.5%	N=700 28 weeks	Primary: Change in HbA_{1c} from baseline to end point, frequency of patients who experienced hypoglycemic episodes during the study Secondary: HbA_{1c} ≤7.5%, FBG ≤100 mg/dL, response rates, mean 24-hour	Primary: Over the 24-week treatment period, HbA_{1c} levels improved by -1.24% (two-sided 90% CI, -1.10 to -1.38) with morning insulin glargine, -0.96% (90% CI, -0.81 to -1.10) with bedtime insulin glargine and -0.84% (90% CI, -0.69 to -0.98) with bedtime NPH (P values not reported). Improvement in HbA_{1c} was significant in patients receiving morning insulin glargine than in patients receiving NPH (-0.40%; 90% CI, -0.23 to -0.58; P<0.001) and bedtime insulin glargine (-0.28%; 90% CI, -0.11 to -0.46; P=0.008). Secondary: More patients in the morning insulin glargine group achieved HbA_{1c} level of <7.5% (43%) than patients in the bedtime NPH (32%) and bedtime insulin glargine groups (33%; P=0.021).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
NPH insulin HS and glimepiride 3 mg QD			blood glucose values, hypoglycemic events and adverse events	FPG levels improved in all three groups. The average reduction in FPG level achieved over the 24-week treatment did not differ among the groups (P>0.2). The morning insulin glargine group showed a greater decrease in mean daily blood glucose levels compared to both the bedtime NPH group (P<0.001) and the bedtime insulin glargine group (P=0.002). Hypoglycemic events were similar among the three groups. The number of patients experiencing nocturnal hypoglycemia was lower in both the morning and bedtime insulin glargine groups than with the bedtime NPH group (P<0.001). Fewer patients experienced symptomatic hypoglycemia with bedtime insulin glargine (43%) than with bedtime NPH (58%; P=0.001) and morning insulin glargine (56%; P=0.004). Adverse event rates were similar in all three groups (P values not reported).
Pan et al.[113] (2007) Insulin glargine HS and glimepiride 3 mg QD vs NPH insulin HS and glimepiride 3 mg QD	MN, NI, OL, PG, RCT Insulin-naïve Asian patients 40 to 80 years of age with type 2 diabetes and random venous plasma glucose concentration ≥11.1 mmol/L, FPG ≥7 mmol/L, or PPG ≥11.1 mmol/L 2 hours after oral glucose tolerance test, poorly controlled on oral antidiabetic drug for ≥3 months prior to study entry, BMI 20 to	N=448 24 weeks	Primary: Change in HbA_{1c} from baseline to endpoint Secondary: Mean FPG level, eight-point blood glucose profiles, proportion of patients with HbA_{1c} <7.5%, proportion of combined responders (defined as HbA_{1c} <7.5% and FPG ≤120 mg/dL), change in BMI, hypoglycemia	Primary: The insulin glargine group had a decrease of -1.10% in HbA_{1c} vs -0.92% in the NPH group. There was not a statistically significant difference between both groups (P=0.0631). The results were confirmed in a full analysis set, the difference between adjusted mean changes in the two groups was 0.22 (95% CI, 0.02 to 0.42; P=0.0319). Secondary: FPG decreased to a similar extent in both the insulin glargine and NPH groups (-106 and -104 mg/dL, respectively; P value not reported). At study end, the eight-point blood glucose profiles were similar in both the insulin glargine and NPH groups, except at postdinner time, when the use of insulin glargine resulted in lower glucose concentrations (P=0.0436). The insulin glargine group had greater decreases in daily blood glucose levels than the NPH group (-94 vs -80 mg/dL, respectively; P=0.018). The proportion of patients achieving HbA_{1c} <7.5% at the end of the study was greater for the insulin glargine group than the NPH group (38.1 vs 30.3%, respectively). This was also consistent with the proportion of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	35 kg/m^2, HbA_{1c} 7.5 to 10.5%, and FPG >120 mg/dL			patients achieving target FPG (62.3 vs 58.7%, respectively). In the insulin glargine group, a greater proportion of patients achieved HbA_{1c} <7.5% without experiencing nocturnal symptomatic hypoglycemia (P=0.0174). Both groups had similar changes in BMI from baseline (1.40 and 1.29 kg/m^2 in the insulin glargine and NPH groups, respectively). The number of hypoglycemic episodes was significantly lower with insulin glargine than with NPH (P<0.004). These differences were seen in particular with symptomatic hypoglycemia (P<0.0003), severe hypoglycemia (P<0.03), and nocturnal hypoglycemia (P<0.001).
Eliaschewitz et al.[114] (2006) Insulin glargine HS and glimepiride 4 mg QD vs NPH insulin HS and glimepiride 4 mg QD Insulin doses were titrated to achieve target FPG ≤100 mg/dL.	MC, OL, RCT Men and women ≤75 years of age with type 2 diabetes, who had not achieved good metabolic control on oral antidiabetic drugs for at least 6 months, with HbA_{1c} levels 7.5 to 10.5%, FPG ≥100 mg/dL, and BMI ≤35 kg/m^2	N=528 24 weeks	Primary: Change in HbA_{1c} from baseline to end of study Secondary: Percentage of patients who responded to treatment (defined as those who achieved HbA_{1c} ≤7.5% and FPG ≤100 mg/dL by end of study), change in FPG from baseline, hypoglycemia	Primary: At 24 weeks, both groups demonstrated equivalence in change in HbA_{1c} (adjusted mean difference, -0.047; 90% CI, -0.232 to 0.138). Based on equivalence result, an analysis was conducted and also revealed no significant difference between groups (adjusted mean difference, -0.029; 90% CI, -0.210 to 0.153; P=0.795). Secondary: The percentages of responders were similar in both the insulin glargine group and NPH group for HbA_{1c} ≤7.5% (50.4 vs 48.0%, respectively; P=0.529) and FPG ≤100 mg/dL (42.1 vs 39.8%, respectively; P=0.752). There was no significant difference between groups in changes in FPG (P=0.298). The insulin glargine group had a lower RR of hypoglycemia than the NPH group (RR, 1.27; 95% CI, 1.03 to 1.57). There was also a greater reduction in the risk of nocturnal hypoglycemia (RR, 1.2; 95% CI, 1.09 to 1.37) and confirmed nocturnal events (RR, 1.19; 95% CI, 1.07 to 1.31) in the insulin glargine group than the NPH group (P value not reported).
Yki-Järvinen et al.[115] (2006)	MC, OL, PG, RCT Men and women 35 to 75 years of age with type 2 diabetes previously	N=110 36 weeks	Primary: Change in HbA_{1c} from baseline Secondary:	Primary: At 36 weeks, HbA_{1c} decreased from 9.13±0.15% to 7.14±0.12% and from 9.26±0.15% to 7.16±0.14% in the G+MET and NPH+MET groups, respectively. The changes in HbA_{1c} were determined to be not significant between groups (P value not reported).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Insulin glargine HS and metformin (G+MET) vs NPH insulin HS and metformin (NPH+MET) Insulin doses were titrated to achieve an FPG 72 to 100 mg/dL in both groups.	treated with a stable dose of sulfonylurea and metformin (>1.5 g) or metformin alone for at least 3 months prior to screening, with a BMI 20 to 40 kg/m^2, HbA_{1c} ≥8.0%, FPG ≥7 mmol/L measured during self monitoring of blood glucose between 4 and 2 weeks prior to study start, and fasting C-peptide ≥0.33 nmol/L		Diurnal glucose concentrations, symptomatic hypoglycemia	Secondary: The diurnal profiles were consistently lower in the G+MET group compared to the NPH+MET group (8.6±0.3 vs 10.1±0.3 mmol/L, respectively; P=0.002). During the first 12 weeks, the G+MET group had significantly lower number of episodes of symptomatic hypoglycemia than the NPH+MET group, but the rates became similar thereafter. The frequency of hypoglycemia averaged 5.4 and 8.0 episodes/patient-year for the G+MET and NPH+MET groups, respectively (P=0.12).
Meneghini et al.[116] (2020) ACHIEVE Control Insulin glargine 300 U/mL (Gla-300) vs standard-of-care basal insulin analogues (SOC-BI)	MC, OL, PRO, RCT Insulin-naïve adults with type 2 diabetes and HbA_{1c} 8.0% to 11.0% after ≥1 year of treatment with two or more anti-hyperglycemic agents	N=3,304 12 months	Primary: The proportion of adults with individualized HbA_{1c} target attainment at 6 months with no documented symptomatic (≤3.9 mmol/L) or severe hypoglycemia at any time of day from baseline to 6 months Secondary:	Primary: The 6-month results demonstrated superiority of Gla-300 over SOC-BI for the proportion of adults achieving individualized HbA_{1c} targets without documented symptomatic and/or severe hypoglycemia at any time of day from baseline to six months (composite primary endpoint: OR, 1.19; 95% CI, 1.01 to 1.39; P=0.03). Secondary: At 12 months, 26.1% (Gla-300) and 23.7% (SOC-BI) of adults achieved HbA_{1c} targets without documented symptomatic (≤3.9 mmol/L [≤70 mg/dL]) or severe hypoglycemia (OR, 1.14; 95% CI, 0.97 to 1.35; 33.0% and 29.5%, respectively, achieved HbA_{1c} targets without documented symptomatic (<3.0 mmol/L [<54 mg/dL]) or severe hypoglycemia (OR, 1.19; 95% CI, 1.02 to 1.38).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			HbA_{1c} target attainment without documented symptomatic (≤3.9 mmol/L [≤70 mg/dL]) or severe hypoglycemia at 12 months	
Vilsbøll et al.[117] (2020) Insulin glargine (INS) vs dapagliflozin plus saxagliptin (DAPA + SAXA)	OL, PG, RCT Patients ≥18 years of age with type 2 diabetes and inadequate glycemic control (HbA_{1c} ≥8% to ≤12%) receiving stable metformin therapy (≥1500 mg/day) with or without sulphonylurea (≥50% of maximal dose) for at least 8 weeks before screening	N=600 52 weeks	Primary: mean change in HbA_{1c} and body weight from baseline and achieving an optimal glycemic response (HbA_{1c} <7.0%) without hypoglycemia Secondary: Proportion of patients requiring rescue medication or discontinuing due to lack of glycemic control and change from baseline in the average postprandial glucose values; safety	Primary: At 52 weeks, HbA_{1c} decreased more with DAPA + SAXA (adjusted least squares (LS) mean, −1.5%; 95% CI, −1.6% to −1.4%) than with INS (adjusted LS mean, −1.3%; 95% CI, −1.4% to −1.1%); the LS mean difference (95% CI) was −0.25% (−0.4% to −0.1%; P=0.009). Total body weight reduced with DAPA + SAXA (LS mean, -1.8 kg; 95% CI, -2.4 to -1.3) and increased with INS (LS mean, +2.8 kg; 95% CI, 2.2 to 3.3). More patients on DAPA + SAXA (17.6%) achieved HbA_{1c} <7.0% without hypoglycemia versus those on INS (9.1%). Secondary: Overall, 174 patients required rescue medication or discontinued the study due to lack of glycemic control: 77 (23.8%) in the DAPA + SAXA group and 97 (30.4%) in the INS group at week 52. The adjusted percentage of patients requiring rescue medication or discontinuation at week 52 was 21.0% (95% CI, 16.7% to 26.1%) and 27.7% (95% CI, 22.8% to 33.3%) in the DAPA + SAXA and INS groups, respectively (OR, 0.7; 95% CI, 0.5 to 1.0). At least one adverse event was reported by 209 patients (64.5%) in the DAPA + SAXA group and 217 (68.0%) in the INS group. Adverse events considered by the investigator to be treatment-related were more common in the DAPA + SAXA group (11.1%) versus the INS group (4.7%).
Holman et al.[118] (2007)	MC, OL, RCT	N=708 1 year	Primary: HbA_{1c} at one year	Primary: At 52 weeks, the reduction in HbA_{1c} from baseline was 1.3% in the biphasic group, 1.4% in the prandial group, and 0.8% in the basal group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Biphasic insulin aspart 30 BID vs insulin aspart TID before meals vs insulin detemir HS to BID (AM and HS) Insulin doses were titrated to achieve pre-meal capillary blood glucose 72 to 99 mg/dL or PPG 90 to 126 mg/dL. Existing oral antidiabetic drug regimens were continued.	Patients ≥18 years of age with type 2 diabetes who had not been previously treated with insulin, HbA_{1c} 7.0 to 10.0%, on maximum tolerated doses of metformin and a sulfonylurea for ≥4 months, and BMI ≤40 kg/m^2		Secondary: Proportion of patients with HbA_{1c} ≤6.5%, proportion of patients with ≤ 6.5% but without hypoglycemia during weeks 48 to 52, rate of hypoglycemia, weight gain, eight-point self monitoring blood glucose	The difference between the HbA_{1c} levels in the biphasic group (7.3%) and the prandial group (7.2%) were not significant (P=0.08); however, the HbA_{1c} level was higher in the basal group (7.6%; P<0.001 for both comparisons with the basal group). Secondary: The proportion of patients with an HbA_{1c} ≤6.5% was 17% in the biphasic group and 23.9% in the prandial group (P=0.08). The proportion of patients in the basal group was 8.1%, which was lower than the other groups (P=0.001 for the comparison with the biphasic group and P<0.001 for the comparison with the prandial group). The proportion of patients with an HbA_{1c} ≤6.5% without hypoglycemia during weeks 48 to 52 were 52.5, 43.9, and 78.9% in the biphasic, prandial, and basal groups, respectively (P=0.001). The proportion of patients with an HbA_{1c} level of ≤7.0% was significantly different between the basal group (27.8%) and each of the two other groups (biphasic group, 41.7%; prandial group, 48.7%; P<0.001 for both comparisons). Patients gained weight on all regimens, with a greater increase in the prandial group (5.7 kg; P<0.001 vs basal) than in the biphasic group (4.7 kg; P=0.005 vs prandial and P<0.001 vs basal) or the basal group (1.9 kg). There were no significant differences in overall mean self monitoring blood glucose among the treatment groups. Overall rates of hypoglycemia were 91.9% in the biphasic group (P=0.08 vs prandial), 96.2% in the prandial group (P<0.001 vs basal), and 73.9% in the basal group (P<0.001 vs biphasic). The mean numbers of hypoglycemic events per patient per year were 5.7 in the biphasic group, 12.0 in the prandial group, and 2.3 in the basal group.
Holman et al.[119] (2009)	MC, OL, RCT Patients ≥18 years of age with type 2	N=708 3 years	Primary: HbA_{1c} at three years	Primary: The mean reduction in HbA_{1c} from baseline to year three was 1.3% in the biphasic group, 1.4% in the prandial group, and 1.2% in the basal group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Biphasic insulin aspart 30 BID vs insulin aspart TID before meals vs insulin detemir HS to BID (AM and HS) Insulin doses were titrated to achieve pre-meal capillary blood glucose 72 to 99 mg/dL or PPG 90 to 126 mg/dL. Existing oral antidiabetic drug regimens were continued.	diabetes who had not been previously treated with insulin, HbA_{1c} 7.0 to 10.0%, on maximum tolerated doses of metformin and a sulfonylurea for ≥4 months, and BMI ≤40 kg/m^2		Secondary: Proportion of patients with HbA_{1c} ≤6.5%, rate of hypoglycemia, weight gain, self monitoring blood glucose	Secondary: The proportion of patients with an HbA_{1c} ≤6.5% was 31.9% in the biphasic group and 44.7%% in the prandial group (P=0.006). The proportion of patients in the basal group was 43.2% (P=0.03 vs biphasic). The proportion of patients with an HbA_{1c} ≤7.0%was 49.4% in the biphasic group, 67.4% in the prandial group (P<0.001 vs biphasic) and 63.2% in the basal group (P=0.02 vs biphasic). Self monitoring blood glucose values were significantly lower in the prandial group than in the biphasic group (P=0.001), but were not significantly different than in the basal group (P=0.06). No significant differences were seen in fasting glucose values in the three groups. A greater mean reduction in postprandial glucose values was seen in the prandial group than in either the biphasic group (P<0.001) or the basal group (P=0.007), with a greater reduction in the basal group than in the biphasic group (P=0.04). The reduction in 3 a.m. glucose values was significantly greater in the basal group than in the prandial group (P=0.02) Patients gained weight on all regimens, with a greater increase in the prandial group (6.4 kg; P<0.001 vs basal) than in the biphasic group (5.7 kg; P=0.20 vs prandial and P=0.005 vs basal) or the basal group (3.6 kg). Overall rates of hypoglycemia were 49.4% in the biphasic group (P=0.68 vs prandial), 51.0% in the prandial group (P=0.14 vs basal), and 44.0% in the basal group (P=0.29 vs biphasic). The median number of hypoglycemic events per patient per year during the trial was 3.0 in the biphasic group, 5.5 in the prandial group, and 1.7 in the basal group. At 3 years, no differences were seen in changes from baseline in either systolic or diastolic blood pressure, high-density lipoprotein or low-density lipoprotein cholesterol, triglycerides, or the ratio of urinary albumin to creatinine, although the differences in high-density lipoprotein cholesterol were significant (P=0.03).
Garber et al.[120] (2007)	MC, OL, PG, pooled analysis, RCT	N=1,374	Primary: Difference in HbA_{1c} at study	Primary: HbA_{1c} with insulin detemir was as effective as NPH after 22 to 26 weeks (mean treatment difference, 0.035%; 95% CI, -0.114 to 0.183 for older

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Insulin detemir QD or BID and prandial insulin (insulin aspart or regular insulin) or oral antidiabetic drug treatment vs NPH insulin QD or BID and prandial insulin (insulin aspart or regular insulin) or oral antidiabetic drug treatment Insulin doses were adjusted to achieve target FBG 72 to 126 mg/dL, FPG <108 mg/dL, PPG <180 mg/dL or <162 mg/dL.	Patients ≥18 years of age with type 2 diabetes for at least 1 year treated with insulin, insulin analogs, or oral antidiabetic drugs for at least 2 months, HbA_{1c} ≤12.0% (in study 3, patients with HbA_{1c} 7.5 to 10% were enrolled); patients were stratified to older (aged ≥65 years) and younger (18 to 64 years of age) subgroups	22 to 26 weeks	endpoint between younger and older patients Secondary: Glucose variability, FPG, insulin doses, body weight, hypoglycemia	persons and 0.100%; 95% CI, -0.017 to 0.217 for younger persons; P value not reported). Secondary: After 22 to 26 weeks, within-person variation was significantly lower with insulin detemir than with NPH for older persons (24.3 vs 27.2 mg/dL for insulin detemir and NPH, respectively; P<0.05) and for younger persons (22.6 vs 25.8 mg/dL for insulin detemir and NPH, respectively; P<0.001). FPG with insulin detemir was similar to that with NPH after 24 or 26 weeks for both older and younger patients (mean treatment difference, 0.97 mg/dL; 95% CI, -8.01 to 9.95 for older persons and 4.69 mg/dL; 95% CI, -2.30 to 11.67 for younger persons; P value not reported). The mean daily insulin dose was 0.63±0.45 IU/kg for insulin detemir and 0.48±0.28 IU/kg for NPH in younger patients. Older patients had similar doses to younger patients (0.59±0.44 IU/kg for insulin detemir and 0.46±0.26 IU/kg for NPH; P value not reported). The RR for overall hypoglycemia was statistically lower with insulin detemir than with NPH in both older and younger patients (0.59; P=0.002 and 0.75; P=0.022, respectively). The RR for all nocturnal episodes was significantly lower with insulin detemir (P<0.001) in younger patients, but was not significant in older patients.
Raslová et al.[121] (2007) Insulin detemir QD or BID and prandial insulin (insulin aspart or regular insulin) vs NPH insulin QD or BID and prandial	PG, pooled analysis, RCT Patients with insulin-treated type 2 diabetes	N=900 22 to 24 weeks	Primary: Weight gain, HbA_{1c} Secondary: Not reported	Primary: Patients taking insulin detemir had little weight gain, regardless of BMI at study entry. However, patients taking NPH had increased weight gain as baseline BMI increased (P=0.025). Glycemic control was similar with both treatment groups (P value not reported). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
insulin (insulin aspart or regular insulin)				
Siegmund et al.[122] (2007) Insulin glargine plus premeal rapid-acting insulin analogs vs NPH plus premeal rapid-acting insulin analogs	OS, PRO Patients with type 2 diabetes	N=119 18 months	Primary: Change in HbA_{1c} from baseline Secondary: Weight gain, incidence of hypoglycemia	Primary: For the insulin glargine group, results showed statistically significant reductions in HbA_{1c} compared to baseline (-0.49%; 95% CI, -0.26 to -0.71; P<0.001). However, the reduction from baseline in HbA_{1c} for the NPH group was determined to be not significant (-0.12%; 95% CI, -0.31 to 0.06; P=0.189). After 18 months, the difference between the two treatment groups was 0.37% (P<0.015). Secondary: Average weight gain was significantly higher in the NPH group than in the glargine group (2.10 vs 0.25 kg, respectively; P=0.025). Although there was a lower risk of hypoglycemia in the insulin glargine group than in the NPH group (0.50 vs 0.71 episodes/patient/month, respectively), the results did not reach statistical significance (P=0.081).
Rosenstock et al.[123] (2005) Insulin glargine HS vs NPH insulin QD or BID	MA MA of 4 randomized trials in type 2 diabetics comparing insulin glargine to NPH, baseline HbA_{1c} 8.8% in the insulin glargine group and 8.7% in the NPH group	N=2,304 20 to 24 weeks	Primary: Incidence of hypoglycemia Secondary: Effect on HbA_{1c}, percentage of patients reaching target HbA_{1c} ($\leq$7.0%), effect on FPG, and insulin dose	Primary: Significant reductions in symptomatic hypoglycemic risk (-11%; P=0.0006) and nocturnal hypoglycemic risk (-26%; P<0.0001) were reported with insulin glargine compared to NPH. Secondary: No significant difference was noted between groups in HbA_{1c} reduction or percentage of patients reaching target HbA_{1c} $\leq$7.0%. FPG was significantly lower with insulin glargine (155 mg/dL) compared to NPH (161 mg/dL; P=0.0233). Both groups had similar mean basal and total insulin doses at all study endpoints.
Berard et al.[124] (2015) Insulin glargine vs	OL, RCT Patients from the Winnipeg ACCORD trial center who were	N=66 6 months	Primary: Rate of symptomatic hypoglycemias Secondary:	Primary: For each hypoglycemic category, the semiannual rates ± SE per 100 patients were determined. The rates of symptomatic hypoglycemia did not differ significantly between groups, with 37.5±2.2 for the insulin glargine group and 31.1±2.1 for the NPH insulin group. Patients treated with NPH insulin had higher frequencies of severe hypoglycemia (6.1±0.9)

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
NPH insulin	receiving basal insulin therapy with a long-acting insulin analogue		Effect on HbA_{1c}, weight, FPG	compared with 2.7±0.6 for the insulin glargine group. The rates of nocturnal hypoglycemia were comparable between the groups, with 4.2±0.7 for the insulin glargine group and 4.4±0.8 for the NPH group. Secondary: A significant difference in HbA_{1c} changes was observed in the two groups. The mean ± SE HbA_{1c} decreases from baseline were –0.34%±0.11 for the insulin glargine group vs –0.01%±0.10 for the NPH insulin group. Changes in FPG from baseline to endpoint were not statistically significant between groups. Changes in FPG from baseline to endpoint for the insulin glargine and NPH groups were –0.98±0.34 and –0.46±0.33, respectively. Weight gain was similar in the treatment groups. Over the course of the trial, the insulin glargine-treated group experienced a 0.82±0.47 kg weight increase, while the NPH insulin-treated group showed a slight decrease of –0.08±0.44 kg.
Horvath et al.[125] (2007) Insulin analogs (insulin glargine or insulin detemir) vs NPH insulin	MA Analysis of 8 studies comparing long-acting insulin analogs to NPH in patients with type 2 diabetes	N=2,293 24 to 52 weeks	Primary: Change in HbA_{1c} from baseline to endpoint Secondary: Number of overall, severe, and nocturnal hypoglycemia	Primary: In a MA of studies with relevant data available comparing insulin glargine vs NPH when both agents were administered in the evening, the WMD of change of HbA_{1c} from baseline was estimated to be 0.1% (95% CI, -0.1 to 0.2; P=0.49) in favor of NPH. In all studies comparing evening insulin glargine to NPH, the WMD of change of HbA_{1c} was estimated to be 0.00% (95% CI, -0.1 to 0.1; P=0.93) which confirmed the previous result. In both analyses that compared change in HbA_{1c} with insulin detemir to NPH, NPH was favored (WMD, 0.1%; 95% CI, 0.01 to 0.20; P=0.03 when standard deviations were calculated and 0.2%; 95% CI, 0.02 to 0.30; P=0.08 using pooled standard deviations). Even though this result indicated a statistically significant difference in change of HbA_{1c} between insulin detemir and NPH, the difference was within the "non-inferiority" margin of 0.4% for both studies. Secondary: In both comparisons of insulin glargine vs NPH and insulin detemir vs NPH, both long-acting agents had statistically lower rates of severe hypoglycemia (OR, 0.70; 95% CI, 0.40 to 1.23; P value not reported and 0.50; 95% CI, 0.18 to 1.38; P=0.18, respectively).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Insulin glargine was found to have a lower frequency of symptomatic hypoglycemia than NPH (RR, 0.84; 95% CI, 0.75 to 0.95; P=0.005). In terms of overall hypoglycemia, there was no difference in the rates of at least one hypoglycemic episode between insulin glargine in the morning, insulin glargine in the evening, and NPH at bedtime (74, 68 and 75%, respectively; P=NS). When comparing insulin detemir to NPH, insulin detemir had significantly lower rates of symptomatic and overall hypoglycemia (RR, 0.56; 95% CI, 0.42 to 0.74; P<0.001 and 0.82; 95% CI, 0.74 to 0.90; P<0.0001, respectively). Both insulin glargine and insulin detemir resulted in significantly lower rates of nocturnal hypoglycemia in comparison to NPH (RR, 0.66; 95% CI, 0.55 to 0.80; P<0.0001 and 0.63; 95% CI, 0.52 to 0.76; P<0.00001, respectively).
Bazzano et al.[126] (2008) Insulin glargine vs NPH insulin	MA, SR (12 RCTs) Patients with type 2 diabetes with or without oral antidiabetic agents, and not receiving insulin	N=4,385 ≥4 weeks	Primary: Change in baseline HbA_{1c}, FPG, and body weight Secondary: Incidence of hypoglycemia	Primary: Changes in HbA_{1c}, FPG, and body weight demonstrate positive values favoring insulin glargine and negative values favoring NPH. The pooled net change for FPG was 0.21 mmol/L (95% CI, -0.02 to 0.45). Final HbA_{1c} was 7.9 and 7.7% with insulin glargine and insulin NPH, respectively. Pooled net change in body weight was -0.33 kg (95% CI, -0.61 to -0.06). Secondary: The proportions of patients reporting any (59.0 vs 53.0%; P<0.001), symptomatic (51.4 vs 42.9%; P<0.001) and nocturnal hypoglycemia (33.3 vs 19.1%; P<0.001) were significantly greater with insulin NPH. The rates of confirmed (10.0 vs 6.3%; P=0.11) and severe hypoglycemia (2.5 vs 1.4%; P=0.07) were not different between the two treatments.
Davidson et al.[127] (2009) Biphasic insulin aspart 30 (BIAsp 30)	MA Patients with type 2 diabetes who received treatment	N=1,674 (9 trials) 12 to 48 weeks	Primary: Overall rate of nocturnal hypoglycemia (all major, minor, and symptoms-only)	Primary: No significant difference was found between treatments with respect to the rate of overall hypoglycemia (RR, 1.08; 95% CI, 0.94 to 1.24; P=NS). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs biphasic human insulin 30 (BHI 30)	with biphasic insulin aspart 30 or biphasic human insulin 30		Secondary: Major hypoglycemia, minor hypoglycemia, daytime hypoglycemia, overall hypoglycemia (the sum of all major, minor, and symptoms-only episodes), change in weight from baseline to 12 to 16 weeks of treatment	BIAsp 30 had a significantly lower rate of nocturnal hypoglycemia than BHI 30 (RR, 0.50; 95% CI, 0.38 to 0.67; P<0.01). BHI 30 was associated with a significantly lower rate of daytime hypoglycemia (RR, 1.24; 95% CI, 1.08 to 1.43; P<0.01). Significantly fewer patients experienced a major hypoglycemic episode with BIAsp 30 compared with BHI 30 (P<0.05). Rates of minor hypoglycemia were not significantly different between treatments. BIAsp 30 treatment was associated with a larger reduction in PPG than BHI 30 (P<0.01). BHI 30 treatment was associated with a significantly larger reduction in FPG than BIAsp 30 (P<0.01). There were no significant differences in HbA_{1c} among the treatment groups. Both BIAsp 30 and BHI 30 were associated with an increase in weight from base line (0.2 and 0.7 kg, respectively; P=NS).
Fakhoury et al.[128] (2008) NPH QD vs insulin detemir in the evening vs insulin glargine in the evening	MA (5 OL, PG, RCTs) Patients between 55.5 and 61.0 years of age with type 2 diabetes who were insulin-naïve and currently receiving oral diabetes medications, with HbA_{1c} 8.6 to 9.6% and BMI of 28.5 to 32.0 kg/m^2	N=2,092 5 to 12 months	Primary: Weight gain, hypoglycemia, HbA_{1c} Secondary: Not reported	Primary: Patients receiving insulin detemir experienced significantly less weight gain compared to those receiving insulin glargine (WMD, -1.22 kg; 95% CI, -2.15 to -0.29; P=0.01). Fewer episodes of hypoglycemia was reported with insulin detemir compared to insulin glargine (OR, 0.52; 95% CI, 0.28 to 0.98; P=0.044). No significant difference was seen in the mean HbA_{1c} between insulin detemir and insulin glargine (standardized mean difference, 0.09; 95% CI, -0.16 to 0.33; P=0.48). No significant differences were seen in weight gain, incidence of hypoglycemia and mean HbA_{1c} between NPH and insulin glargine.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
All patients remained on oral diabetes medications.				Secondary: Not reported
Singh et al.[129] (2009) Insulin analogs vs conventional insulin	MA Adult and pediatric patients with type 1 diabetes and type 2 diabetes, and women with gestational diabetes	117 Trials 4 to 30 weeks	Primary: HbA_{1c} and hypoglycemia Secondary: Not reported	Primary: *Adults – Type 1 Diabetes Mellitus* The use of insulin lispro resulted in a lower HbA_{1c} (difference, –0.09%, 95% CI, –0.16 to –0.02), a lower risk of severe hypoglycemia (RR, 0.80; 95% CI, 0.67 to 0.96) and a lower rate of nocturnal hypoglycemia (RR, 0.51; 95% CI, 0.42 to 0.62) compared to regular insulin. For overall hypoglycemia, the rate was similar between the groups receiving insulin lispro and those receiving regular human insulin. For insulin aspart, the mean HbA_{1c} was lower than with regular insulin (difference, –0.13%; 95% CI, –0.20 to –0.07). There were no significant differences between treatments in the risk of severe hypoglycemia or the rate of overall hypoglycemia. The rate of nocturnal hypoglycemia (reported in one study) in patients receiving insulin aspart (CSII) was significantly lower than in patients receiving regular insulin (RR, 0.55; 95% CI, 0.43 to 0.70). There was no significant difference in HbA_{1c} (reported in one study) with insulin lispro or insulin aspart administered through CSII (difference, 0.25%; 95% CI, –0.20 to 0.71). There was also no significant difference in the rates of nocturnal hypoglycemia among the two treatment groups (RR, 1.20; 95% CI, 0.89 to 1.68). The rate of overall hypoglycemia was higher with insulin lispro than with insulin aspart (RR, 1.49; 95% CI, 1.37 to 1.63). Insulin glargine led to greater reductions in HbA_{1c} compared to NPH insulin (difference, –0.11%; 95% CI, –0.21 to –0.02). There were no significant differences for any type of hypoglycemia when the same bolus insulin was used in each treatment arm. There was no significant difference in HbA_{1c} with insulin detemir and NPH insulin (difference, –0.06%; 95% CI, –0.13 to 0.02). There was a lower risk of severe hypoglycemia (RR, 0.74; 95% CI, 0.58 to 0.96) and nocturnal

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				hypoglycemia (RR, 0.92; 95% CI, 0.85 to 0.98) with insulin detemir compared to NPH; however, there was no difference in overall hypoglycemia. There was no significant difference in HbA_{1c} (reported in one study) between insulin detemir and insulin glargine (difference, –0.03%; 95% CI, –0.26 to 0.20). The risk of severe hypoglycemia (RR, 0.25; 95% CI, 0.07 to 0.86), as well as the risk for severe and nocturnal hypoglycemia were significantly lower with insulin detemir. *Children and Adolescents – Type 1 Diabetes Mellitus* Only one trial compared insulin lispro with regular insulin in adolescents with type 1 diabetes. This study found no difference in HbA_{1c} (difference, –0.01%; 95% CI, –0.21 to 0.19) or the risk of severe hypoglycemia (RR, 1.00; 95% CI, 0.29 to 3.43) among the two treatment groups. The risk of nocturnal hypoglycemia (RR, 0.61; 95% CI, 0.57 to 0.64) and overall hypoglycemia favored insulin lispro. There was no significant difference between insulin lispro and regular insulin in preadolescent patients for the following outcomes: HbA_{1c} (difference, 0.14%; 95% CI, –0.18 to 0.46), risk of severe hypoglycemia (RR, 0.69; 95% CI, 0.24 to 2.01), rates of nocturnal hypoglycemia (RR, 0.96; 95% CI, 0.74 to 1.26), and overall hypoglycemia. Only one trial compared insulin aspart and regular insulin in preadolescent patients with type 1 diabetes. This study found no difference in HbA_{1c} or risk of overall hypoglycemia among the treatment groups. There was no significant difference between insulin glargine and intermediate-acting insulins (mostly NPH insulin) in children and adolescents with type 1 diabetes in HbA_{1c} (difference, –0.25%; 95% CI, –0.55 to 0.05) or any type of hypoglycemia. Only one trial compared insulin detemir with NPH insulin in children and adolescents with type 1 diabetes. This study showed no significant differences between treatments in HbA_{1c} (difference, 0.10%; 95% CI,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				–0.10 to 0.30) or severe hypoglycemia (RR, 0.80; 95% CI, 0.50 to 1.28). The risk of nocturnal hypoglycemia (RR, 0.85; 95% CI, 0.77 to 0.94), as well as for nocturnal and overall hypoglycemia demonstrated small, statistically significant benefits in favor of insulin detemir. *Adults – Type 2 Diabetes Mellitus* There was no significant difference in HbA_{1c} (difference, –0.03%; 95% CI, –0.12 to 0.06) or risk of severe hypoglycemia (RR, 0.43; 95% CI, 0.08 to 2.37), nocturnal hypoglycemia (RR, 1.63; 95% CI, 0.71 to 3.73) or overall hypoglycemia with insulin lispro and regular insulin. There was no significant difference in HbA_{1c} (difference, –0.09%; 95% CI, –0.21 to 0.04) or risk of any type of hypoglycemia with insulin aspart and regular insulin. Only one trial compared biphasic insulin lispro and biphasic insulin aspart. This study showed no significant difference in HbA_{1c} (difference, 0.14%; 95% CI, –0.02 to 0.30) or overall hypoglycemia in adults with type 2 diabetes. Most of the studies with insulin glargine and NPH insulin have allowed the use of oral antidiabetic drugs. Only one study compared insulin glargine and NPH insulin in combination with a prandial insulin without the use of oral antidiabetic drugs. Glycemic control was no better in the insulin glargine group regardless of the type of combined therapy (difference in $HbA_{1c,}$ –0.05%; 95% CI, –0.13 to 0.04, for insulin glargine with oral antidiabetic therapy; 0.28%, 95% CI, 0.07 to 0.49, for insulin glargine with prandial insulin). There was no significant difference in the risk of severe hypoglycemia in the studies that used oral antidiabetic therapy (RR, 0.66; 95% CI, 0.29 to 1.48). The relative risk for nocturnal hypoglycemia significantly favored insulin glargine in both the prandial insulin study (RR, 0.78; 95% CI, 0.62 to 0.98) and the studies that allowed oral antidiabetic drugs (RR, 0.56; 95% CI, 0.47 to 0.68). There was a significant reduction in risk of overall hypoglycemia in favor of insulin glargine in the studies allowing oral antidiabetic therapy but not in the bolus insulin study.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Most of the studies with insulin detemir and NPH insulin have been conducted in patients receiving oral antidiabetic drugs. One study used prandial insulin (insulin aspart) before meals. There was a significant reduction in HbA_{1c} with NPH insulin compared to insulin detemir in studies that allowed the use of oral antidiabetic drugs (difference, 0.13%; 95% CI, 0.03 to 0.22). The risk for severe hypoglycemia was not statistically significant. The risk for nocturnal hypoglycemia (RR, 0.53; 95% CI, 0.31 to 0.91) and overall hypoglycemia significantly favored insulin detemir. There was no significant difference between treatment groups in terms of HbA_{1c} (difference, 0.10%; 95% CI, –0.18 to 0.38) or risk of overall hypoglycemia in the study that used prandial insulin. The risk of nocturnal hypoglycemia was lower in the insulin detemir group (RR, 0.66; 95% CI, 0.45 to 0.96). Two studies compared insulin detemir with insulin glargine in patients with type 2 diabetes. One of the studies allowed the use of oral antidiabetic therapy and showed no significant difference in HbA_{1c} (difference, 0.10%; 95% CI, –0.06 to 0.26) or nocturnal hypoglycemia. The other study used prandial insulin (insulin aspart) and reported a higher HbA_{1c} with insulin detemir (difference, 0.20%; 95% CI, 0.10 to 0.30). There was no difference in risk of overall hypoglycemia. *Pregnant Women With Diabetes* There were no significant differences in HbA_{1c} with insulin lispro or regular insulin (difference, 0.20%; 95% CI, –1.03 to 1.43) or the risk of severe hypoglycemia (RR, 0.21; 95% CI, 0.01 to 4.10) among pregnant women with type 1 diabetes. There was no significant difference in HbA_{1c} with insulin lispro or regular insulin (difference, 0.06%; 95% CI, –0.11 to 0.23) among women with gestational diabetes. Results from a single trial comparing insulin aspart with regular insulin in pregnant women with type 1 diabetes were similar to those for insulin lispro in terms of HbA_{1c} (difference, –0.08%; 95% CI, –0.28 to 0.12), risk

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				of severe hypoglycemia (RR, 1.14; 95% CI, 0.76 to 1.71) and risk of overall hypoglycemia (RR, 1.04; 95% CI, 0.98 to 1.11). Secondary: Not reported
Intermediate-Acting and Long-acting Insulins: Type 1 and 2 Diabetes				
Yenigun et al.[130] (2009) Insulin detemir QD Patients were originally receiving insulin glargine (QD or BID), and then were switched to insulin detemir.	Subgroup analysis of PREDICTIVE study (MC, OL, OS, PRO) Patients with type 1 or 2 diabetes, with or without concomitant oral antidiabetic agents	N=1,285 12 weeks	Primary: Change in baseline HbA_{1c} Secondary: Changes in baseline FPG, insulin dose, and body weight; incidence of hypoglycemia; safety	Primary: Switching to insulin detemir significantly decreased HbA_{1c} (insulin glargine QD and type 1 diabetes, -0.47; P<0.0001, insulin glargine QD and type 2 diabetes, -0.51%; P<0.0001, insulin glargine BID and type 1 diabetes; -0.31%; P<0.05, insulin glargine BID and type 2 diabetes; -0.89%; P<0.05). Secondary: Significant decreases in self-monitored FPG and within-patient FPG variability were reported in patients who switched from insulin glargine QD to insulin detemir (P<0.000 for all). Results were not significant in patients who switched from insulin glargine BID because of a small sample size. Except for type 2 diabetics who switched from insulin glargine BID, total daily insulin dose increased by 1 to 5% in patients transferring to insulin detemir. There was a significant decrease in body weight in patients who switched from insulin glargine QD (P<0.05). Body weight decreased in patients who switched from insulin glargine BID; however, it did not reach significance. On case of serious hypoglycemia was reported in a patient who switched from insulin glargine QD. No serious adverse events were reported in type 2 diabetes, although three patients experienced major hypoglycemia that were not reported as a severe adverse event. The number of hypoglycemic episodes was significantly reduced in patients with type 1 and 2 diabetes who switched from insulin glargine QD, as well as type 2 diabetes who switched from insulin glargine BID (P<0.0001). There was also a

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				significant decrease in the number of major and nocturnal hypoglycemic events in patients who switched from insulin glargine QD (P<0.0001).
Trials Comparing Insulin Devices				
Ignaut et al.[131] (2009) Insulin lispro administered via KwikPen® device vs insulin lispro administered via vial/syringe vs insulin aspart administered via FlexPen® device	OL, RCT, XO Patients 40 to 75 years of age with type 1 or type 2 diabetes who had been preparing and self-injecting insulin using vial and syringe for at least the previous 3 months, and who were pen device-naïve	N=232 1 day	Primary: Preference (responses to Question 13 of the insulin device preference battery post-assessment and the final preference question) Secondary: Characteristics of different insulin pen devices (overall ease of use, ease of handling, ease of pressing injection button while injecting)	Primary: The KwikPen® was significantly preferred to vial and syringe, with 89% of patients preferring KwikPen® (95% CI, 0.8437-0.9284). KwikPen® was significantly preferred to FlexPen®, with 67% of patients preferring KwikPen® (95% exact CI, 0.6063-0.7312). FlexPen® was significantly preferred to vial and syringe (81%; 95% CI, 0.7529-0.8581). Secondary: For the ease of use assessment, 94% of KwikPen® users and 84% of FlexPen® users either strongly agreed or agreed that the device was easy to use (P=0.006). For the ease of handling assessment, 87% of KwikPen® users and 73% of FlexPen® users either strongly agreed or agreed that the pen was easy to hold in their hand when they injected insulin (P=0.002). For the ease of injection assessment, 85% of KwikPen® users and 66% of FlexPen® users either strongly agreed or agreed that the injection buttons on their respective pens were easy to press when injecting their dose (P<0.001). When comparing preference with the KwikPen® to vial/syringe, all comparison were statistically significant favoring KwikPen® in terms of appearance, quality of the device, discretion, convenience, use in public, easy to learn, easy to use, reliability, dose confidence, ability to follow an insulin regimen, overall satisfaction, and recommendation to others.
Korytkowski et al.[132] (2003) Insulin aspart protamine and insulin aspart 70/30 mix vial/syringe for 4 weeks	OL, RCT, XO Patients with type 1 diabetes and type 2 diabetes were stabilized on 70% insulin aspart and 30% insulin aspart	N=121 12 weeks	Primary: Patient preference Secondary: Effect on glycemic control (HbA_{1c}, FPG, fructosamine,	Primary: Seventy-four percent indicated preference for prefilled pen over the vial/syringe (95% CI, 71 to 87) compared to 20% who indicated a preference for the vial/syringe. Secondary: Overall, a significant reduction in HbA_{1c} (-3%; P<0.05) was observed during the entire study (no comparison between treatment groups made).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs biphasic insulin aspart protamine and insulin aspart 70/30 mix prefilled pen for 4 weeks	protamine then randomized to use vial/syringe or a prefilled pen for 4 weeks; after 4 weeks, patients were XO to the other administration method; baseline HbA_{1c} 8.7%		and four-point glucose profile)	There was no significant difference in FPG, fructosamine or four-point glucose profile between treatment groups. There was no difference in safety profile between treatment groups.
Insulin and Non-Insulin Combination Products: Type 2 Diabetes				
Gough et al.[133] (2014) DUAL-I Insulin degludec-liraglutide (IDegLira) vs insulin degludec vs liraglutide	OL, RCT Adults with type 2 diabetes, HbA_{1c} of 7 to 10% (inclusive), a BMI ≤40 kg/m^2, and treated with metformin with or without pioglitazone (insulin-naïve)	N=1,663 26 weeks	Primary: Change in HbA_{1c} after 26 weeks of treatment Secondary: Achievement of end-of-trial HbA_{1c} of less than 7.0%, or 6.5% or less, and changes in laboratory-measured fasting plasma glucose, bodyweight, insulin dose, and nine-point self-monitored blood glucose profile	Primary: After 26 weeks, mean HbA_{1c} had decreased by 1.9% to 6.4% with IDegLira, by 1.4% to 6.9% with insulin degludec, and by 1.3% to 7.0% with liraglutide. IDegLira was associated with a greater reduction in HbA_{1c} than insulin and liraglutide, meeting the criteria for non-inferiority to insulin degludec (estimated treatment difference, −0.47%; 95% CI, −0.58 to −0.36; P<0.0001) and superiority to liraglutide (–0.64%; –0.75 to –0.53; P<0.0001). Secondary: A higher proportion of patients achieved an HbA_{1c} of less than 7.0% after 26 weeks with IDegLira than with insulin degludec (81% vs 65%, OR, 2.38; 95% CI, 1.78 to 3.18, P<0.0001) or liraglutide (60%; OR, 3.26; 95% CI, 2.45 to 4.33; P<0.0001). Similarly, the proportion of patients who attained an HbA_{1c} of 6.5% or less was higher for IDegLira than for insulin degludec (70% vs 47%; OR, 2.82; 95% CI, 2.17 to 3.67; P<0.0001) or liraglutide (41%; OR, 3.98; 95% CI, 3.05 to 5.18; P<0.0001). There was no significant difference between IDegLira and insulin degludec with respect to reduction in fasting plasma glucose from baseline (P=0.16), whereas the reduction was greater for IDegLira than for liraglutide (P<0.0001). The reduction in mean plasma glucose concentrations was greater for IDegLira than for insulin degludec (3.2 vs 3.0 mmol/L; estimated treatment difference, –0.30 mmol/L; 95% CI, –0.50 to –0.09; P=0.0040) or liraglutide (2.1 mmol/L; estimated treatment difference, –0.93 mmol/L, 95% CI, –1.13 to –0.73, P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				From baseline to the end of the trial, mean bodyweight decreased by 0.5 kg with IDegLira, increased by 1.6 kg with insulin degludec, and decreased by 3.0 kg with liraglutide (estimated treatment difference for IDegLira vs insulin degludec, –2.22 kg, P<0.0001; IDegLira vs liraglutide, 2.44 kg, P<0.0001).
Linjawi et al.[134] (2017) DUAL III Insulin degludec-liraglutide (IDegLira) vs maximum dose GLP-1 therapy (liraglutide once daily or exenatide twice daily) Patients continued oral antidiabetic drugs at pre-trial dose	OL, MC, RCT Type 2 diabetes patients (insulin-naïve) on maximum-dose GLP-1 therapy (liraglutide once daily or exenatide twice daily) with metformin alone or with pioglitazone and/or sulfonylurea who had an HbA_{1c} of 7.0 to 9.0%, both inclusive), and a BMI ≤40 kg/m^2	N=438 26 weeks	Primary: Change in HbA_{1c} after 26 weeks of treatment Secondary: Responders for HbA_{1c} (predefined targets of <7% and ≤6.5%) after 26 weeks of treatment, change from baseline in body weight, laboratory-measured FPG, and nine-point self-monitored blood glucose profile	Primary: After 26 weeks, HbA_{1c} reductions were greater with IDegLira versus GLP-1 therapy (estimated treatment difference, -0.94%; P<0.001). Mean HbA_{1c} reduced from 7.8 to 6.4% with IDegLira and from 7.7 to 7.4% with GLP-1 therapy. Secondary: With IDegLira, 75% and 63% of patients achieved HbA_{1c} <7% and ≤6.5%, compared with 36% and 23% on GLP-1 therapy, respectively. Fasting plasma glucose and self-monitored blood glucose profiles improved more with IDegLira versus unchanged GLP-1RA (P<0.001 for both parameters). The mean change in weight was +2.0 kg with IDegLira, versus -0.8 kg with GLP-1 therapy (P<0.001). Rates of confirmed hypoglycemia were low, but higher with IDegLira versus GLP-1 therapy.
Rodbard et al.[135] (2017) DUAL IV Insulin degludec-liraglutide (IDegLira) vs placebo	DB, MC, RCT Adults with type 2 diabetes, HbA_{1c} of 7.0 to 9.0%, and BMI of ≤40 kg/m^2, previously treated with a stable daily dose of sulphonylureas (≥ half of the maximum approved dose	N=435 26 weeks	Primary: Change in HbA_{1c} after 26 weeks of treatment Secondary: Responders for HbA_{1c} (<7%) after 26 weeks of treatment, change from baseline in body weight,	Primary: The mean HbA_{1c} decreased from 63 mmol/mol (7.9%) to 46 mmol/mol (6.4%) with IDegLira and to 57 mmol/mol (7.4%) with placebo (estimated treatment difference, -11 mmol/mol; 95% CI, -13 to -10; or -1.02%; 95% CI, -1.18 to -0.87; P<0.001). Secondary: The HbA_{1c} target of <7% was achieved by 79.2% of participants in the IDegLira group vs 28.8% in the placebo group (estimated odds ratio, 11.95; 95% CI, 7.22 to 19.77; P<0.001). Mean weight change was +0.5 kg with IDegLira vs -1.0 kg with placebo (estimated treatment difference, 1.48 kg; 95% CI, 0.90 to 2.06; P<0.001). Confirmed hypoglycemia occurred in 41.7

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Sulphonylureas and metformin were maintained at pre-trial dose and frequency	according to local label) ± metformin (≥1500 mg or maximum tolerated dose) for at least 90 days before screening. Participants were insulin- and GLP-1 receptor agonist-naïve.		laboratory-measured FPG, and nine-point self-monitored blood glucose profile	and 17.1% of IDegLira- and placebo-treated participants, respectively, with rates of 3.5 vs 1.4 events/patient-years of exposure (estimated rate ratio, 3.74; 95% CI, 2.28 to 6.13; P<0.001). Change in laboratory-measured FPG was greater for participants receiving IDegLira vs placebo: –2.60 mmol/l vs –0.31 mmol/l, respectively, with an estimated treatment difference of –2.30 mmol/l (95% CI, –2.72 to –1.89; P<0.001]. The mean reduction in mean nine-point self-monitored blood glucose profile was 2.2 mmol/l for IDegLira vs 0.7 mmol/l for placebo, with an estimated treatment difference of –1.55 mmol/l (95% CI, –1.86 to –1.24; P<0.001).
Lingvay et al.[136] (2016) DUAL V Insulin degludec-liraglutide (IDegLira) vs continued titration of insulin glargine	MC, OL, RCT Patients with uncontrolled type 2 diabetes on insulin glargine 20 to 50 units/day and metformin, HbA_{1c} of 7.0 to 10.0%, and BMI of ≤40 kg/m^2	N=557 26 weeks	Primary: Change in HbA_{1c} after 26 weeks of treatment Secondary: Change from baseline in body weight and number of treatment-emergent hypoglycemic episodes	Primary: Baseline HbA_{1c} level was 8.4% for the IDegLira group and 8.2% for the glargine group. HbA_{1c} level reduction was greater with IDegLira vs glargine (-1.81% for the IDegLira group vs -1.13% for the glargine group; estimated treatment difference, -0.59%; 95% CI, -0.74 to -0.45%), meeting criteria for noninferiority (P<0.001). Secondary: A reduction in body weight of 1.4 kg was observed in the IDegLira group from 88.3 kg to 86.9 kg, whereas the glargine group had an increase in body weight of 1.8 kg from 87.3 kg to 89.1 kg (estimated treatment difference, –3.20 kg; 95% CI, –3.77 to –2.64; 1-sided P<0.001). Confirmed hypoglycemia occurred in fewer patients receiving IDegLira than those receiving glargine (28.4% for the IDegLira group and 49.1% for the glargine group), with reduced rates of 2.23 episodes vs 5.05 episodes per patient-year of exposure (estimated rate ratio, 0.43; 95% CI, 0.30 to 0.61; 1-sided P<0.001).
Billings et al.[137] (2018) DUAL VII Insulin degludec-liraglutide (IDegLira) vs	MC, OL, RCT Patients were ≥18 years of age with uncontrolled type 2 diabetes, HbA_{1c} 7.0 to 10.0%, BMI ≤40 kg/m^2, and on stable daily doses of	N=506 26 weeks	Primary: Change in HbA_{1c} after 26 weeks of treatment Secondary: Number of treatment-emergent severe or blood	Primary: HbA_{1c} decreased from 8.2% to 6.7% with IDegLira and from 8.2% (67 mmol/mol) to 6.7% with basal-bolus (estimated treatment difference, -0.02%; 95% CI, -0.16 to 0.12), confirming IDegLira noninferiority versus basal-bolus (P<0.0001). Secondary: During 26 weeks of treatment, 19.8% of patients on IDegLira experienced one or more severe or blood glucose-confirmed symptomatic hypoglycemic

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insulin glargine and insulin aspart (basal-bolus)	insulin glargine 100 units/mL (IGlar U100) 20 to 50 units and metformin ≥1,500 mg or maximum tolerated dose for >90 days prior to screening		glucose-confirmed symptomatic hypoglycemic episodes during 26 weeks of treatment and change in body weight from baseline after 26 weeks of treatment	episodes vs. 52.6% with basal-bolus treatment, corresponding to a 61% lower risk with IDegLira compared with basal-bolus (estimated risk ratio, 0.39; 95% CI, 0.29 to 0.51; P<0.0001). Over 26 weeks of treatment, observed mean body weight decreased by 0.9 kg with IDegLira from 87.2 kg and increased with basal-bolus by 2.6 kg from 88.2 kg (estimated treatment difference, −3.6 kg; 95% CI, −4.2 to −2.9; P<0.0001).
Aroda et al.[138] (2019) DUAL VIII Insulin degludec-liraglutide (IDegLira) vs insulin glargine 100 units/mL (IGlar U100)	MC, OL, RCT Patients ≥18 years of age with type 2 diabetes who were insulin-naïve with HbA_{1c} between 7.0 to 11.0%, BMI of 20 kg/m^2 or higher, on stable doses of oral antidiabetic drugs	N=1,012 104 weeks	Primary: Time from randomization to inadequate glycemic control and need for treatment intensification, defined as HbA_{1c} of 7.0% or higher at two consecutive visits from week 26 Secondary: Change from baseline after 104 weeks of treatment in FPG, 9-point self-measured blood glucose (SMBG) profile, bodyweight, and insulin dose	Primary: The time from randomization to inadequate glycemic control and need for treatment intensification was significantly longer for patients in the IDegLira group than those in the IGlar U100 group, accounting for baseline strata (baseline HbA_{1c} group and background sulphonylurea; P<0.0001, stratified log-rank test). The median time to treatment intensification was beyond two years for IDegLira and approximately one year for IGlar U100. A greater proportion of patients achieved HbA_{1c} of less than 7.0% in the IDegLira group versus the IGlar U100 group (56% vs 29%; odds ratio, 3.01; 95% CI, 2.29 to 3.95; P<0.0001). Secondary: Patients on treatment had similar reductions in observed mean fasting SMBG over 104 weeks of treatment with IDegLira and IGlar U100, with reductions being greater in the IDegLira group in the first 26 weeks of treatment. After 104 weeks, bodyweight had increased in both treatment groups, but patients in the IDegLira group had significantly less weight gain than those in the IGlar U100 group (least squares means [LSMeans] +1.7 kg [SE 0.3] vs +3.4 kg [0.3]; ETD, −1.70; 95% CI, −2.47 to −0.93; P<0.0001). Patients in the IDegLira group had a lower estimated mean total insulin dose than those in the IGlar U100 group after 104 weeks (LSMeans 37 U [0.8] vs 52 U [1.0]; ETD, −14.94; 95% CI, –17.41 to −12.47; P<0.0001). From baseline to week 104, a significant reduction in FPG was shown in patients in the IDegLira group compared with the IGlar U100 group (ETD, −0.48; 95% CI, –0.76 to −0.19; P=0.0010).
Philis-Tsimikas et al.[139] (2019)	OL, RCT	N=420 26 weeks	Primary: Change in HbA_{1c} from baseline	Primary: Mean HbA_{1c} reductions were 21 mmol/mol (1.9%-points) with IDegLira and 18 mmol/mol (1.7%-points) with IGlar U100; confirming non-

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Insulin degludec/ liraglutide (IDegLira) vs insulin glargine 100 units/mL (IGlar U100)	Insulin-naïve people aged ≥18 years with HbA_{1c} 7.0 to 11.0%, body mass index 20 to 40 kg/m^2 and inadequately controlled type 2 diabetes on SGLT2 inhibitor ± oral antidiabetic drugs		Secondary: Body weight, insulin dose, adverse events	inferiority (P<0.0001) and superiority of IDegLira (difference in HbA_{1c} change -3.90 mmol/mol; 95% CI, -5.45 to -2.35 (-0.36%-points; 95% CI, -0.50 to -0.21)). Secondary: Superiority for IDegLira over IGlar U100 was confirmed for: body weight (difference, -1.92 kg; 95% CI, -2.64 to -1.19); severe or blood-glucose-confirmed symptomatic hypoglycemia (rate ratio, 0.42; 95% CI, 0.23 to 0.75); total daily insulin dose (difference, -15.37 U; 95% CI, -19.60 to -11.13). The overall treatment-emergent adverse event rate was higher with IDegLira as a result of higher increased lipase and nausea rates.
Aroda et al.[140] (2016) LixiLan-L Insulin glargine-lixisenatide (iGlarLixi) vs insulin glargine	MC, OL, RCT Patients ≥18 years of age with type 2 diabetes inadequately controlled on basal insulin with or without up to two oral glucose-lowering agents	N=736 30 weeks	Primary: Change in HbA_{1c} from baseline Secondary: Percentage of patients reaching target HbA_{1c} <7.0% and ≤6.5% at week 30 and the change in 2-h PPG during the standardized liquid meal test	Primary: HbA_{1c} decreased from 8.5% to 8.1% during the run-in period. After randomization, iGlarLixi showed greater reductions in HbA_{1c} from baseline compared with glargine (-1.1% vs -0.6%, P<0.0001), reaching a mean final HbA_{1c} of 6.9% compared with 7.5% for glargine. Secondary: A greater proportion of patients treated with iGlarLixi had reached the HbA_{1c} targets of <7.0% (55% vs 30%) and ≤6.5% (34% vs 14%) compared with glargine (P<0.0001 in each case) at week 30. Mean body weight decreased by 0.7 kg with iGlarLixi and increased by 0.7 kg with glargine (1.4 kg difference, P<0.0001). Documented symptomatic hypoglycemia (≤70 mg/dL) was comparable between groups.
Evans et al.[141] (2018) Insulin degludec-liraglutide (IDegLira) vs insulin glargine-lixisenatide (iGlarLixi)	MA (indirect comparison) Patients with type 2 diabetes who had previously failed to achieve satisfactory glucose control using basal insulin-only regimens	N=not reported (data from phase 3 trials: DUAL II, DUAL V, LixiLan-L, SWITCH 2) 6 months	Primary: Changes in HbA_{1c}, body weight and insulin dose, and rate ratio of hypoglycemia Secondary: Not reported	Primary: In the primary network, IDegLira was estimated to provide a 0.44 (95% CI, 0.17 to 0.71) %-point reduction in HbA_{1c} compared with iGlarLixi. Body weight was reduced by 1.42 (95% CI, 0.35 to 2.50) kg with IDegLira compared with iGlarLixi. Insulin dose was comparable between the two interventions (estimated treatment difference IDegLira vs iGlarLixi, –3.6; 95% CI, –10.3 to 3.3 U). In the sensitivity analysis, results were in the same direction, except for insulin dose, which was 0.3 (95% CI, –2.2 to 2.7) U higher with IDegLira. The rate for severe or blood glucose-confirmed hypoglycemia with IDegLira was approximately half the rate with iGlarLixi (rate ratio, 0.51;

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				95% CI, 0.29 to 0.90); however, it should be noted that blood glucose-confirmed hypoglycemia was defined as self-measured plasma glucose ≤3.3 mmol/L in LixiLan-L, as opposed to self-measured plasma glucose ≤3.1 mmol/L in the other trials. Based on the ADA definition of documented symptomatic hypoglycemia (SMPG ≤3.9 mmol/L), the rate was comparable between the two treatments (rate ratio, 1.07; 95% CI, 0.90 to 1.28]). Secondary: Not reported
Insulin Therapy Compared to Other Antidiabetic Medications: Type 2 Diabetes				
Mu et al.[142] (2012) Insulin glargine vs no additional treatment All patients received oral antidiabetic medications. Active treatments were stopped after normoglycemia was maintained for 3 months. Patients were then followed-up with diet and physical exercise at 1 year.	RCT Patients 35 to 50 years of age with newly diagnosed type 2 diabetes, FPG ≥9.0 mmol/L, and HbA_{1c} ≥9.0%	N=129 1 year	Primary: Effects on β-cell function, diabetes remission rate Secondary: Not reported	Primary: Both treatment groups improved HOMA-B and HOMA-IR significantly. They had similar effects on insulin resistance (0.50±0.09 vs 0.48±0.09; P=0.23). However, the addition of insulin therapy could recover β-cell function much more than no additional treatment (2.17±0.14 vs 2.11±0.13; P=0.03). More patients achieved target glycemic control with the addition of insulin therapy (98.3% [58 of 59]) in less time (10.4±2.5 days) compared to no additional treatment (95.7% [67 of 70] and 12.4±3.4 days). At one year follow-up, more patients maintained target glycemia without any drugs in patients who received additional insulin therapy compared to patients who received no additional treatment (37.9 vs 20.9%). Secondary: Not reported
Weissman et al.[143] (2014)	MC, OL, NI, RCT	N=779	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
HARMONY 4 Insulin glargine (10 U once a day) vs albiglutide (30 mg once a week)	Patients ≥18 years of age with type 2 diabetes treated with metformin (±sulfonylurea) for at least 3 months with a baseline HbA_{1c} 7.0 to 10.0%	52 weeks	Change in HbA_{1c} from baseline to 52 weeks Secondary: Change from baseline in FPG at week 52, changes from baseline in HbA_{1c} and FPG over time, time to hyperglycemic rescue, proportion of patients achieving HbA_{1c} goals, body weight	In the albiglutide group, HbA_{1c} declined from 8.28 ± 0.90% (mean ± SD) at baseline to 7.62 ± 1.12% at week 52. A similar reduction occurred in the insulin glargine group (8.36 ± 0.95% to 7.55 ± 1.04%). The model-adjusted treatment difference of 0.11% (95% CI, −0.04 to 0.27%) indicated non-inferiority of albiglutide to insulin glargine based on the pre-specified non-inferiority margin of 0.3% (P=0.0086). Secondary: At week 52, FPG had declined by a mean 0.87 mmol/l in the albiglutide group and by 2.06 mmol/l in the insulin glargine group; the treatment difference was significant in favor of insulin glargine (P<0.0001). Body weight increased in the insulin glargine group and decreased in the albiglutide group, with a mean treatment difference of −2.61 kg (95% CI, −3.20 to −2.02; p<0.0001). Documented symptomatic hypoglycemia occurred in a higher proportion of patients in the insulin glargine group than in the albiglutide group (27.4 vs 17.5%, P=0.0377).
Giorgino et al.[144] (2015) AWARD-2 Insulin glargine once-daily vs dulaglutide 1.5 mg once-weekly vs dulaglutide 0.75 mg once-weekly	OL, MC, RCT Adults with an HbA_{1c} of ≥7.0% and ≤11.0%, BMI ≥23 and ≤45 kg/m^2, and stable weight for ≥3 months, who were not optimally controlled with one, two, or three oral antihyperglycemic medications (of which one had to be metformin or a sulfonylurea) for at least three months	N=810 78 weeks	Primary: Change in HbA_{1c} from baseline to 52 weeks Secondary: Changes in HbA_{1c} from baseline to 26 and 78 weeks, the percentage of patients achieving HbA_{1c} <7.0% and ≤6.5%, and changes in FPG, 8-point self-monitored plasma glucose profiles, adverse events	Primary: The mean HbA_{1c} change from baseline to the 52-week primary end point was −1.08 ± 0.06%, −0.76 ± 0.06%, and −0.63 ± 0.06% for dulaglutide 1.5 mg, dulaglutide 0.75 mg, and glargine, respectively. Statistical criteria for superiority was met with dulaglutide 1.5 mg, LS mean difference of −0.45% (CI, −0.60 to −0.29; adjusted one-sided P<0.001). Statistical criteria for noninferiority were met for dulaglutide 0.75 mg, −0.13% (CI, −0.29 to 0.02; adjusted one-sided P<0.001). Secondary: There was no significant difference in percentages of patients who achieved the HbA_{1c} target of <7.0% for dulaglutide 0.75 mg (37.1%) compared with glargine. Greater percentages of patients on dulaglutide 1.5 mg (27.0%) and dulaglutide 0.75 mg (22.5%) achieved an HbA_{1c} target ≤6.5% than with glargine (13.5%) (P<0.001 and P=0.004, respectively). At 78 weeks, percentages of patients attaining HbA_{1c} targets were generally maintained, except for the percentage of patients with an HbA_{1c} of ≤6.5%, which was similar for dulaglutide 0.75 mg and glargine. At 52 weeks, the FPG from 8-point SMPG profiles decreased more with glargine than with dulaglutide 1.5 mg and dulaglutide 0.75 mg. More patients on dulaglutide 1.5 mg achieved HbA_{1c} targets <7.0% versus glargine (P<0.001). Body

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				weight decreased with dulaglutide and increased with glargine. Total hypoglycemia rates were lower with dulaglutide; severe hypoglycemia was minimal. Increases in pancreatic enzymes were observed for dulaglutide. Incidence of nausea (15.4, 7.7, and 1.5%) and diarrhea (10.6, 9.2, and 5.7%) were more common with dulaglutide 1.5 mg and 0.75 mg than with glargine.
Okerson et al.[145] (2010) Exenatide 5 µg SC BID for 4 weeks, followed by 10 µg SC BID vs placebo or insulin All patients also received existing antidiabetic treatment regimens.	Post-hoc analysis (6 RCTs) Type 2 diabetics ≥18 years of age with HbA_{1c} ≥6.5 to ≤11.0%, BMI ≥25 to ≤45 kg/m^2, and stable body weight	N=2,171 24 to 52 weeks	Primary: Change in baseline BP and pulse pressure Secondary: Not reported	Primary: In the overall study population, by the end of the six month trial period, exenatide was associated with a significantly greater decrease in SBP compared to placebo (-2.20±0.56 vs 0.60±0.56 mm Hg; treatment difference, -2.80±0.75 mm Hg; P=0.002) and insulin (-4.5±0.6 vs -0.9±0.6 mm Hg; treatment difference, -3.7±0.85 mm Hg; P<0.0001). In contrast, DBP was minimally decreased and not different between exenatide and placebo (-0.70±0.33 vs -0.20±0.33 mm Hg; P=0.21) or insulin (-1.60±0.35 vs -0.80±0.36 mm Hg; P=0.16). No differences in the proportions of patients altering the number, type, or intensity of ongoing antihypertensive regimens were observed between treatments (data not reported). Patients with abnormal SBP at baseline achieved the greatest decreases with exenatide (exenatide vs placebo, -8.3 vs -4.5 mm Hg; treatment difference, -3.8 mm Hg; P=0.0004 and exenatide vs insulin, -8.3 vs -4.2 mm Hg; treatment difference, -4.0 mm Hg; P<0.0001). In patients with normal BP at baseline, no differences in the decreases in SBP or DBP were observed between any of the treatments (P values not reported). Pulse pressure effects trended similarly to SBP effects, with the most pronounced decrease occurring in exenatide-treated patients with baseline pulse pressures ≥40 mm Hg. In this subgroup, the reduction in pulse pressure was significantly greater with exenatide compared to placebo (-3.5 vs -0.5 mm Hg; treatment difference, -2.9 mm Hg; P<0.0001) and insulin (-4.0 vs -0.9 mm Hg; treatment difference, -3.0 mm Hg; P<0.0001). By the end of the six month treatment period, a significantly greater proportion of exenatide-treated patients with elevated baseline SBP (26%) achieved the SBP goal for type 2 diabetics compared to insulin (treatment difference, 19%; P=0.03); however, no treatment effect on DBP was observed. In contrast, although no significant exenatide-related shifts were observed in SBP classifications, a significantly greater proportion of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				exenatide-treated patients were favorably shifted from a baseline classification of "abnormal DBP" to "normal DBP" compared to placebo (treatment difference, 41.4 vs 32.4%; P=0.02). Secondary: Not reported
Diamant et al.[146] (2010) DURATION-3 Exenatide ER 2 mg SC once weekly vs insulin glargine SC QD All patients received existing background oral glucose-lowering regimens.	OL, PG, RCT Type 2 diabetics ≥18 years of age with suboptimum glycemic control despite maximum tolerated doses of metformin (stable dose of ≥1,500 mg for ≥8 months) or combined metformin and sulfonylurea treatment ≥3 months, HbA_{1c} 7.1 to 11.0%, BMI 25 to 45 kg/m^2, and a stable body weight ≥3 months	N=456 26 weeks	Primary: Change in baseline HbA_{1c} Secondary: Proportion of patients achieving HbA_{1c} <7.0 or <6.5%, fasting serum glucose, self-monitored blood glucose concentrations, body weight, fasting lipid profile, BP, markers of cardiovascular risk, β cell function, insulin profile, patient-reported quality of life, safety	Primary: Decreases in HbA_{1c} were significantly greater with exenatide ER (-1.5±0.05%) compared to insulin glargine (-1.3±0.06%; treatment difference, -0.16±0.07%; 95% CI, -0.29 to -0.03; P=0.017). In patients receiving exenatide ER or insulin glargine plus metformin only, HbA_{1c} was decreased by -1.5±0.06 and -1.4±0.07% (treatment difference, -1.8±0.08%; 95% CI, -0.34 to -0.02; P=0.031). Secondary: Significantly greater proportions of exenatide ER-treated patients achieved HbA_{1c} <7.0 (60 vs 48%; P=0.010) and <6.5% (35 vs 23%; P=0.004) compared to insulin glargine treated patients. Fasting serum glucose decreased with both treatments (-2.1±0.2 vs -2.8±0.2 mmol/L); however, insulin glargine significantly decreased values compared to exenatide ER (treatment difference, -0.6 mmol/L; 95% CI, 0.2 to 1.0; P=0.001). With regards to self-monitored blood glucose concentrations, both treatments significantly decreased FPG and PPG at all eight time points (P<0.0001 for all). Significantly lower concentrations with insulin glargine compared to exenatide ER were observed at 0300 hour (P=0.022) and before breakfast (P<0.0001), and significantly lower concentrations with exenatide ER were observed after dinner (P=0.004). Exenatide ER resulted in significantly greater reductions in post-prandial glucose excursions compared to insulin glargine after morning (P=0.001) and evening meals (P=0.033). Seventy nine percent of patients receiving exenatide ER experienced both a decrease in HbA_{1c} and body weight compared to 63% of patients receiving

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				insulin glargine who experienced a decrease in HbA_{1c} and increase in body weight. Only exenatide ER resulted in a significant decrease in TC (-0.12 mmol/L; P<0.05). There were no differences between the two treatments in the decreases in TC (treatment difference, -0.07 mmol/L; 95% CI, -0.21 to 0.06) and LDL-C (treatment difference, -0.09 mmol/L; 95% CI, -0.21 to 0.03), and the increase in HDL-C (treatment difference, -0.02; 95% CI, -0.05 to 0.02) observed. Only exenatide ER resulted in a significant decrease in SBP (-3 mm Hg; P<0.05). There were no differences between the two treatments in the decreases in SBP (treatment difference, -2 mm Hg; 95% CI, -4 to 1) and DBP (treatment difference, 0 mm Hg; 95% CI, -2 to 1) observed. Only exenatide ER resulted in a significant decrease in high-sensitivity CRP (-2.0 mg/dL; P<0.05). There were no differences between the two treatments in the decreases in high-sensitivity CRP (-1.2 mg/dL; 95% CI, -2.8 to 0.3) and urinary albumin:creatinine ratio (0.06 mg/mmoL; 95% CI, -1.70 to 1.80) observed. Both treatments resulted in improvements in IWQOL-Lite, binge eating scale, and DTSQ total scores, with only patients receiving exenatide ER achieving significant improvements on the EQ-5D index. Significant improvements with exenatide ER compared to insulin glargine were observed for one of the IWQOL-Lite domains (self-esteem) and one EQ-5D dimension (usual activities) (data not reported). Gastrointestinal events including nausea and diarrhea were among the most common reported adverse events with exenatide ER, with nasopharyngitis and headache being the most commonly reported with insulin glargine. Gastrointestinal events were all mild or moderate and no serious adverse events were reported by more than one patient, except chest pain (two patients).
Diamant et al.[147] (2012) DURATION-3	ES Type 2 diabetics ≥18 years of age	N=390 84 weeks	Primary: Change in baseline HbA_{1c}	Primary: At 84 weeks, HbA_{1c} decreased from baseline by -1.2% with exenatide ER compared to -1.0% with insulin glargine (P=0.029).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Exenatide ER 2 mg SC once weekly vs insulin glargine SC QD All patients received existing background oral glucose-lowering regimens.	with suboptimum glycemic control despite maximum tolerated doses of metformin (stable dose of ≥1,500 mg for ≥8 months) or combined metformin and sulfonylurea treatment ≥3 months, HbA_{1c} 7.1 to 11.0%, BMI 25 to 45 kg/m^2, and a stable body weight ≥3 months		Secondary: Proportions of patients achieving HbA_{1c} <7.0 and ≤6.5%, body weight, incidence of hypoglycemia, safety	Secondary: The proportions of patients who achieved end point HbA_{1c} targets <7.0 and ≤6.5% were 44.6 and 36.8% with exenatide ER and insulin glargine (P=0.084) and 31.3 and 20.2% with exenatide ER and insulin glargine (P=0.009), respectively. Patients receiving exenatide ER lost 2.1 kg of body weight compared to patients receiving insulin glargine who gained 2.4 kg (P<0.001). Among patients receiving metformin plus a sulfonylurea, the incidence of minor hypoglycemia was 24 and 54% with exenatide ER and insulin glargine (P<0.001). Among adverse events occurring in ≥5% of all patients, diarrhea (12 vs 6%) and nausea (15 vs 1%) occurred more frequently (P<0.05) with exenatide ER compared to insulin glargine.
Bergenstal et al.[148] (2009) Exenatide 5 µg BID for 4 weeks, then 10 µg BID vs insulin aspart 12 units QD before dinner (BIAsp 30 QD) vs insulin aspart 12 units divided equally before breakfast and dinner (BIAsp 30 BID)	OL, PG, RCT Patients 18 to 80 years of age with type 2 diabetes mellitus and HbA_{1c} ≥8.0%, insulin-naïve, and receiving treatment with metformin and a sulfonylurea for at least 3 months prior to enrolling in the study	N=372 24 Weeks	Primary: Change in HbA_{1c} from baseline Secondary: FPG, eight-point plasma glucose profiles, changes in body weight	Primary: At 24 weeks, HbA_{1c} values were 7.61, 7.75, 8.46% for BIAsp 30 BID, BIAsp 30 QD, and exenatide, respectively (both P<0.0001 compared to exenatide). At the end of the study, 37% of patients in the BIAsp 30 BID group achieved an HbA_{1c} <7.0% compared to 20% of patients in the exenatide group (P=0.0060). Additionally, 25% of patients in the BIAsp 30 BID group achieved an HbA_{1c} ≤6.5% compared with 8% in the exenatide group (P=0.0004). At the end of the study, 26% of patients in the BIAsp 30 QD group achieved an HbA_{1c} <7.0% compared to 20% of patients in the exenatide group (P=0.3488). Additionally, 12% of patients in the BIAsp 30 QD group achieved an HbA_{1c} ≤6.5% compared with 8% in the exenatide group (P=0.3802). The percentage of patients who achieved HbA_{1c} ≤6.5% was higher with BIAsp 30 BID compared to BIAsp 30 QD (25 vs 12%; P=0.0122). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
All patients were receiving metformin with or without a sulfonylurea. Insulin dose was titrated as necessary.				There were significant changes in FPG with BIAsp 30 BID (-62.7 mg/dL; P<0.0001 vs exenatide) and BIAsp 30 QD (-52.4 mg/dL; P=0.0002 vs exenatide) compared to exenatide (-21.4 mg/dL). At the end of the study, the eight-point plasma glucose profiles were significantly lower with BIAsp 30 BID and BIAsp 30 QD than exenatide. At 24 weeks, hypoglycemia was reported in 56% of patients in the BIAsp 30 QD group, 61% of patients in the BIAsp 30 BID group, and 29% in the exenatide group. Weight loss was reported in the exenatide group (-1.9 kg) compared with weight gain in the BIAsp 30 QD (+2.8 kg) and BIAsp 30 BID (4.1 kg). There were more reports of nausea and vomiting with exenatide than in the insulin groups.
Heine et al.[149] (2005) Exenatide 5 µg BID for 4 weeks, then 10 µg BID vs insulin glargine QD at bedtime All patients were receiving existing metformin and/or sulfonylurea regimens.	OL, RCT Patients 30 to 75 years of age with type 2 diabetes not adequately controlled (defined as HbA_{1c} 7.0 to 10.0%) with combination metformin and sulfonylurea therapy at maximally effective doses, BMI between 25 to 45 kg/m^2 and a history of stable body weight (≤10% variation for ≥3 months before screening)	N=551 26 weeks	Primary: Change in HbA_{1c} Secondary: Change in FPG, fasting glucose <100 mg/dL and body weight loss	Primary: At 26 weeks, similar reductions in HbA_{1c} were noted between exenatide and insulin glargine (–1.11%; CI, –0.123 to 0.157). Secondary: A significantly reduction in fasting plasma glucose from baseline was observed in the insulin glargine group (–51.5 mg/dL; P<0.001). The reduction from baseline in the exenatide group was not significant (–25.7 mg/dL). A significant reduction was observed in the insulin group when compared to the exenatide group (95% CI, 20 to 34 mg/dL). A significantly greater proportion of patients taking insulin glargine (21.6%) achieved fasting glucose of <100 mg/dL than those taking exenatide (8.6%; P<0.001). A significant weight loss was experienced in the exenatide group (–2.3 kg) compared to a gain of +1.8 kg in the insulin group (CI, –4.6 to –3.5; P<0.001). Similar rates of hypoglycemia were reported with both agents (CI, –1.3 to 3.4 events/patient-year). Exenatide patients had a higher incidence of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				daytime hypoglycemia (CI, 0.4 to 4.9 events/patient-year), and a lower rate of nocturnal hypoglycemia than insulin glargine patients (CI, –2.3 to –0.9 events/patient-year). A significantly higher incidence of gastrointestinal side effects, including nausea (57.1 vs 8.6%; P<0.001), vomiting (17.4 vs 3.7%; P<0.001) and diarrhea (8.5 vs 3%; P=0.006), upper abdominal pain (P=0.012), constipation (P=0.011), dyspepsia (P=0.011), decreased appetite (P=0.021), and anorexia (P=0.002) were reported in the exenatide group vs the insulin group. Withdrawals due to adverse events occurred in 9.5% of exenatide patients vs 0.7% of insulin patients.
Secnik Boye et al.[150] (2006) Exenatide 5 µg BID for 4 weeks, then 10 µg BID vs insulin glargine QD at bedtime All patients were receiving existing metformin and/or sulfonylurea regimens.	MC, OL, RCT Secondary analysis on patients with type 2 diabetes inadequately controlled (defined as an HbA_{1c} between 7.0 and 10.0%) with sulfonylurea and metformin therapy at maximally effective doses, enrolled in a previous 26 week study	N=455 26 weeks	Primary: Patient-reported health outcome measures: Diabetes Symptom Checklist-revised, DTSQ, EQ-5D, Medical Outcomes Study 36-Item Short-Form Health Survey, Diabetes Medical Outcomes Study 36-Item Short-Form Health Survey Secondary: Not reported	Primary: Both exenatide and insulin glargine groups experienced a significant improvement from baseline in patient-reported health outcome measures as demonstrated by Diabetes Symptom Checklist-revised overall scores, DTSQ, EQ-5D and Medical Outcomes Study 36-Item Short-Form Health Survey scores (P<0.05 for all measures). There was not a statistical difference between treatment groups in any of the outcome measures (P>0.05 for all measures). Neither the exenatide nor the insulin glargine group experienced a significant improvement in Medical Outcomes Study 36-Item Short-Form Health Survey scores (P=0.93 for both groups). Secondary: Not reported
Nauck et al.[151] (2007) Exenatide 5 µg BID for 4 weeks, then 10 µg BID	MC, OL, RCT Patients 30 and 75 years of age who had suboptimal	N=501 52 weeks	Primary: Mean change in HbA_{1c} levels, weight, fasting serum glucose levels,	Primary: There was not a significantly different change from baseline in mean HbA_{1c} levels between the exenatide (–1.04%) and insulin aspart groups (–0.89%, 95% CI, −0.32% to 0.01%; P=0.067).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs insulin aspart BID All patients were receiving existing metformin and/or sulfonylurea regimens.	glycemic control despite receiving optimally effective metformin and sulfonylurea therapy for ≥3 months, HbA_{1c} ≥7.0 and ≤11.0%, a BMI ≥25 and ≤40 kg/m^2, and a history of stable body weight (≤10% variation for ≥3 months)		postprandial glucose levels, adverse events Secondary: Not reported	Patients in the exenatide group experienced a gradual weight loss of –2.5 kg, compared to a gradual weight gain of 2.9 kg in the insulin aspart group, (95% CI, −5.9 to −5.0; P<0.001) at the end of 52 weeks. Patients in both exenatide (–1.8 mmol/L) and insulin aspart (–1.7 mmol/L) groups had a significant decrease in fasting serum glucose compared to baseline (P<0.001 for both groups). There was not a significant difference between groups (CI, −0.6 to 0.4; P=0.689). Patients in the insulin aspart group had significantly lower mean glucose values at pre-breakfast (P=0.037), pre-lunch (P=0.004) and 03.00 hours (P=0.002). Patients in the exenatide group had a greater reduction in postprandial glucose excursions following morning (P<0.001), midday (P=0.002) and evening meals (P<0.001). The withdrawal rate was 21.3% in the exenatide group and 10.1% in the insulin aspart group. Adverse events that were more commonly reported in the exenatide vs insulin aspart group included: nausea (33.2 vs 0.4%), vomiting (15.0 vs 3.2%), diarrhea (9.5 vs 2%) and other clinically relevant adverse events (13.4 vs 6.4%). Secondary: Not reported
Xu et al.[152] (2015) CONFIDENCE Exenatide twice daily vs insulin (75% insulin lispro protamine suspension and 25% insulin lispro injection) twice daily	MC, PG, RCT Treatment-naïve patients 30 to 70 years of age with newly diagnosed type 2 diabetes	N=416 48 weeks	Primary: Change in baseline HbA_{1c} Secondary: Effects on weight, blood pressure, lipid profiles and β-cell function	Primary: At week 48, mean (95% CI) HbA_{1c} changes from baseline were −1.8% (−1.55 to −2.05%) with exenatide, −1.7% (−1.52 to −1.96%) with insulin and −1.5% (−1.23 to −1.71%) with pioglitazone. Treatment differences were −0.20% (95% CI, −0.46 to 0.06%) for exenatide vs insulin (P=0.185), and −0.37% (95% CI, −0.63 to −0.12%) for exenatide vs pioglitazone (P=0.002). Secondary: Mean weight change was significantly different between the exenatide group and the insulin and pioglitazone groups from weeks four and eight until the end of the study, with weight decreasing in the exenatide group. Decreases in mean systolic and diastolic blood pressures at 48 weeks were not statistically different between groups, although significant decreases in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs pioglitazone once daily				systolic and diastolic blood pressures were observed with exenatide (P<0.05 vs baseline), and a significant decrease in diastolic blood pressure alone was found with pioglitazone (P<0.001). Exenatide treatment resulted in improvements in overall lipid profiles, with significant decreases in TG, total cholesterol and LDL cholesterol levels, and an increase in HDL cholesterol (P<0.05 vs baseline for all variables). HDL cholesterol increased with pioglitazone (P<0.001), and LDL cholesterol decreased with insulin (P<0.05). At week 48, HOMA-B (which, together with fasting proinsulin-to-insulin ratio (PI/I), provides an indication of β-cell function during the fasting state) increased in patients treated with insulin (P<0.001 vs baseline). Improvements from baseline were similar in all treatment groups with regard to PI/I, as well as acute insulin response (AIR, which represents β-cell function during the stimulated state after intravenous glucose injection). Disposition index (DI), which provides a measure of β-cell function during the stimulated state under near-physiological conditions of food intake via the gastrointestinal system, increased significantly in all treatment groups (P<0.001 vs baseline for exenatide; P<0.05 vs baseline for insulin and pioglitazone). The greatest mean improvements from baseline in DI and AIR were observed in the exenatide treatment group.
Hollander et al.[153] (2015) Insulin glargine+ one oral antidiabetes drug (metformin or sulfonylurea) wherein previous TZD therapy was dropped and replaced with insulin glargine (GLAR +1 OAD) vs	MC, OL, RCT Type 2 diabetes patients 18 to 79 years of age with a HbA_{1c} of 7.5 to 12.0% despite ≥3 months of treatment with a TZD plus metformin or a sulfonylurea	N=337 48 weeks	Primary: Change in HbA_{1c} Secondary: Changes in FPG, weight, BMI, and serum lipid profile	Primary: Substitution of insulin glargine for a TZD and addition of a third OAD resulted in an adjusted mean change in HbA_{1c} from baseline of −1.66% and −1.86%, respectively (adjusted mean difference 0.20; 95% CI, −0.11 to 0.51). The upper limit of the 95% CI for the difference in the adjusted mean changes from baseline to endpoint for HbA_{1c} was 0.51%; therefore, the primary efficacy analysis did not demonstrate equivalent glycemic control during treatment with GLAR + 1 OAD and 3OAD as measured by HbA_{1c} levels. In patients originally taking sulfonylurea, there was a significantly greater reduction in HbA_{1c} in those adding metformin to TZD and sulfonylurea versus those switching the TZD for GLAR + SU at weeks 12, 24, and 48. Secondary: Adjusted mean FPG at baseline was similar between the two treatment arms (GLAR + 1 OAD 193.0 mg/dL vs 3OAD 199.5 mg/dL; P=0.4299).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
three oral antidiabetes drugs (3OAD) wherein patients receiving TZD and metformin received add-on sulfonylurea (glyburide) and patients receiving TZD and sulfonylurea received add-on metformin (3OAD)				FPG reduced significantly from baseline to endpoint (P<0.0001 for both arms). Weight gain was observed in both treatment arms at each study visit and at endpoint. At each visit, patients in the GLAR + 1 OAD arm gained less weight than those in the 3OAD arm; this difference was significant at week 12 (P=0.0035). A similar pattern was observed for BMI. Overall, insulin glargine + metformin was as effective as 3OAD in achieving glycemic control but with greater improvements in lipid parameters, less weight gain, and lower hypoglycemia rates.
Kabadi et al.[154] (2003) Tolazamide 1 gram daily plus premixed 70% NPH and 30% regular insulin daily vs glyburide 20 mg daily plus premixed 70% NPH and 30% regular insulin daily vs glipizide XL plus premixed 70% NPH and 30% regular insulin daily vs	PC, RCT Patients with type 2 diabetes mellitus with a lapse of glycemic control, established by documentation of HbA_{1c} >7.4% on ≥2 occasions at an interval of ≥3 months in each patient while taking oral sulfonylureas consisting of one of these drugs in the maximum recommended daily dose: tolazamide 1 g daily, glyburide 20 mg daily, glipizide XL 20 mg daily, or glimepiride 8 mg daily	N=40 7 months	Primary: Changes in body weight, HbA_{1c}, and fasting C-peptide concentrations Secondary: Changes in daily insulin dose and the number of hypoglycemic episodes confirmed by finger stick blood glucose <60 mg/ dL	Primary: Changes in body weight were 2.5±0.8 kg for the tolazamide group, 2.6±1.0 kg for the glyburide group, 2.4±0.9 kg for the glipizide XL group, and 2.2±0.7 kg for the glimepiride group, all were significant compared to placebo (P<0.01) after the addition of insulin. All groups achieved optimal glycemic control as expressed by HbA_{1c} <7.4%, 1% above the highest normal level of 6.4% in our laboratory as recommended by the American Diabetes Association after the addition of insulin. HbA_{1c} was 6.8±0.4% for tolazamide, 6.9±0.4% for glyburide, 6.7±0.4% for glipizide XL, 6.7±0.3% for glimepiride, and 7.0±0.3% for placebo. C-peptide levels decreased in all groups. The reduction in the C-peptide level was significantly greater (P<0.05) in the placebo group compared to the sulfonylurea groups. There were no significant differences among the sulfonylurea groups. Secondary: Patients receiving sulfonylureas required a significantly lower (P<0.01) daily insulin dose, as well as dose per kilogram of body weight in comparison to patients receiving placebo (P<0.01).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
glimepiride 8 mg daily plus premixed 70% NPH and 30% regular insulin daily vs placebo plus premixed 70% NPH and 30% regular insulin daily				The daily insulin dose and units per kilogram of body weight was significantly lower (P<0.05) in patients receiving glimepiride in comparison to those receiving tolazamide, glyburide, or glipizide XL. The number of hypoglycemic episodes during the last four weeks of the study were significantly lower in the sulfonylurea groups as compared to the placebo group (P<0.01). The differences among the individual sulfonylurea groups were not significantly different.
Russell-Jones et al.[155] (2009) LEAD-5 Liraglutide 1.8 mg SC QD vs placebo vs insulin glargine (OL) All patients also received metformin 2,000 mg/day and glimepiride 4 mg/day.	PC, PG, RCT Type 2 diabetic patients 18 to 80 years of age with oral glucose lowering agents ≥3 months before screening, HbA_{1c} 7.5 to 10.0% (previous oral glucose lowering agent monotherapy) or 7.0 to 10.0% (previous oral glucose lowering agent combination therapy), and BMI ≤45 kg/m^2	N=581 26 weeks	Primary: Change in baseline in HbA_{1c} Secondary: Change in baseline body weight, waist circumference, FPG, eight-point self-monitored glucose concentrations, β cell function, and BP	Primary: Decreases in HbA_{1c} were -1.33, -0.24, and -1.09% with liraglutide, placebo, and insulin. Decreases achieved with liraglutide were significantly greater compared to placebo and insulin (differences for liraglutide vs placebo, -1.09%; 95% CI, -1.28 to -0.90; P<0.0001 and differences for liraglutide vs glargine, -0.24%; 95% CI, -0.39 to -0.08; P=0.0015). Secondary: The decrease in body weight with liraglutide (-1.8 kg) was significantly greater compared to placebo (0.42 kg; treatment difference, -1.39 kg; 95% CI, -2.10 to -0.69; P=0.0001). Additionally, patients gained weight with insulin (1.6 kg; treatment difference, -3.43 kg; 95% CI, -4.00 to -2.86; P<0.0001). The decrease in waist circumference with liraglutide (-1.50 cm) was significantly greater compared to insulin (0.89 cm; treatment difference, -2.40 cm; 95% CI, -3.14 to -1.65; P<0.0001), but not compared to placebo (-0.62 cm; treatment difference, -0.88 cm; 95% CI, -1.81 to 0.04; P=0.0608). Final decreases in FPG were -1.55, -1.79, and -0.53 mmol/L with liraglutide, insulin, and placebo. The decrease with liraglutide, and the likelihood of achieving American Diabetes Association targets (FPG 5.0 to 7.2 mmol/L) was significantly greater compared to placebo (treatment difference, -2.08 mmol/L; 95% CI, 2.53 to -1.64; P<0.0001; OR, 4.99; 95% CI, 2.65 to 9.39), but not compared to insulin (data not reported).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Decreases in PPG were achieved with liraglutide (-1.81 mmol/L) and insulin (-1.61 mmol/L), with liraglutide being significantly greater compared to placebo (0.03 mmol/L; treatment difference, -1.84 mmol/L; 95% CI, -2.63 to -1.33; P<0.0001), but not compared to insulin (data not reported). Significant improvements in β cell function as demonstrated by the proinsulin:C-peptide ratio compared to insulin (treatment difference, -0.00366; 95% CI, -0.00597 to -0.00136; P=0.0019) and placebo (treatment difference, -0.00671; 95% CI, -0.00964 to -0.00377; P<0.0001) were achieved with liraglutide. A significant decrease in SBP was achieved with liraglutide (-4.00 mm Hg) compared to insulin (-0.54 mm Hg; treatment difference, -4.51 mm Hg; 95% CI, -6.82 to -2.20; P=0.001), but not compared to placebo (-1.4 mm Hg; treatment difference, -2.53 mm Hg; 95% CI, -5.36 to 0.29; P=0.0791). No significant decreases in DBP were achieved with liraglutide relative to either placebo or insulin.
Civera et al.[156] (2008) Repaglinide 2 mg TID before meals plus metformin 850mg BID plus NPH insulin before dinner vs metformin 850mg BID plus NPH insulin before dinner vs NPH insulin BID	OL, PG Patients with poorly controlled type 2 diabetes despite being on two or more oral antidiabetic drugs	N=37 24 weeks	Primary: HbA_{1c}, hypoglycemia, body weight Secondary: Not reported	Primary: The HbA_{1c} was lower in the repaglinide triple therapy group (7.2%) compared to the metformin plus NPH insulin group (8.8%; P=0.02) and the NPH insulin group (8.4%; P=0.02). The absolute reduction in HbA_{1c} was -2.4% in the repaglinide triple therapy group compared to -0.7% (P=0.01) in the metformin plus NPH insulin group and -1.4% in the insulin NPH group. Lower PPG values were seen with the repaglinide triple therapy group compared to the other two treatment groups (P<0.01). Significant differences in weight gain and hypoglycemia were not seen. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Cesur et al.[157] (2007) Repaglinide up to 4 mg QD vs glimepiride up to 8 mg QD vs insulin glargine up to 36 U QD	MC, OL, OS, PRO Patient 33 to 67 years of age with type 2 diabetes, HbA_{1c} 6.0 to 8.0% taking oral diabetes agents, who were willing to fast throughout Ramadan month	N=65 Duration not specified	Primary: FBG, PPG, HbA_{1c}, fructosamine, BMI, lipid metabolism and hypoglycemia in pre-Ramadan and post-Ramadan fasting Secondary: Not reported	Primary: In the fasting group, both FPG and PPG levels showed no significant changes at post-Ramadan and one-month post-Ramadan compared to pre-Ramadan. In the nonfasting group, FPG levels did not change significantly throughout the study, whereas PPG levels increased at post-Ramadan ($P<0.05$ and $P<0.01$, respectively). At post-Ramadan and one-month post-Ramadan, changes in PPG values in the fasting group were lower compared to the nonfasting group ($P<0.01$ for both time periods). There was no significant change in HbA_{1c} levels between the nonfasting and fasting groups. There was a significant increase in fructosamine levels in both fasting group and non-fasting group at one-month post-Ramadan ($P<0.01$ for both). BMI did not change during the study in fasting group but a gradual increase in BMI was seen in the nonfasting group ($P<0.05$ between pre-Ramadan and post-Ramadan in nonfasting group). TC, LDL-C and TG did not change throughout the study period but HDL-C levels significantly increased at post-Ramadan in the fasting group ($P<0.01$). In nonfasting group, LDL-C and TG levels significantly increased at post-Ramadan ($P<0.05$ for both). At least one hypoglycemia episode was reported in 12.2% of patients in the fasting group and 12.5% of patients in the nonfasting group. Hypoglycemia was seen in 14.3% of patients in the glimepiride group, 11.1% in the repaglinide group and 10% in the insulin group. There was no significant difference between three drug groups regarding the rate of hypoglycemia. Secondary: Not reported
Chisalita et al.[158] (2009)	XO	N=5	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Repaglinide 4mg TID before meals for 10 weeks vs insulin aspart 13 to 46 units/day (4 to 20 units at breakfast, 5 to 15 units at lunch and 4 to 15 units at dinner) for 10 weeks	Patients ≥60 years of age with type 2 diabetes	20 weeks	HbA_{1c}, blood glucose, C-peptide, free human insulin, free total (human and analogue) insulin, proinsulin, islet amyloid polypeptide, growth hormone binding protein, and plasma lipoprotein concentrations were measured Secondary: Not reported	The HbA_{1c} was 6.1% at the end of repaglinide therapy and 5.9% at the end of insulin aspart therapy (P=NS). C-peptide concentrations were significantly higher during repaglinide treatment compared to insulin aspart treatment (AUC 2,453 vs 1,153; P=0.02). Free human insulin levels were significantly higher on repaglinide than on insulin aspart therapy (AUC 215 vs128; P<0.05). Proinsulin levels were higher when measured during repaglinide treatment than during treatment with insulin aspart. Islet amyloid polypeptide levels tended to be higher during repaglinide compared to insulin aspart treatment (P=NS). Fasting plasma insulin like growth factor-I concentration was 220 ng/mL during treatment with insulin aspart and 226 ng/mL during treatment with repaglinide (P=NS). Compared to fasting levels, the insulin like growth factor binding protein-1 levels were lower during repaglinide (P<0.05), but not during insulin aspart treatment (P=NS). Repaglinide treatment increased plasma growth hormone binding protein concentration compared with insulin aspart (1,094 vs 942 pmol/L; P=0.02). Repaglinide treatment resulted in higher postprandial plasma TC, TG and apolipoprotein B concentrations compared with insulin aspart. There was no significant difference in LDL-C or HDL-C Secondary: Not reported
Meneghini et al.[159] (abstract) (2010)	MC, OL, PG Adults with poorly controlled type 2	N=389 48 weeks	Primary: Change in baseline HbA_{1c}	Primary: At trial end, insulin glargine resulted in a significantly greater reduction in HbA_{1c} compared to pioglitazone (-2.48 vs -1.86%; 95% CI, -0.93 to -0.31; P=0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Insulin glargine vs pioglitazone	diabetes (HbA_{1c} 8.0 to 12.0%), despite ≥3 months of sulfonylurea or metformin monotherapy		Secondary: Change in baseline FPG, BMI, body weight, safety	Secondary: Insulin glargine resulted in significantly greater reductions in FPG at all time points (trial end difference, -34.9 mg/dL; 95% CI, -47.6 to -22.2; P<0.0001). Changes in weight and BMI were similar between the two treatments. Compared to pioglitazone, insulin glargine resulted in a lower overall incidence of possibly treatment-emergent adverse events (12.0 vs 20.7%) and fewer study discontinuations (2.2 vs 9.1%), but a higher rate (per patient-year) of confirmed clinically relevant hypoglycemic episodes (4.97 vs 1.04; P<0.0001) and severe hypoglycemia (0.07 vs 0.01; P=0.0309).
Dorkhan et al.[160] (2008) Pioglitazone 30 to 45 mg QD and existing oral hypoglycemic therapy vs insulin glargine 6 to 10 IU/day administered in the morning (titrated as necessary) and existing oral hypoglycemic therapy	RCT, OL Patients with type 2 diabetes and inadequate glycemic control (defined as treatment with metformin and sulfonylurea/ meglitinide in doses ≥50% of maximum recommended doses and HbA_{1c} >6.2%	N=36 26 weeks	Primary: Change in HbA_{1c}, β-cell function, insulin sensitivity, degree of patient satisfaction Secondary: Not reported	Primary: After 26 weeks, the change in HbA_{1c} from baseline was -1.3% (P<0.01) for pioglitazone and -2.2% (P<0.01) for insulin glargine. There was no significant difference between the treatment groups (P=0.050). There was no difference in insulin, β-cell function, or insulin sensitivity among the two treatment groups (P value not significant). Insulin glargine resulted in a greater reduction in proinsulin concentrations than pioglitazone (-55 vs -25%; P<0.01). Pioglitazone increased HDL-C (0.14 mmol/L) compared to a slight decrease in the insulin glargine group (-0.04 mmol/L; P<0.01 between groups). There were no significant differences between the treatment groups with regards to other lipid parameters (P value not significant). The degree of satisfaction with treatment was similar in the pioglitazone and insulin glargine treatment groups. There was a doubling of serum adiponectin levels in the pioglitazone group (7.5 to 15; P<0.01) compared to a significant decrease in the insulin glargine group (8.7 to 7.6; P=0.04; P<0.01 between groups). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Aljabri et al.[161] (2004) Pioglitazone 30 to 45 mg QD vs NPH insulin 0.3 unit/kg QD All patients were receiving existing sulfonylurea or metformin therapy	OL, RCT Patients with poorly controlled type 2 diabetes (HbA_{1c} >8%) with insulin secretagogues and metformin monotherapy	N=62 16 weeks	Primary: Effect on HbA_{1c}, FPG, incidence of hypoglycemia (< 68 mg/dL), effect on lipoproteins, quality of life (assessed using the DTSQ) Secondary: Not reported	Primary: Similar reductions in HbA_{1c} were observed in pioglitazone-treated (–1.9%) and NPH insulin-treated patients (–2.3%; P=0.32). Nonsignificant differences in reduction in FPG were observed with NPH insulin (–77 mg/dL) and pioglitazone (–52 mg/dL; P=0.07). Significantly more patients reported hypoglycemia with NPH insulin (19) than with pioglitazone (11; P=0.02). Significant increases in HDL-C were observed with pioglitazone (4 mg/dL) compared to NPH insulin (0 mg/dL; P=0.02). No significant differences in total cholesterol, LDL cholesterol and triglycerides were reported between the two treatment groups. No significant differences were noted for the DTSQ scores between the two treatment groups. Secondary: Not reported
Ligvay et al.[162] (2009) Pioglitazone 15 to 45 mg QD plus glyburide 1.25 mg BID vs insulin aspart protamine and insulin aspart (NovoLog Mix 70/30) 0.2 units/kg divided twice daily	RCT, OL Patients 21 to 70 years of age with type 2 diabetes who were treatment naïve	N=58 36 months	Primary: HbA_{1c}, rate of treatment failures (defined as HbA_{1c} >8.0%), hypoglycemia, weight gain, compliance, QOL, and patient satisfaction Secondary: Not reported	Primary: After 36 months, HbA_{1c} was 6.1 % in the insulin-treated group compared to 6.0% in the triple oral group (P=0.26). The percentage of patients achieving HbA_{1c} <7.0% was 100% in both groups at baseline; 92% of patients in the insulin group and 76% of patients in the triple oral group met the HbA_{1c} goal at the end of 36 months. Three patients in each group reached the “treatment failure” end point. The insulin group had 0.51 mild hypoglycemia events/person month and the triple oral group had 0.68 event/person-month (P=0.18). The insulin group averaged 0.04 severe hypoglycemic event/person-year, and the triple oral group averaged 0.09 event/ person-year (P=0.53).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
All patients were receiving metformin 1,000 mg BID Doses of medications could be titrated at the investigator's discretion.				In the completer analysis, the triple oral group experienced more weight gain than the insulin group: 10.10 kg (95% CI, 4.46 to 15.74) versus 3.36 kg (-0.47 to 7.20; P=0.04). Compliance was high throughout the trial: 93% in the insulin-treated group and 90% in the triple oral group. There were differences between the groups for any of the 12 QoL domains evaluated. All patients receiving insulin reported satisfaction with insulin treatment and willingness to continue insulin at 18 months after randomization. Secondary: Not reported
Ibrahim et al.[163] (2013) Group I: oral metformin (500 mg TID) without increasing the insulin dose vs group II: increased insulin dose	NI, RCT Pregnant women with gestational or pre-existing DM at gestations between 20 and 34 weeks who showed insulin resistance (defined as poor glycemic control at a daily dose of ≥1.12 units/kg)	N=90 Variable duration	Primary: Maternal glycemic control Secondary: Maternal hypoglycemia, hospital admissions, neonatal outcomes	Primary: Glycemic control was achieved in 76.1% of patients in group I and 100% of patients in group II (P=0.001). Secondary: Readmission for poor glycemic control was not significantly different between groups (P=0.471). Bouts of maternal hypoglycemia occurred in 6.5% of patients in group I and 22.7% in group II (P=0.029). Only two neonatal/delivery outcomes showed a statistical difference: Neonatal hypoglycemia occurred in 7.0% of cases in group I vs 38.5% in group II (P=0.001). Neonatal Intensive Care Unit admission occurred in 18.6% of group I neonates and 41% of group II neonates (P=0.026).
Spaulonci et al.[164] (2013) Metformin vs insulin	PRO, RCT Women with gestational diabetes with singleton pregnancy, use of diet and exercise for a minimum period of 1 week without	N=92 Variable duration	Primary: Maternal glycemic control Secondary: Neonatal outcomes	Primary: Higher mean glucose levels were observed in the insulin group (P=0.020), mainly because of higher levels observed after dinner (P=0.042). Twenty-one percent of women using insulin and 27% of women using metformin achieved adequate glycemic control in the first week of treatment (P=0.11). Twelve (26.08%) of the 46 women in the metformin group required supplemental insulin for adequate glycemic control. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	satisfactory glycemic control, absence of risk factors for lactic acidosis, and absence of anatomic and/or chromosome anomalies of the conceptus detected by ultrasonography.			No significant differences between the two groups were observed regarding the following neonatal outcomes: gestational age at birth, 1-minute Apgar score, 5-minute Apgar score, umbilical artery pH at birth, or newborn weight. There were no fetuses with macrosomia in the group metformin vs three (6.5%) cases in the insulin group (P=0.242). A higher frequency of neonatal hypoglycemia was observed in cases treated with insulin (22.2%) compared with newborns from the metformin group (6.5%) (P=0.032).
Niromanesh et al.[165] (2012) Metformin vs insulin	RCT, SB Gestational diabetes mellitus women with singleton pregnancy and gestational age between 20 and 34 weeks who did not achieve glycemic control on diet	N=160 Variable duration	Primary: Maternal glycemic control, birth weight Secondary: Neonatal and obstetric complications	Primary: The two groups were comparable with respect to mean fasting blood sugar and postprandial measurements throughout pregnancy after randomization until delivery. The mean fasting blood sugar was <95 mg/dL in 74% and 79% of women in the metformin and insulin groups, respectively (P=0.457). Neonates from the metformin group had a significantly lower circumference of head, arm and chest (P<0.05) and had lower birth weight (P=0.005) and height (P=0.033). The frequency rate of SGA (small for gestational age; birth weight < 10th percentile) was 3.8% in the metformin group and 2.5% in the insulin group. The relative risk of LGA (large for gestational age; birth weight > 90th percentile) in the metformin group was half that of the insulin group (RR, 0.5; 95% CI, 0.3 to 0.9, P=0.012). Secondary: The relative risk of emergency cesarean and preterm delivery was 1.6 and 2.2 times higher, respectively, in the metformin group; however, this was not statistically significant. The two groups were not statistically different in terms of need for phototherapy, incidence of hypoglycemia, and birth defects. The two groups were comparable with respect to umbilical artery pH, Apgar score at 5 min, and hospitalization days. Neonatal Intensive Care Unit admission and respiratory distress syndrome was nonsignificantly more frequent in the metformin group (RR, 2.5; 95% CI, 0.5 to 12.5, P=0.443).
Poolsup et al.[166] (2014)	MA	N=2,151 (13 RCTs)	Primary:	Primary: <u>Pool A</u>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Pool A: metformin vs insulin Pool B: glyburide vs insulin	Women with gestational diabetes mellitus	Variable duration	Safety and efficacy of oral antidiabetic agents compared to insulin Secondary: Not reported	There was a nonsignificant difference in the risk of macrosomia (RR, 0.93; 95% CI, 0.61 to 1.41) and large for gestational age (LGA) births (RR, 0.88; 95% CI, 0.70 to 1.12) between the two study groups. A significant increase in the risk of preterm births occurred in the metformin group as compared to insulin (RR, 1.51; 95% CI, 1.04 to 2.19; P=0.03). Rate of neonatal/perinatal mortality was very low in both groups and results remained statistically non-significant. Risk of shoulder dystocia, neonatal hypoglycemia, congenital abnormality, and small for gestational age (SGA) births tended to be lower with metformin but statistical significance was not achieved. A non-significant decrease in risk of caesarean section, pre-eclampsia, and labor induction was noticed with metformin compared to insulin. A significant decrease in the risk of gestational hypertension was observed in the metformin arm (RR, 0.54; 95% CI, 0.31 to 0.91; P=0.02). A significant decrease in PPG levels occurred (mean difference, -2.47 mg/dL; 95% CI, -4.00 to -0.94, P=0.002) in metformin group compared to insulin, while results were statistically nonsignificant between the two groups for FPG levels (mean difference, 0.74 mg/dL; 95% CI, -0.52 to -2.01). <u>Pool B</u> Glyburide significantly increased the risk of macrosomia (RR, 3.07; 95% CI, 1.14 to 8.23; P=0.03) and neonatal hypoglycemia (RR, 2.30; 95% CI, 1.28 to 4.11; P=0.005) compared to insulin. There was no difference between glyburide and insulin with regard to risk for LGA births; statistically significant heterogeneity was detected for this outcome. There were no significant differences in the risk of preterm births, neonatal mortality, congenital abnormality, or SGA births for glyburide versus insulin. None of the maternal outcomes (caesarean section, pre-eclampsia, maternal hypoglycemia, glycemic levels) displayed a significant difference between glyburide and insulin. The effect estimate for fasting glucose levels (mean difference, 1.90 mg/dL; 95% CI, -0.38 to 4.18) and postprandial glucose levels (mean difference, 3.42 mg/dL; 95% CI, -1.17 to 8.02) favored the insulin group, but results remained nonsignificant. Secondary: Not reported
Rosenstock et al.[167]	AC, MC, OL	N=298	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2016) GETGOAL-DUO 2 Lixisenatide 20 µg QD vs insulin glulisine QD vs. insulin glulisine TID On run-in entry, oral antidiabetic drugs other than metformin (DPP-4 inhibitors, sulfonylureas, and glinides) were discontinued, and insulin glargine was optimally titrated. After the run-in phase, if HbA_{1c} remained between ≥7% to ≤9% and mean FPG was ≤140 mg/dL patients were randomized.	Adult patients with type 2 DM (diagnosed for at least one year) uncontrolled on ≥6 months' basal insulin, with or without one to three oral antidiabetic agents and a HbA_{1c} ≥7% to ≤9% at study start and BMI> 20 and ≤40 kg/m^2	24 weeks	Noninferiority of lixisenatide versus insulin glulisine once daily in HbA_{1c} reduction; and for lixisenatide vs. insulin glulisine thrice daily, either noninferiority in HbA_{1c} reduction or superiority of lixisenatide vs. insulin glulisine thrice daily in body weight change. Secondary: Percentage of patients achieving glycemic goals, FPG, post-prandial glucose, body weight and adverse events	All coprimary end points were met. HbA_{1c} improved from 8.5% to 7.9% with glargine optimization and further to 7.2%, 7.2%, and 7.0% with lixisenatide and glulisine once daily and thrice daily, respectively. Lixisenatide demonstrated statistical superiority in change from baseline at week 26 in body weight compared with insulin glulisine thrice daily (coprimary end point LS mean treatment difference, –2.0 kg (95% CI, –2.59 to –1.40; P<0.0001). Secondary: At week 26, the change from baseline in body weight in the three treatment groups was –0.6, 1.0 and 1.4 kg, for lixisenatide and insulin glulisine once daily and thrice daily, respectively. LS mean reductions from baseline in 2-hour post prandial glucose after a standardized breakfast at week 26 were greater in the lixisenatide arm compared with the insulin glulisine. Symptomatic hypoglycemia was lower in lixisenatide compared to glulisine patients. More gastrointestinal events occurred with lixisenatide.
Aroda et al.[168] (2017) SUSTAIN 4	AC, MC, OL, PG Patients ≥18 years with type 2 DM inadequately	N=1,089 30 weeks	Primary: HbA_{1c} Secondary:	Primary: Treatment with semaglutide 0.5 mg and 1 mg once weekly resulted in a reduction in HbA_{1c} compared with the insulin glargine (1.2% and -1.5% and -0.9%; P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Semaglutide 0.5 mg SC weekly vs semaglutide 1 mg SC weekly vs insulin glargine 10 units QD titrated to a pre-breakfast SMPG target of 72 to 99 mg/dL Subjects with unacceptable hyperglycemia were to be offered metformin (first choice) or other antidiabetic medications (not GLP-1, DPP-4 inhibitors or amylin analogs) as add-on to their randomized treatment (rescue medication) at the discretion of the investigator.	controlled with metformin with or without a sulfonylurea ≥90 days before screening, an HbA_{1c} ≥7% to ≤10% and who were insulin naïve		Change in body weight, FPG, SMPG, BMI, waist circumference, SBP and safety evaluations.	Secondary: The mean changes from baseline to week 30 were -3.2 kg, -4.7 kg and 0.9 kg in the semaglutide 0.5 mg, 1 mg, and insulin glargine arms, respectively. The semaglutide treatment had significantly greater reductions in FPG (only semaglutide 1 mg), mean 8-point SMPG (only semaglutide 1 mg), mean prandial increment (across all meals) of the 8-point SMPG, BMI and waist circumference. Further, the odds of achieving HbA_{1c} targets and categorical weight loss targets were significantly greater with semaglutide 0.5 mg or 1 mg compared with insulin glargine. The most frequently reported adverse events were nausea with semaglutide, reported in 77 (21%) patients with 0.5 mg and in 80 (22%) with 1.0 mg, and nasopharyngitis reported in 44 (12%) patients with insulin glargine.
Marso et al.[169] (2016) SUSTAIN 6	DB, MC, PC, PG, RCT	N=3,297 N=104	Primary: MACE Secondary:	Primary: The total number of primary component MACE endpoints was 254 (108 [6.6%] with semaglutide and 146 [8.9%] with placebo).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Semaglutide 0.5 mg SC weekly vs semaglutide 1 mg SC weekly vs insulin glargine 10 units QD titrated to a pre-breakfast SMPG target of 72 to 99 mg/dL Subjects with unacceptable hyperglycemia were to be offered metformin (first choice) or other antidiabetic medications (not GLP-1, DPP-4 inhibitors or amylin analogs) as add-on to their randomized treatment (rescue medication) at the discretion of the investigator.	Patients ≥50 years with type 2 DM inadequately and established cardiovascular disease, chronic heart failure or chronic kidney disease or ≥60 years with at least one cardiovascular risk factor, antihyperglycemic drug-naïve, or treated with one or two oral antihyperglycemic agents, with or without basal or pre-mixed insulin and HbA_{1c} ≥7%		Safety evaluations	For the MACE components, the results for non-fatal MI (HR, 0.74; 95% CI, 0.51 to 1.08; P=0.12) and non-fatal stroke (HR, 0.61; 95% CI, 0.38 to 0.99; P=0.04) contributed to the favorable overall treatment effect of semaglutide on MACE. The occurrence of cardiovascular death was similar with semaglutide and placebo (HR, 0.98; 95% CI, 0.65 to 1.48; P=0.92). Rates of new or worsening nephropathy were lower in the semaglutide group, but rates of retinopathy complications (vitreous hemorrhage, blindness, or conditions requiring treatment with an intravitreal agent or photocoagulation) were significantly higher (HR, 1.76; 95% CI, 1.11 to 2.78; P=0.02). Secondary: Fewer serious adverse events occurred in the semaglutide group, although more patients discontinued treatment because of adverse events, mainly gastrointestinal.
Kellerer et al.[170] (2022) SUSTAIN 11	MC, OL, PG, RCT Adults with inadequately controlled type 2	N=1,748 52 weeks	Primary: HbA_{1c} Secondary:	Primary: HbA_{1c} (randomization: 8.6%) decreased by 1.5% points and 1.2% points with semaglutide (n=874) and IAsp (n=874), respectively (estimated treatment difference [ETD], -0.29% points; 95% CI, -0.38 to -0.20; P<0.0001 for non-inferiority).

<table>
<tr><th>Study and Drug Regimen</th><th>Study Design and Demographics</th><th>Study Size and Study Duration</th><th>End Points</th><th>Results</th></tr>
<tr><td>Semaglutide once weekly

vs

insulin aspart (IAsp) thrice-daily (TID)

Treatments as add-on to optimized insulin glargine (IGlar) and metformin</td><td>diabetes (HbA_{1c} >7.5% to ≤10.0%) with IGlar and metformin ± one additional oral antihyperglycaemic drug (OAD), who were willing to undergo individualized treatment intensification toward an HbA_{1c} target of 6.5% to 7.5%</td><td></td><td>Occurrence of severe hypoglycemic episodes and change in body weight</td><td>Secondary:
Few severe hypoglycemic episodes were recorded in either group, with no statistically significant difference between the groups. Change in body weight from randomization (87.9 kg) to week 52 was in favor of semaglutide (-4.1 kg) versus IAsp (+2.8 kg) (ETD, -6.99 kg; 95% CI, -7.41 to -6.57). A higher proportion of participants experienced adverse events with semaglutide (58.5%) versus IAsp (52.1%); most were mild to moderate.</td></tr>
<tr><td>SURPASS Clinical Trials Program[171-175]

Tirzepatide

vs

comparators</td><td>Adult patients with type 2 diabetes mellitus</td><td colspan="3">
<table>
<tr><th>Trial (size)</th><th>Background Therapy</th><th>Key Comparator</th><th colspan="2">Key Glycemic Efficacy Comparison (HbA1c % decrease)</th><th colspan="2">Key Body Weight Comparison Loss (kg)</th></tr>
<tr><td colspan="7">Efficacy and Safety Confirmatory Trials</td></tr>
<tr><td rowspan="3">SURPASS-1 (N=478)</td><td rowspan="3">Diet/exercise alone</td><td rowspan="3">Placebo</td><td>5 mg</td><td>-1.87% vs 0.04% (P<0.0001)</td><td>5 mg</td><td>-7.0 vs -0.7 (P<0.001)</td></tr>
<tr><td>10 mg</td><td>-1.89% vs 0.04% (P<0.0001)</td><td>10 mg</td><td>-7.8 vs -0.7 (P<0.0001)</td></tr>
<tr><td>15 mg</td><td>-2.07% vs 0.04% (P<0.0001)</td><td>15 mg</td><td>-9.5 vs -0.7 (P<0.0001)</td></tr>
<tr><td rowspan="3">SURPASS-2 (N=1,878)</td><td rowspan="3">Metformin</td><td rowspan="3">Semaglutide 1 mg weekly</td><td>5 mg</td><td>-2.01% vs -1.86% (P=0.02)</td><td>5 mg</td><td>-7.6 vs -5.7 (P<0.001)</td></tr>
<tr><td>10 mg</td><td>-2.24% vs -1.86% (P<0.001)</td><td>10 mg</td><td>-9.3 vs -5.7 (P<0.001)</td></tr>
<tr><td>15 mg</td><td>-2.30% vs -1.86% (P<0.001)</td><td>15 mg</td><td>-11.2 vs -5.7 (P<0.001)</td></tr>
<tr><td rowspan="2">SURPASS-3 (N=1,437)</td><td rowspan="2">Metformin (w/ or w/o SGLT2)</td><td rowspan="2">Insulin degludec QD</td><td>5 mg</td><td>-1.93% vs -1.34% (P<0.0001)</td><td>5 mg</td><td>-7.5 vs +2.3 (P<0.001)</td></tr>
<tr><td>10 mg</td><td>-2.20% vs -1.34% (P<0.0001)</td><td>10 mg</td><td>-10.7 vs +2.3 (P<0.001)</td></tr>
</table>
</td></tr>
</table>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				15 mg: -2.37% vs -1.34% (P<0.0001); 15 mg: -12.9 vs +2.3 (P<0.001)
		SURPASS-4 (N=1,995)	Metformin or sulfonylurea, or SGLT2 vs Insulin glargine QD	5 mg: -2.24 vs -1.44 (P<0.0001); 5 mg: -7.1 vs +1.9 (P<0.0001)
				10 mg: -2.43 vs -1.44 (P<0.0001); 10 mg: -9.5 vs +1.9 (P<0.0001)
				15 mg: -2.58 vs -1.44 (P<0.0001); 15 mg: -11.7 vs +1.9 (P<0.0001)
		SURPASS-5 (N=475)	Insulin glargine (w/ or w/o metformin) vs Placebo	5 mg: -2.11 vs -0.86 (P<0.001); 5 mg: -5.4 vs +1.6 (P<0.001)
				10 mg: -2.40 vs -0.86 (P<0.001); 10 mg: -7.5 vs +1.6 (P<0.001)
				15 mg: -2.34 vs -0.86 (P<0.001); 15 mg: -8.8 vs +1.6 (P<0.001)
Nichols et al.[176] (2007) Metformin vs sulfonylurea vs insulin vs TZDs	MC, OS, RETRO Patients who initiated metformin, sulfonylurea, insulin or TZDs between 1996 and 2002 and continued use of that drug for at least 12 months without adding other therapies	N=9,546 ≥12 months	Primary: Weight changes Secondary: Not reported	Primary: Patients treated with metformin lost an average of 2.4 kg, sulfonylurea-treated patients gained 1.8 kg, insulin-treated patients gained 3.3 kg, and thiazolidinedione-treated patients gained 5.0 kg. All comparisons with metformin were statistically significant. Secondary: Not reported
Black et al.[177] (2007) Meglitinide vs	MA (15 trials) Patients with type 2 diabetes	N=3,781 Duration varied	Primary: Mortality and morbidity Secondary:	Primary: No trials reported the effect of meglitinides on mortality and morbidity. Secondary: In the 11 trials comparing meglitinides to placebo, both repaglinide and nateglinide resulted in reductions in HbA_{1c} (0.1 to 2.1% and 0.2 to 0.6%,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
meglitinide plus metformin vs meglitinide plus insulin vs metformin vs placebo			Change in HbA_{1c}, weight or BMI, hypoglycemia, adverse effects, quality of life	respectively). In two trials comparing repaglinide to nateglinide, reduction in HbA_{1c} was similar. When compared to metformin, both repaglinide and nateglinide showed similar or slightly smaller reduction in HbA_{1c} compared to metformin. The combination therapy of metformin plus a meglitinide showed a clinically significant reduction in HbA_{1c} compared to metformin. Weight gain was generally greater in patients receiving meglitinides compared to patients receiving metformin. Evidence from the meglitinide trials with metformin suggests that both repaglinide and nateglinide had fewer gastrointestinal adverse events including diarrhea. There was no evidence of serious adverse events associated with meglitinides. There were more reports of hypoglycemia episodes in patients receiving meglitinides compared to patients receiving placebo. In the two head-to-head trials of repaglinide and nateglinide, fewer patients receiving nateglinide reported hypoglycemia symptoms (2 vs 7%). When compared to metformin, patients receiving meglitinides reported more hypoglycemia episodes. There were two trials that assessed quality of life in patients receiving repaglinide vs placebo and in patients receiving repaglinide plus insulin vs metformin plus insulin. There were no substantial changes in quality of life using a variety of validated diseases specific and nonspecific tools. Treatment satisfaction using the World Health Organization DTSQ improved significantly in patients receiving repaglinide compared to patients receiving placebo.
Saenz et al.[178] (2005) Metformin monotherapy vs	MA (29 RCTs) Adult patients with type 2 diabetes	N=5,259 ≥3 months	Primary: Incidence of any diabetes-related outcomes (sudden death, death from hyperglycemia or hypoglycemia, fatal or nonfatal	Primary: Obese patients receiving metformin showed a greater benefit than chlorpropamide, glibenclamide†, or insulin for any diabetes-related outcomes (P=0.009) and for all-cause mortality (P=0.03). Obese patients receiving metformin showed a greater benefit than overweight patients on conventional treatment (diet) for any diabetes-

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo, sulfonylureas, TZDs, meglitinides, α-glucosidase inhibitors, diet, any other oral antidiabetic intervention, insulin			MI, angina, heart failure, stroke, renal failure, amputation [of at least one digit], vitreous hemorrhage, retinopathy requiring photo-coagulation, blindness in one eye, or cataract extraction); diabetes-related death (death from MI, stroke, peripheral vascular disease, renal disease, hypo-glycemia or hyperglycemia, and sudden death); all-cause mortality Secondary: Changes in HbA_{1c}, FPG, quality of life, weight, BMI, lipids, insulin, C-peptide, BP, micro-albuminuria, glomerular filtration rate, renal plasma flow	related outcomes (P=0.004), diabetes-related death (P=0.03), all cause mortality (P=0.01), and MI (P=0.02). Secondary: Patients receiving metformin monotherapy showed a significant benefit for glycemic control, weight, dyslipidemia, and DBP. Metformin presents a strong benefit for HbA_{1c} when compared to diet and placebo. Additionally, metformin showed a moderate benefit for glycemic control, LDL-C, and BMI or weight when compared to sulfonylureas.
Monami et al.[179] (2011)	MA (53 trials)	N=33,881 ≥24 weeks	Primary: Incidence of cancer	Primary: There were 176 cases of cancer (107 and 69 in patients receiving DPP-4 inhibitors and comparators, respectively); 12.5% were gastrointestinal,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
DPP-4 inhibitors (linagliptin, alogliptin, sitagliptin, saxagliptin, vildagliptin*) vs placebo or active comparator (oral hypoglycemic agents and/or insulin)	Patients with type 2 diabetes who were receiving a DPP-4 inhibitor		Secondary: Incidence of pancreatitis, all-cause and cardiovascular mortality, incidence of major cardiovascular events	5.7% were pancreatic, 6.2% were pulmonary, 14.7% were mammary gland/female genital tract, 11.3% were male urogenital tract, 3.4% were thyroid, and 26.1% were of another origin. There was no difference in the proportion of cases between patients receiving DPP-4 inhibitors or a comparator (P=0.90). Secondary: The risk of pancreatitis with DPP-4 inhibitors was 0.786 (P=0.55). The number of reported deaths was 28 and 31 with DPP-4 inhibitors and comparators, respectively. Cardiovascular deaths occurred in 10 patients receiving DPP-4 inhibitors and 20 patients receiving comparators. The risk for all-cause death and cardiovascular death in patients receiving DPP-4 inhibitors was 0.668 (P=0.149 and P=0.054, respectively). There were 137 and 120 major cardiovascular events reported with DPP-4 inhibitors and comparators, respectively. DPP-4 inhibitors were associated with a significantly lower risk of major cardiovascular events (OR, 0.689; P=0.006).
Shyangdan et al.[180] (2011) GLP-1 receptor agonist based therapies (albiglutide*, exenatide ER, liraglutide, lixisenatide*, semaglutide*, and taspoglutide*) vs non-GLP-1 receptor based therapies (placebo, TZDs,	MA (RCTs) Type 2 diabetics ≥18 years of age	N=not reported 8 to 26 weeks	Primary: Change in baseline HbA_{1c}, incidence of hypoglycemia, weight change Secondary: Health-related quality of life, safety, mortality, morbidity, BP, FPG, PPG, lipid profile, β cell function	Primary: Change in baseline HbA_{1c} Exenatide ER significantly decreased HbA_{1c} compared to TZDs (-1.5 vs -1.2%; P=0.02), DPP-4 inhibitors (-1.5 vs -0.9%; P<0.0001), and insulin glargine (-1.5 vs -1.3%; treatment difference, -0.2%; 95% CI, -0.35 to -0.05; P=0.03). There was no difference in the proportion of patients achieving an HbA_{1c} <7.0% between exenatide ER and TZDs (60 vs 52%; P=0.15). A significantly greater proportion of patients receiving exenatide ER achieved an HbA_{1c} <7.0% compared to patients receiving DPP-4 inhibitors (60 vs 35%; P<0.0001) and patients receiving insulin glargine (60 vs 48%; P=0.03). Compared to placebo, treatment with liraglutide 1.2 mg significantly decreased HbA_{1c} (-1.15%; 95% CI, -1.33 to -0.96; P<0.00001). Patients receiving liraglutide 1.2 mg were more likely to achieve an HbA_{1c} <7.0% compared to patients receiving placebo (OR, 2.91; 95% CI, 1.74 to 4.87; P<0.05). Liraglutide 1.2 mg decreased HbA_{1c} to a greater extent compared to TZDs (-0.64%; 95% CI -0.83 to -0.45; P value not reported). The

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
DPP-4 inhibitors, insulin glargine, and sulfonylureas)				likelihood of achieving an HbA_{1c} <7.0% was greater with liraglutide 1.2 mg compared to TZDs (OR, 1.60; 95% CI, 1.18 to 2.15; P value not reported). Liraglutide 1.2 mg decreased HbA_{1c} to a greater extent compared to DPP-4 inhibitors (-0.34%; 95% CI -0.53 to -0.15; P value not reported). The likelihood of achieving an HbA_{1c} <7.0% was greater with liraglutide 1.2 mg compared to DPP-4 inhibitors (OR, 2.56; 95% CI, 1.94 to 3.37; P value not reported). Liraglutide 1.2 mg was not associated with a decrease in HbA_{1c} compared to sulfonylureas (-0.01%; 95% CI, -0.27 to 0.29; P value not reported). The likelihood of achieving an HbA_{1c} <7.0% was not greater with liraglutide 1.2 mg compared to sulfonylureas (OR, 0.98; 95% CI, 0.84 to 1.14; P=0.78). Compared to placebo, liraglutide 1.8 mg significantly decreased an HbA_{1c} (-1.15%; 95% CI, -1.31 to -0.99; P<0.05). Patients receiving liraglutide 1.8 mg were more likely to achieve HbA_{1c} <7.0% compared to patients receiving placebo (OR, 3.25; 95% CI, 1.97 to 5.36; P<0.05). Liraglutide 1.8 mg decreased HbA_{1c} to a greater extent compared to TZDs (-0.69%; 95% CI -0.88 to -0.50%; P value not reported). The likelihood of achieving an HbA_{1c} <7.0% was greater with liraglutide 1.8 mg compared to TZDs (OR, 1.91; 95% CI, 1.43 to 2.53; P value not reported). Liraglutide 1.8 mg decreased HbA_{1c} to a greater extent compared to DPP-4 inhibitors (-0.60%; 95% CI -0.78 to -0.42; P value not reported). The likelihood of achieving HbA_{1c} <7.0% was greater with liraglutide 1.8 compared to DPP-4 inhibitors (OR, 1.99; 95% CI, 1.48 to 2.66; P value not reported). Liraglutide 1.8 mg was not associated with a reduction in HbA_{1c} compared to sulfonylureas (-0.02%; 95% CI -0.30 to 0.26; P value not reported). The likelihood of achieving an HbA_{1c} <7.0% was not greater with liraglutide 1.8 mg compared to sulfonylureas (OR, 1.09; 95% CI, 0.94 to 1.26; P=0.27). Liraglutide decreased HbA_{1c} to a greater extent compared to insulin glargine (-0.24%; 95% CI, -0.49 to 0.01; P value not reported). The likelihood of achieving an HbA_{1c} <7.0% was not different between insulin glargine and liraglutide (OR, 1.16; 95% CI, 0.96 to 1.40; P value not reported).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Liraglutide 1.2 mg was associated with a non-significant increase in HbA_{1c} compared to 1.8 mg (0.10%; 95% CI, -0.03 to 0.23; P=0.13). Patients receiving liraglutide 1.2 mg were not more likely to achieve an HbA_{1c} <7.0% compared to the 1.8 mg dose (P=0.92). Incidence of hypoglycemia The incidence of minor hypoglycemia was similar between exenatide ER and TZDs. The incidence of minor hypoglycemia was higher with DPP-4 inhibitors (five vs two patients) and insulin glargine (26 vs 8%) compared to exenatide ER. The incidence of major hypoglycemia was higher with insulin glargine compared to exenatide ER (two vs one patients). Overall, there was no difference in the incidence of minor hypoglycemia between liraglutide 1.2 mg and placebo (P=0.42), and there was significantly more hypoglycemia with liraglutide 1.8 mg (OR, 1.66; 95% CI, 1.15 to 2.40; P=0.007). The incidence of minor hypoglycemia was higher with insulin glargine compared to liraglutide (29 vs 27%). Liraglutide was associated with a significantly higher rate of minor hypoglycemia compared to TZDs (P=0.048), and similar rates compared to DPP-4 inhibitors (P values not reported). Liraglutide was associated with a significantly lower incidence of hypoglycemia compared to sulfonylureas (P<0.00001). Weight loss Exenatide ER significantly decreased weight compared to TZDs (-2.3 vs 2.8 kg; P<0.00001), DPP-4 inhibitors (-2.3 vs -0.8 kg; P=0.0009), and insulin glargine (-2.6 vs 1.4 kg; P<0.00001). Patients receiving liraglutide 1.2 mg experienced an average weight loss of -0.75 kg (95% CI, -1.95 to 0.45; P=0.22). Liraglutide 1.2 mg was associated with a greater decrease in weight compared to insulin glargine (-3.40 kg; 95% CI, -4.31 to -2.49; P value not reported), TZDs (-3.40 kg; 95% CI, -4.31 to -2.49; P value not reported), DPP-4 inhibitors (-1.90 kg; 95% CI, -2.65 to -1.15; P value not reported), and sulfonylureas (-3.60 kg; 95% CI, -4.15 to -3.05; P value not reported).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Patients receiving liraglutide 1.8 mg experienced a significant weight loss compared to placebo (-1.33 kg; 95% CI, -2.38 to 0.27; P=0.0014). Liraglutide 1.8 mg was associated with a greater decrease in weight compared to TZDs (-2.30 kg; 95% CI, -2.85 to -1.75; P value not reported), DPP-4 inhibitors (-2.42 kg; 95% CI, -3.17 to -1.67; P value not reported), and (-3.80 kg; 95% CI, -4.35 to -3.25; P value not reported). Patients were more likely to experience weight gain with liraglutide 1.2 mg compared to 1.8 mg (0.48 kg; 95% CI, 0.16 to 0.80; P value not reported). Secondary: Data on mortality and morbidity were not reported for any treatment. Quality of life Exenatide ER significantly improved weight-related QOL and IWQOL total scores compared to TZDs (IWQOL treatment difference, 3.94; 95% CI, 1.28 to 6.61; P=0.0038). Both exenatide ER (IWQOL total score, 5.15; 95% CI, 3.11 to 7.19) and DPP-4 inhibitors (4.56; 95% CI, 2.56 to 6.57) resulted in significant improvements in weight-related QOL and IWQOL total scores. Treatment satisfaction was significantly greater with exenatide ER compared to DPP-4 inhibitors (treatment difference, 1.61; 95% CI, 0.07 to 3.16; P=0.0406). Exenatide ER significantly improved the self-esteem IWQOL domain and one EQ-5D dimensions compared to insulin glargine. Data for liraglutide were not reported. Safety Withdrawals due to adverse events were greater with exenatide ER compared to TZDs (6.9 vs 3.6%), DPP-4 inhibitors (6.9 vs 3.0%), and insulin glargine (4.7 vs 0.9%). More serious adverse events occurred with TZDs (6 vs 3%) compared to exenatide ER. The incidence of serious adverse events was similar between exenatide ER and DPP-4 inhibitors (3 vs 3%) and insulin glargine (5 vs 4%). Compared to placebo, withdrawals due to adverse events were between 5 and 10% with liraglutide 1.2 mg and between 4 and 15% with liraglutide 1.8 mg. Withdrawals were also higher with liraglutide compared to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				sulfonylureas (9.4 to 12.9 vs 1.3 to 3.0%). Liraglutide was associated with more gastrointestinal adverse events (nausea, vomiting, and diarrhea) compared to insulin glargine, TZDs, DPP-4 inhibitors, and sulfonylureas. BP There was no difference in the decreases in SBP and DBP between exenatide ER and TZDs. Exenatide ER significantly decreased SBP compared to DPP-4 inhibitors (treatment difference, -4 mm Hg; 95% CI, -6 to -1; P=0.0055). There was no difference in the decrease in DBP between treatments. Data comparing exenatide ER and insulin glargine were not reported. Liraglutide 1.2 mg did not significantly decrease SBP (P=0.15) compared to placebo (P=0.15) and DPP-4 inhibitors (P=0.76). Liraglutide 1.8 mg significantly decreased SBP (P=0.05) compared to placebo, but not DPP-4 inhibitors (P=0.86). Liraglutide also significantly decreased SBP compared to insulin glargine (P=0.0001) and sulfonylureas (P value not reported). No difference in SBP was observed between liraglutide and DPP-4 inhibitors. There was no difference between liraglutide in the decrease in DBP compared to placebo, insulin glargine, or sulfonylureas. DPP-4 inhibitors significantly decreased DBP compared to liraglutide 1.8 mg (P value not reported). Data comparing liraglutide and TZDs were not reported. FPG There was no difference in the decrease in FPG between exenatide ER and TZDs (-1.8 vs -1.5 mmol/L; P=0.33). Exenatide ER significantly decreased FPG compared to DPP-4 inhibitors (-0.90 mmol/L; 95% CI, -1.50 to -0.30; P=0.0038), and insulin glargine significantly decreased FPG compared to exenatide ER (-0.70 mmol/L; 95% CI, 0.14 to 1.26; P=0.01). Liraglutide significantly decreased FPG compared to placebo (1.2 mg; P<0.0001 and 1.8 mg; P<0.00001), TZDs (P≤0.006), and DPP-4 inhibitors (P<0.00001). There was no difference between liraglutide and insulin glargine or sulfonylureas in decreases in FPG (P value not reported). PPG

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				There was no difference in the decrease in PPG between exenatide ER and TZDs. Exenatide ER significantly decreased PPG at all measurements on a 6-point self-monitored glucose concentrations profile compared to DPP-4 inhibitors (P<0.05). Both exenatide ER and insulin glargine decreased PPG at all eight time points, with significant difference in favor of exenatide ER after dinner (P=0.004) and insulin glargine at 03000 hour (P=0.022) and before breakfast (P<0.0001). Liraglutide significantly decreased PPG compared to placebo (P value not reported), TZDs (P<0.05), and sulfonylureas (liraglutide 1.8 mg; P<0.0001). There was no difference between liraglutide and insulin glargine in decreases in PPG (P value not reported). It was reported that PPG recorded in trials comparing liraglutide and DPP-4 inhibitors was highly variable. Lipid profile TZDs significantly decreased TG compared to exenatide ER. Exenatide ER decreased TC and LDL-C, while TZDs and DPP-4 inhibitors increased these measures. All treatments increased HDL-C. Data comparing exenatide ER and insulin glargine were not reported. Compared to placebo, liraglutide 1.2 decreased TG (P<0.05) and LDL-C (P<0.05), and no difference was observed with liraglutide 1.8 mg. Data comparing liraglutide to insulin glargine, TZDs, DPP-4 inhibitors, and sulfonylureas were not reported. β cell function Data for exenatide ER are not reported. Liraglutide significantly improved HOMA-B compared to placebo (P value not reported), TZDs (P<0.05), and DPP-4 inhibitors (P value not reported); and proinsulin:insulin ratio compared to placebo (P value not reported), insulin glargine (P=0.0019), and TZDs (P≤0.02). There was no difference between liraglutide and sulfonylureas in the improvements in HOMA-B and proinsulin:insulin ratio.
Gangji et al.[181] (2007)	MA (21 trials)	N=not reported	Primary: Hypoglycemia, glycemic control,	Primary: Glyburide was associated with a 52% higher risk of experiencing at least one episode of hypoglycemia compared to other secretagogues (RR, 1.52;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Glyburide vs sulfonylureas, meglitinides, insulin	Patients with type 2 diabetes	Duration varied	cardiovascular events, body weight, death Secondary: Not reported	95% CI, 1.21 to 1.92) and with an 83% higher risk compared to other sulfonylureas (RR, 1.83; 95% CI, 1.35 to 2.49). Glyburide was not associated with a higher risk of cardiovascular events (RR, 0.84; 95% CI, 0.56 to 1.26), death (RR, 0.87; 95% CI, 0.70 to 1.07), or end-of-trial weight (95% CI, -0.4 to 3.80) compared to other secretagogues. Secondary: Not reported
Lincoff et al.[182] (2007) Pioglitazone monotherapy vs metformin (1 trial), placebo (4 trials), sulfonylureas (6 trials) or rosiglitazone (1 trial) or pioglitazone combination therapy (7 trials) with insulin, metformin, or sulfonylureas vs active comparator or placebo	DB, MA, RCT with placebo or active comparator Adult patients with type 2 diabetes and inadequate glycemic control	N=16,390 (19 trials) 4 months to 3.5 years	Primary: Composite of death from any cause, MI or stroke Secondary: Incidence of serious heart failure	Primary: Death, MI, or stroke occurred in 375 of 8,554 patients (4.4%) receiving pioglitazone and 450 of 7,836 patients (5.7%) receiving control therapy (HR, 0.82; 95% CI, 0.72 to 0.94; P=0.005). Individual components of the primary end point were reduced with pioglitazone treatment with varying degrees of statistical significance (death: HR, 0.92; P=0.38, MI: HR, 0.81; P=0.08, death and MI: HR, 0.85; P=0.04, and stroke: HR, 0.80; P=0.09). Progressive separation of time-to-event curves became apparent after approximately one year of therapy. Secondary: Serious heart failure was reported in 2.3% of the pioglitazone-treated patients and 1.8% of the control treated patients (HR, 1.41; 95% CI, 1.14 to 1.76; P=0.002). The composite of serious heart failure and death was not significantly increased among patients receiving pioglitazone (HR, 1.11; 95% CI, 0.96 to 1.29; P=0.17).
Karter et al.[183] (2005) Patients initiated pioglitazone (15.2%), sulfonylureas (25.3%), metformin	Cohort study of all patients in the Kaiser Permanente Medical Care Program with type 2 diabetes (Kaiser Permanente	N=23,440 10.2 months (mean)	Primary: Time-to-incident admission to hospital for congestive heart failure	Primary: Three hundred and twenty admissions for congestive heart failure were observed during the follow-up (mean, 10.2 months) after drug initiation. Relative to patients initiating sulfonylureas, there were no significant increases in the incidence of hospitalization for congestive heart failure in those initiating pioglitazone (HR, 1.28; 95% CI, 0.85 to 1.92). There was a significantly higher incidence among those initiating insulin (HR, 1.56;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(50.9%), and insulin (8.6%) alone, or in addition to pre-existing therapies	Northern California Diabetes Registry) who initiated any new diabetes pharmacotherapy between October 1999 and November 2001		Secondary: Not reported	95% CI, 1.00 to 2.45) and lower incidence among those initiating metformin (HR, 0.70; 95% CI, 0.49 to 0.99). Secondary: Not reported
Nissen et al.[184] (2007) Rosiglitazone monotherapy or combination therapy vs placebo or active comparators (including gliclazide*, glimepiride, glipizide, glyburide, insulin, and metformin)	MA of RCTs of more than 24 weeks that had outcome data for MI and death from cardiovascular causes (included ADOPT and DREAM trials) Mean age of participants was 56 years, mean baseline HbA_{1c} 8.2%	42 trials n=15,560 for rosiglitazone; n=12,283 for comparator 24 to 208 weeks	Primary: MI and death from cardiovascular causes Secondary: Not reported	Primary: Rosiglitazone was associated with a significant increase in the risk of MI compared to the control agent (OR, 1.43; 95% CI, 1.03 to 1.98; P=0.03). Compared to the control agent, rosiglitazone was associated with a trend toward increased cardiovascular death (OR, 1.64; 95% CI, 0.98 to 2.74; P=0.06). Although not a prespecified end point, the OR for death from any cause with rosiglitazone was 1.18 (95% CI, 0.89 to 1.55; P=0.24). Secondary: Not reported
GRADE Study Research Group[185] (2022) Insulin glargine U-100 administered daily at an initial dose of up to 20 U and adjusted according to glucose levels	MC, PG, RCT Participants with type 2 diabetes of less than 10 years' duration who were receiving metformin and had glycated hemoglobin levels of 6.8 to 8.5%	N=5,047 5 years	Primary: Cumulative incidence of a glycated hemoglobin level of 7.0% or higher Secondary: Cumulative incidence of a glycated	Primary: Over the mean 5-year follow-up, 71% of the cohort had a primary metabolic outcome event, with the highest frequency in the sitagliptin group (77%), intermediate frequency in the glimepiride group (72%), and the lowest frequency in the liraglutide (68%) and glargine (67%) groups. The between-group differences in the Kaplan–Meier estimates of the cumulative incidence of a primary-outcome event were significant (P<0.001 by the log-rank test). Secondary: The differences among the groups with respect to a glycated hemoglobin level greater than 7.5% (the secondary outcome) paralleled those of the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs glimepiride, increased from 1 to 2 mg to a maximum of 8 mg per day, administered in divided doses and adjusted according to glucose levels vs liraglutide initiated at a dose of 0.6 mg, with escalation to a maximum dose of 1.8 mg daily, depending on gastrointestinal side effects vs sitagliptin at a dose of 100 mg, with the dose adjusted according to kidney function Metformin was supplied to all the participants			hemoglobin level of 7.5% or higher	primary outcome. A secondary-outcome event occurred in 55% of the participants in the sitagliptin group over a mean follow-up of 5 years, followed by glimepiride (in 50%), liraglutide (in 46%), and glargine (in 39%).
GRADE Study Research Group[186] (2022)	MC, PG, RCT Participants with type 2 diabetes of less than 10 years'	N=5,047 5 years	Primary: Hypertension and dyslipidemia, confirmed moderately or	Primary: There were no material differences among the interventions with respect to the development of hypertension or dyslipidemia or with respect to microvascular outcomes; the mean overall rate (i.e., events per 100 participant-years) of moderately increased albuminuria levels was 2.6, of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Insulin glargine U-100 administered daily at an initial dose of up to 20 U and adjusted according to glucose levels vs glimepiride, increased from 1 to 2 mg to a maximum of 8 mg per day, administered in divided doses and adjusted according to glucose levels vs liraglutide initiated at a dose of 0.6 mg, with escalation to a maximum dose of 1.8 mg daily, depending on gastrointestinal side effects vs sitagliptin at a dose of 100 mg, with the dose adjusted according to kidney function	duration who were receiving metformin and had glycated hemoglobin levels of 6.8 to 8.5%		severely increased albuminuria or an estimated glomerular filtration rate of less than 60 ml/min/1.73 m^2, diabetic peripheral neuropathy, cardiovascular events (major adverse cardiovascular events [MACE], hospitalization for heart failure, or an aggregate outcome of any cardiovascular event), and death Secondary: Not reported	severely increased albuminuria levels 1.1, of renal impairment 2.9, and of diabetic peripheral neuropathy 16.7. The treatment groups did not differ with respect to MACE (overall rate, 1.0), hospitalization for heart failure (0.4), death from cardiovascular causes (0.3), or all deaths (0.6). There were small differences with respect to rates of any cardiovascular disease, with 1.9, 1.9, 1.4, and 2.0 in the glargine, glimepiride, liraglutide, and sitagliptin groups, respectively. When one treatment was compared with the combined results of the other three treatments, the hazard ratios for any cardiovascular disease were 1.1 (95% confidence interval [CI], 0.9 to 1.3) in the glargine group, 1.1 (95% CI, 0.9 to 1.4) in the glimepiride group, 0.7 (95% CI, 0.6 to 0.9) in the liraglutide group, and 1.2 (95% CI, 1.0 to 1.5) in the sitagliptin group. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Metformin was supplied to all the participants				
Kheirbek et al.[187] (2013) Hypoglycemic medications (metformin, glyburide, glipizide, rosiglitazone, acarbose, chlorpropamide, glimepiride, pioglitazone, tolazamide, repaglinide, troglitazone, insulin, and DPP-4 inhibitors) *Defined as any use of the medication independent of dose or days of use	OS, RETRO Veterans with diabetes cared for at a Veterans Administration Capital area medical center	N=17,773 Variable duration	Primary: All-cause mortality Secondary: Not reported	Primary: After adjustments were made for severity of illness and patient demographics, the remaining variance in mortality was explained by exposure to five medications, listed in order of impact on risk-adjusted mortality: glipizide (OR=1.566), glyburide (OR=1.804), rosiglitazone (OR=1.805), insulin (OR=2.382), and chlorpropamide (OR=3.026). None of the other medications (metformin, acarbose, glimepiride, pioglitazone, tolazamide, repaglinide, troglitazone, and DPP-4 inhibitors) were associated with excess mortality beyond what could be expected from the patients' severity of illness or demographic characteristics. Insulin, glyburide, glipizide, and rosiglitazone continued to be associated with statistically significant increased mortality after controlling for possible drug interactions. Secondary: Not reported
Mearns et al.[188] (2015) Hypoglycemic medications (Alpha-glucosidase inhibitors, DPP-4 inhibitors, colesevelam, meglitinides, GLP-1 analogs, long-acting, once-daily basal insulin, SGLT2	Network MA (62 RCTs) Patients with inadequately controlled type 2 diabetes on metformin alone	N=32,185 3 to 12 months	Primary: Changes in HbA_{1c}, body weight, and SBP; risk of developing hypoglycemia and urinary and genital tract infection Secondary: Not reported	Primary: All agents significantly reduced HbA_{1c} vs placebo; although, not to the same extent (range, 0.43% for miglitol to 1.29% for glibenclamide). Glargine, sulfonylureas, and nateglinide were associated with increased hypoglycemia risk vs placebo. SGLT2 inhibitors, GLP-1 analogs, miglitol, and empagliflozin/linagliptin significantly reduced body weight (range, 1.15 to 2.26 kg) whereas sulfonylureas, TZDs, glargine, and alogliptin/pioglitazone caused weight gain (range, 1.19 to 2.44 kg). SGLT2 inhibitors, empagliflozin/linagliptin, liraglutide, and sitagliptin decreased SBP (range, 1.88 to 5.43 mmHg). No therapy increased UTI risk vs placebo; however, SGLT2 inhibitors were associated with an increased risk of genital tract infection (RR range, 2.16 to 8.03).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
inhibitors, sulfonylureas, TZDs, and combinations of the above agents)				Secondary: Not reported
Long-Term Outcomes Trials				
DCCT Research Group[189] (1993) Insulin administered QD or BID vs insulin administered TID or via external pump	RCT Insulin-dependent patients with type 1 diabetes with mild retinopathy (secondary prevention cohort) or without retinopathy (primary prevention cohort), baseline HbA_{1c} 9.1% in both treatment groups	N=1,441 6.5 years (mean)	Primary: Effect on retinopathy development (primary prevention cohort) or progression (secondary prevention cohort) Secondary: Effect on renal function (micro-albuminuria and albuminuria), neuropathy development, and macrovascular disease	Primary: Intensive insulin therapy significantly reduced the risk of retinopathy onset (primary prevention cohort) by 76% compared to standard therapy (P<0.001). Intensive insulin therapy significantly reduced the risk of retinopathy progression (secondary prevention cohort) by 54% compared to standard therapy (P<0.001). Secondary: Intensive insulin therapy significantly reduced the risk of microalbuminuria by 34% in the primary prevention cohort (P=0.04) and by 43% in the secondary prevention cohort (P=0.001) compared to standard therapy. Intensive insulin therapy significantly reduced the risk of albuminuria by 56% in the secondary prevention cohort (P=0.01) compared to standard therapy. Intensive insulin therapy significantly reduced the risk of neuropathy appearance by 69% in the primary prevention cohort (P=0.006) and by 57% in the secondary prevention cohort (P<0.001) compared to standard therapy. Nonsignificant reduction of risk of macrovascular disease was observed with intensive insulin therapy (44%; 95% CI, -10 to 68) compared to standard therapy. Intensive insulin therapy had a threefold higher incidence of hypoglycemic events (P<0.001) compared to standard therapy.
UKPDS Group[190] (1998)	RCT	N=3,867	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Intensive therapy with sulfonylurea (chlorpropamide, glyburide, or glipizide) or insulin vs dietary therapy	Patients newly diagnosed with type 2 diabetes, baseline HbA_{1c} 7.05% in the dietary treatment group and 7.09% in the intensive therapy group	10 years	Time to the first occurrence of any diabetes-related endpoint, time to diabetes-related death, all-cause mortality Secondary: MI, sudden death, stroke, amputation or death due to peripheral vascular disease, microvascular complications, retinopathy, vitreous hemorrhage, and/or fatal or nonfatal renal failure	There was a 12% risk reduction (95% CI, 1 to 21; P=0.029) for any diabetes-related end point, 10% risk reduction (95% CI, -11 to 27; P=0.34) for any diabetes-related death, and a 6% risk reduction (95% CI, -10 to 20; P=0.44) for all-cause mortality when intensive therapy (sulfonylurea or insulin) was compared to conventional therapy with diet. Patients receiving an intensive treatment (sulfonylurea or insulin) had a 25% risk reduction (95% CI, 7 to 40; P=0.0099) in microvascular end points compared with conventional therapy with diet. Most of this reduction was due to fewer cases of retinal photocoagulation. There were no differences between the intensive and conventional treatment groups or between the three intensive treatment groups in the number of patients who had a silent MI, cardiomegaly, evidence of peripheral vascular disease, or absent peripheral pulses. Secondary: There was no significant difference between chlorpropamide, insulin, and glibenclamide in macrovascular events. There was no significant difference between the three intensive treatments in microvascular end points or in the risk reduction for retinal photocoagulation.

*Agent is not available in the United States.
†Glibenclamide is a synonym for glyburide.
Drug regimen abbreviations: BID=twice daily, ER=extended-release, QD=once daily, SC=subcutaneous, TID=three times daily, QID=four times daily
Study abbreviations: AC=active-comparator, CS=comparator study, ES=extension study, MA=meta-analysis, MC=multicenter, MN=multinational, NI=noninferiority, OL=open-label, OS=observational, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized-controlled trial, RETRO=retrospective, SR=systematic review, XO=cross-over
Miscellaneous abbreviations: AUC=area under the curve, BMI=body mass index, BP=blood pressure, CI=confidence interval, CRP=C-reactive protein, CSII=continuous subcutaneous insulin infusion, DBP=diastolic blood pressure, DPP-4 inhibitor=dipeptidyl peptidase-4 inhibitor, DTSQ=Diabetes Treatment Satisfaction Questionnaire, EQ-5D=EuroQol Quality of Life, FPG=fasting plasma glucose, GLP-1=glucagon-like peptide 1, HbA_{1c}=glycosylated hemoglobin, HDL-C=high density lipoprotein cholesterol, HOMA-B=homeostasis model assessment-beta, HOMA-IR=homeostasis model assessment-insulin resistance, HR=hazard ratio, ITT=intention-to-treat, IWQOL=Impact of Weight on Quality of life Questionnaire, LDL-C=low density lipoprotein cholesterol, MI=myocardial infarction, NPH=human insulin isophane (neutral protamine Hagedorn), OR=odds ratio, PP=per protocol, PPG=post-prandial glucose, REG=regular human insulin, RR=relative risk, SBP=systolic blood pressure, SDS=standard deviation score, SEM=standard error of mean, TC=total cholesterol, TG=triglycerides, TZD=thiazolidinedione, WMD=weighted mean difference

Additional Evidence

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

Stable Therapy
Yamada et al. evaluated the effects of switching patients to biphasic insulin lispro. Patients with type 2 diabetes who were receiving biphasic human insulin (70/30 or 50/50 mix) were randomized to continue their regimen or switch to biphasic insulin lispro (50/50 mix). There was a significant improvement in HbA_{1c} following the transition to premixed insulin lispro. This change in therapy did not affect quality of life; however, patients reported an improvement in convenience with biphasic insulin lispro.[191] Sharma et al. evaluated the effects of switching patients to a rapid-acting insulin regimen. Patients with poorly controlled type 2 diabetes mellitus on biphasic human insulin were switched to biphasic insulin aspart 30. There was a significant improvement in HbA_{1c}, fasting plasma glucose and postprandial glucose, as well as a reduction in hypoglycemic episodes following the transition to biphasic insulin aspart 30.[192] Yokoyama et al. evaluated the effects of switching patients from basal NPH insulin (administered at bedtime) to insulin glargine (administered in the morning) or continuing their existing NPH insulin therapy. Patients continued on their existing prandial insulin regimen. There was a significant reduction in HbA_{1c} in patients who used insulin glargine compared to patients who continued NPH insulin. The risk of hypoglycemia did not significantly increase with the switch to morning insulin glargine.[193] Kanazawa et al. evaluated the effects of switching patients with type 1 or type 2 diabetes mellitus to insulin glargine from NPH insulin.[194] After three months, HbA_{1c} levels improved significantly after switching to insulin glargine. The frequency of mild-to-moderate hypoglycemia was lower in the insulin glargine group.[194] Dornhorst et al. evaluated the effects of switching patients with type 2 diabetes who were on NPH insulin or insulin glargine to insulin detemir.[195] All patients continued their current oral antidiabetic medications. Glycemic control improved significantly in patients switched to insulin detemir, regardless of their previous therapy with NPH insulin or insulin glargine. The incidence of total and nocturnal hypoglycemic episodes were reduced in patients who were switch from NPH insulin ($P<0.0001$) or insulin glargine ($P<0.01$ and $P<0.05$, respectively) to insulin detemir. The incidence of major hypoglycemic events did not differ significantly from baseline. Mean body weight was also significantly reduced in patients who were switched from NPH insulin ($P<0.01$) or insulin glargine ($P<0.05$) to insulin detemir.[195]

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 11. Relative Cost of the Insulins

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Rapid-Acting Insulins				
Insulin aspart	injection	Fiasp®, NovoLog®*	$$$$$	$$$$$
Insulin glulisine	injection	Apidra®, Apidra Solostar®	$$$$$	N/A
Insulin lispro	injection	Admelog®, Humalog®*, Lyumjev®	$$$$$	$$$$
Short-Acting Insulins				
Insulin regular, human	inhalation, injection	Afrezza®, Humulin®‡ R, Myxredlin®, Novolin®‡ R	$$$$$	N/A
Intermediate-Acting Insulins				
NPH, human insulin isophane	injection	Humulin®‡ N, Novolin®‡ N	$$$$$	N/A
Long-Acting Insulins				
Insulin degludec	injection	Tresiba®*	$$$$$	$$$$$
Insulin detemir	injection	Levemir®	$$$$$	N/A
Insulin glargine, human recombinant analog	injection	Basaglar®, Lantus®*, Lantus Solostar®*, Rezvoglar®^, Semglee®^*, Toujeo®	$$$$$	$$$$$
Combination Insulins (Intermediate-Acting and Rapid-Acting)				
Insulin aspart protamine and insulin aspart	injection	NovoLog® Mix 70/30*	$$$$$	$$$$$
Insulin lispro protamine and insulin lispro	injection	Humalog® Mix 50/50, Humalog® Mix 75/25*	$$$$$	$$$$$
Combination Insulins (Intermediate-Acting and Short-Acting)				
NPH, human insulin isophane and insulin regular, human	injection	Humulin®‡ 70/30, Novolin®‡ 70/30	$$$$$	N/A
Combination Insulins with Non-Insulins				
Insulin degludec and Liraglutide	injection	Xultophy®	$$$$$	N/A
Insulin glargine and Lixisenatide	injection	Soliqua®	$$$$$	N/A

*Authorized generic/unbranded product is available.
‡Product is available over-the-counter.
^Interchangeable biosimilar insulin product.
N/A=Not available

X. Conclusions

The insulins have been shown to improve glycemic control in adults and children with diabetes mellitus. There are two types of insulin preparations currently available: human insulin and insulin analogs. They are categorized based on their duration of action, which includes rapid-acting, short-acting, intermediate-acting, and long-acting insulins.

According to current clinical guidelines regarding the management of type 1 diabetes, initiation of individualized, intensive insulin therapy at the time of diagnosis is recommended. Furthermore, overall approaches for management include the use of multiple dose injections or a subcutaneous insulin infusion, and matching of pre-prandial insulin to carbohydrate intake, pre-meal blood glucose, and anticipated activity. According to the American Diabetes Association, insulin analogs should be utilized in most patients. In addition, use of a continuous subcutaneous insulin infusion is indicated in certain clinical settings, particularly when glycemic control is difficult to achieve, during pregnancy, or when the patient does not demonstrate a willingness to comply with a multiple injection regimen. As mentioned previously, insulin regimens should be tailored to the specific clinical circumstances in individual patients, and patients should have access to the types (preparation and species) of insulin therapy they find allow them optimal well-being. In general, pre-prandial rapid-acting insulin analogs

should be administered 20 to 30 minutes prior to a meal. Regular insulin might be considered, instead of rapid-acting, to obtain better control of post-prandial and premeal glucose levels in patients with gastroparesis. Some patients treated with basal, or long-acting, insulin may require twice-daily dosing to achieve greater control. Basal insulin should be provided by the use of isophane (NPH) or long-acting insulin analogs. Use of long-acting analogs should occur when nocturnal hypoglycemia is a problem with NPH, when morning hypoglycemia on NPH results in difficult daytime blood glucose control, or when rapid-acting insulin analogs are used for mealtime blood glucose control. Use of biphasic rapid-acting analog mixes (i.e., combination insulins) may be advantageous in patients prone to hypoglycemia at night. In general, no one specific insulin product among the various classifications is recommended or preferred over another. Again, insulin therapy must be individualized as the products within the different classifications play specific roles in achieving adequate glycemic control in patients with type 1 diabetes. Insulin therapy may also be appropriate in the management of type 2 diabetes; however, traditionally oral antidiabetic agents are utilized. Of note, many patients with type 2 diabetes will ultimately require insulin therapy, alone or in combination with other agents, to maintain glucose control. Insulin is recognized as a potential option to be added to current oral antidiabetic agent regimens in patients not achieving glycemic goals. It may also be appropriate to initiate insulin therapy at the time of diagnosis in certain clinical settings, particularly in patients with a high baseline glycosylated hemoglobin (HbA_{1c}) (≥9.0%), or in patients presenting with significant hyperglycemic symptoms and/or has dramatically elevated plasma glucose concentrations or HbA_{1c}. Furthermore, such therapy is mandatory when catabolic features are exhibited or if ketonuria is demonstrated.[6-11]

Numerous clinical trials have established the efficacy/safety of insulin therapy as monotherapy, as well as in combination with other antidiabetic agents.[12-190] For the treatment of type 1 diabetes mellitus, several studies have compared the efficacy and safety of prandial insulin regimens, while maintaining stable basal insulin regimens. The use of rapid-acting insulin analogs has resulted in a similar, or greater, reduction in HbA_{1c} compared to regular insulin. The rate of hypoglycemia was found to be either similar, or lower, with the rapid-acting insulin analogs compared to regular insulin.[12-17,21,23] Head-to-head trials of rapid-acting analogs suggest comparable effectiveness in terms of decreasing HbA_{1c}, achieving similar self-monitored glucose profiles, rates of hyperglycemia, and achieving glycemic goals in type 1 diabetics.[18-20] Other trials have evaluated the efficacy and safety of various basal insulin regimens, while maintaining stable prandial insulin regimens. The use of long-acting insulin analogs has resulted in a similar, or greater, reduction in HbA_{1c} compared to NPH insulin. The rate of hypoglycemia was found to be either similar, or lower, with the long-acting insulin analogs compared to NPH insulin.[53,55-66,68,71,74,76,78] Two trials directly compared insulin detemir and insulin glargine as basal therapy, while maintaining stable therapy with insulin aspart. There was a similar reduction in HbA_{1c} reported in both studies and the overall rates of hypoglycemia did not differ among the treatment groups. However, nocturnal hypoglycemia was significantly lower with insulin detemir (reported in only one study).[53,54] Two studies compared insulin aspart and insulin lispro administered through a continuous subcutaneous insulin infusion. There was no difference in HbA_{1c} at the end of the 16-week trials and the rates of hypoglycemia were similar among the treatment groups.[27,28]

For the treatment of type 2 diabetes mellitus, several studies have compared the efficacy and safety of insulin therapy alone, or in combination with oral antidiabetic drugs. The use of rapid-acting insulin analogs has resulted in a similar, or greater, reduction in HbA_{1c} compared to regular insulin. There was no difference in hypoglycemic episodes reported among the treatment groups.[33,36,37,44,45] The majority of the studies comparing long-acting insulin analogs to NPH insulin have demonstrated similar reductions in HbA_{1c}.[95-97,99,108-110,113-115] However, the long-acting insulin analogs were associated with less hypoglycemia than NPH insulin.[96,97,99,108-115] Two studies directly compared insulin detemir with insulin glargine and showed no difference in HbA_{1c} after 52 weeks of treatment.[89,91] A third study reported a greater reduction in HbA_{1c} with insulin glargine than insulin detemir after 26 weeks of therapy (-1.28% vs -1.08%, respectively; P=0.035); however, the difference between the two treatments (0.207%) was not clinically meaningful.[90] An additional study also found a greater reduction in HbA_{1c} with insulin glargine than insulin detemir, but did not establish significance.[93] There was no difference in the risk of overall hypoglycemia in any of the studies.[89-91] In a study comparing biphasic insulin lispro (75/25 mix) and biphasic insulin aspart (70/30 mix), there was no significant difference in HbA_{1c} or overall hypoglycemia reported among the treatment groups.[35]

In summary, the insulin analogs have been shown to be at least as effective, or more effective, than human insulin. In several studies, there was a lower risk of hypoglycemia with the insulin analogs compared to human insulin. There is insufficient evidence to conclude that one rapid-acting insulin analog is safer or more efficacious than

another. There is also insufficient evidence to conclude that one long-acting insulin analog is safer or more efficacious than another.

Therefore, all brand products within the class reviewed, with the exception of rapid-acting and long-acting insulin analogs, are comparable to each other and to the generics and over-the-counter products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use. Rapid-acting insulin analogs offer significant clinical advantages in general use over short-acting human insulin, but are comparable to each other. Long-acting insulin analogs offer significant clinical advantages in general use over intermediate-acting human insulin, but are comparable to each other.

XI. Recommendations

No brand insulin, with the exception of rapid-acting and long-acting insulin analogs, 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.

Alabama Medicaid should work with manufacturers on cost proposals so that at least one rapid-acting insulin analog is selected as a preferred agent.

Alabama Medicaid should work with manufacturers on cost proposals so that at least one long-acting insulin analog is selected as a preferred agent.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Meglitinides
AHFS Class 682016
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I. Overview

Diabetes mellitus is a chronic condition which results in hyperglycemia. It is differentiated into four main classes: 1) type 1 diabetes; 2) type 2 diabetes; 3) gestational diabetes; and 4) other types (drug- or chemical-induced, genetic defects in β-cell function or insulin action, and diseases of the exocrine pancreas). Type 2 diabetes is the most prevalent form of the disease in the United States. Inadequate glycemic control may lead to both acute and long-term complications, including microvascular and macrovascular events. There are a variety of oral and injectable antidiabetic agents currently available to treat diabetes. The antidiabetic agents are categorized into 12 different American Hospital Formulary Service (AHFS) classes, which differ with regards to their mechanism of action, efficacy, safety profiles, tolerability, and ease of use.

The meglitinides are approved for use as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.[1] They are short-acting agents that decrease blood glucose concentrations by stimulating insulin secretion. Meglitinides interact with the ATP-dependent potassium channel on pancreatic beta cells.[1-3] Blockade of the potassium channel leads to depolarization of the beta cell, which opens the calcium channel. The increased calcium influx induces insulin secretion. Insulin release is glucose dependent and diminishes at low glucose concentrations. Both nateglinide and repaglinide are highly tissue selective with low affinity for heart and skeletal muscle.[1-3]

The meglitinides 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 November 2021.

Table 1. Meglitinides Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Single Entity Agents			
Nateglinide	tablet	N/A	nateglinide
Repaglinide	tablet	N/A	repaglinide

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

II. Evidence-Based Medicine and Current Treatment Guidelines

Current clinical guidelines are summarized in Table 2. Please note that guidelines addressing the treatment of type 2 diabetes are presented globally, addressing the role of various medication classes.

Table 2. Treatment Guidelines Using the Meglitinides

Clinical Guideline	Recommendation(s)
American Diabetes Association: **Standards of Care in Diabetes (2023)**[4]	Current criteria for the diagnosis of diabetes • The following are the criteria for a diagnosis of diabetes: glycosylated hemoglobin (HbA_{1c}) ≥6.5%, or a fasting plasma glucose (FPG) ≥126 mg/dL, or a two-hour plasma glucose ≥200 mg/dL during an oral glucose tolerance test or patients with classic symptoms of hyperglycemia, or classic symptoms of hyperglycemia or hyperglycemic crisis (random plasma glucose ≥200 mg/dL). Prevention or delay of type 2 diabetes • Refer adults with overweight/obesity at high risk of type 2 diabetes, as typified by the Diabetes Prevention Program (DPP), to an intensive lifestyle behavior change program to achieve and maintain a weight reduction of at least 7% of

Clinical Guideline	Recommendation(s)
	initial body weight through healthy reduced-calorie diet and ≥150 minutes/week of moderate-intensity physical activity. • A variety of eating patterns can be considered to prevent diabetes in individuals with prediabetes. • Metformin therapy for prevention of type 2 diabetes should be considered in adults at high risk of type 2 diabetes, as typified by the DPP, especially those aged 25 to 59 years with BMI ≥35 kg/m^2, higher FPG) (e.g., ≥110 mg/dL), and higher A1C (e.g., ≥6.0%), and in individuals with prior gestational diabetes mellitus (GDM). • Long-term use of metformin may be associated with biochemical vitamin B12 deficiency; consider periodic measurement of vitamin B12 levels in metformin-treated individuals, especially in those with anemia or peripheral neuropathy. Glycemic goals in adults • An A1C goal for many nonpregnant adults of <7% (53 mmol/mol) without significant hypoglycemia is appropriate. • If using ambulatory glucose profile (AGP)/glucose management indicator (GMI) to assess glycemia, a parallel goal for many nonpregnant adults is time in range (TIR) of >70% with time below range (TBR) <4% and time <54 mg/dL <1%. For those with frailty or at high risk of hypoglycemia, a target of >50% TIR with <1% TBR is recommended. • On the basis of health care provider judgment and patient preference, achievement of lower A1C levels than the goal of 7% may be acceptable and even beneficial if it can be achieved safely without significant hypoglycemia or other adverse effects of treatment. • Less stringent A1C goals (such as <8% [64 mmol/mol]) may be appropriate for patients with limited life expectancy or where the harms of treatment are greater than the benefits. HCPs should consider deintensification of therapy if appropriate to reduce the risk of hypoglycemia in patients with inappropriate stringent A1C targets. Pharmacologic therapy for type 1 diabetes • Most individuals with type 1 diabetes should be treated with multiple dose insulin injections (three to four injections per day of basal and pre-prandial insulin) or continuous subcutaneous (SC) insulin infusion therapy. • Most patients should use rapid-acting insulin analogs to reduce hypoglycemia risk. • Patients with type 1 diabetes should receive education on how to match prandial insulin doses to carbohydrate intake, premeal blood glucose, and anticipated physical activity. Pharmacologic therapy for type 2 diabetes • Healthy lifestyle behaviors, diabetes self-management education and support, avoidance of clinical inertia, and social determinants of health should be considered in the glucose-lowering management of type 2 diabetes. Pharmacologic therapy should be guided by person-centered treatment factors, including comorbidities and treatment goals. • In adults with type 2 diabetes and established/high risk of atherosclerotic cardiovascular disease, heart failure, and/or chronic kidney disease, the treatment regimen should include agents that reduce cardiorenal risk. • Pharmacologic approaches that provide adequate efficacy to achieve and maintain treatment goals should be considered, such as metformin or other agents, including combination therapy.

Clinical Guideline	Recommendation(s)
	• Weight management is an impactful component of glucose-lowering management in type 2 diabetes. The glucose-lowering treatment regimen should consider approaches that support weight management goals. • Metformin should be continued upon initiation of insulin therapy (unless contraindicated or not tolerated) for ongoing glycemic and metabolic benefits. • Early combination therapy can be considered in some individuals at treatment initiation to extend the time to treatment failure. • The early introduction of insulin should be considered if there is evidence of ongoing catabolism (weight loss), if symptoms of hyperglycemia are present, or when A1C levels (>10% [86 mmol/mol]) or blood glucose levels (≥300 mg/dL [16.7 mmol/L]) are very high. • A person-centered approach should guide the choice of pharmacologic agents. Consider the effects on cardiovascular and renal comorbidities, efficacy, hypoglycemia risk, impact on weight, cost and access, risk for side effects, and individual preferences. • Among individuals with type 2 diabetes who have established atherosclerotic cardiovascular disease or indicators of high cardiovascular risk, established kidney disease, or heart failure, a sodium–glucose cotransporter 2 inhibitor and/or glucagon-like peptide 1 receptor agonist with demonstrated cardiovascular disease benefit is recommended as part of the glucose-lowering regimen and comprehensive cardiovascular risk reduction, independent of A1C and in consideration of person-specific factors. • In adults with type 2 diabetes, a glucagon-like peptide 1 receptor agonist is preferred to insulin when possible. • If insulin is used, combination therapy with a glucagon-like peptide 1 receptor agonist is recommended for greater efficacy, durability of treatment effect, and weight and hypoglycemia benefit. • Recommendation for treatment intensification for individuals not meeting treatment goals should not be delayed. • Medication regimen and medication-taking behavior should be reevaluated at regular intervals (every three to six months) and adjusted as needed to incorporate specific factors that impact choice of treatment. • Clinicians should be aware of the potential for over-basalization with insulin therapy. Clinical signals that may prompt evaluation of over-basalization include basal dose more than ~0.5 units/kg/day, high bedtime–morning or post-preprandial glucose differential, hypoglycemia (aware or unaware), and high glycemic variability. Indication of over-basalization should prompt reevaluation to further individualize therapy.
American Diabetes Association/ European Association for the Study of Diabetes: **Management of Hyperglycemia in Type 2 Diabetes. A consensus report by the American Diabetes Association and the European Association for the Study of Diabetes (2022)**[5]	Consensus recommendations • All people with type 2 diabetes should be offered access to ongoing diabetes self-management education and support programs. • Providers and health care systems should prioritize the delivery of person-centered care. • Optimizing medication adherence should be specifically considered when selecting glucose-lowering medications. • Medical nutrition therapy focused on identifying healthy dietary habits that are feasible and sustainable is recommended in support of reaching metabolic and weight goals. • Physical activity improves glycemic control and should be an essential component of type 2 diabetes management. • Adults with type 2 diabetes should engage in physical activity regularly (>150 min/week of moderate- to vigorous-intensity aerobic activity) and be encouraged to reduce sedentary time and break up sitting time with frequent activity breaks.

Clinical Guideline	Recommendation(s)
	• Aerobic activity should be supplemented with two to three resistance, flexibility, and/or balance training sessions/week. Balance training sessions are particularly encouraged for older individuals or those with limited mobility/poor physical function. • Metabolic surgery should be considered as a treatment option in adults with type 2 diabetes who are appropriate surgical candidates with a BMI ≥40.0 kg/m^2 (BMI ≥37.5 kg/m^2 in people of Asian ancestry) or a BMI of 35.0 to 39.9 kg/m^2 (32.5 to 37.4 kg/m^2 in people of Asian ancestry) who do not achieve durable weight loss and improvement in comorbidities (including hyperglycemia) with nonsurgical methods. • In people with established CVD, a GLP-1 RA with proven benefit should be used to reduce MACE, or an SGLT2i with proven benefit should be used to reduce MACE and HF and improve kidney outcomes. • In people with CKD and an eGFR ≥20 ml/min per 1.73 m^2 and a urinary albumin/creatinine ratio >3.0 mg/mmol (>30 mg/g), an SGLT2i with proven benefit should be initiated to reduce MACE and HF and improve kidney outcomes. Indications and eGFR thresholds may vary by region. If such treatment is not tolerated or is contraindicated, a GLP-1 RA with proven cardiovascular outcome benefit could be considered to reduce MACE and should be continued until kidney replacement therapy is indicated. • In people with HF, SGLT2i should be used because they improve HF and kidney outcomes. • In individuals without established CVD but with multiple cardiovascular risk factors (such as age ≥55 years, obesity, hypertension, smoking, dyslipidemia, or albuminuria), a GLP-1 RA with proven benefit could be used to reduce MACE, or an SGLT2i with proven benefit could be used to reduce MACE and HF and improve kidney outcomes. • In people with HF, CKD, established CVD, or multiple risk factors for CVD, the decision to use a GLP-1 RA or SGLT2i with proven benefit should be independent of background use of metformin. • SGLT2i and GLP-1 RA reduce MACE, which is likely to be independent of baseline HbA1c. In people with HF, CKD, established CVD, or multiple risk factors for CVD, the decision to use a GLP-1 RA or an SGLT2i with proven benefit should be independent of baseline HbA1c. • In general, selection of medications to improve cardiovascular and kidney outcomes should not differ for older people. • In younger people with diabetes (<40 years), consider early combination therapy. • In women with reproductive potential, counseling regarding contraception and taking care to avoid exposure to medications that may adversely affect a fetus are important.
American Association of Clinical Endocrinologists/ American College of Endocrinology: **Clinical Practice Guidelines for Developing a Diabetes Mellitus Comprehensive Care Plan (2022)**[6]	Antihyperglycemic Pharmacotherapy for Persons with Type 2 Diabetes • Individualized pharmacotherapy for persons with T2D should be prescribed based on evidence for benefit that includes glucose lowering, avoidance of hypoglycemia and weight gain, and reduction of cardio-renal risk. • Persons with T2D and their health care professionals should use patient-centered shared decision-making to agree on therapy targets and treatments as well as a regimen for glucose monitoring (i.e., BGM, structured BGM, or CGM). • Glycemic targets include A1C, BGM, and, for those using CGM, achievement of CGM targets such as time in range (TIR), percentage in low and very low range, time above range, and glycemic variability. Nonglycemic targets include avoidance of hypoglycemia, control of BP, lipids, other CVD risk factors, and achieving and maintaining a healthy body weight. • Independent of glycemic control, targets, or treatment, if there is established or high risk for ASCVD, HF, and/or CKD, clinicians should prescribe a GLP-1 RA

Clinical Guideline	Recommendation(s)
	or an SGLT2i with proven efficacy for the specific condition(s) of the person with T2D being treated. • DM therapy should be individualized based on level of glycemia and the presence of comorbidities, complications, and access. Metformin is often the preferred initial therapy. Other agents may be appropriate as first line or in addition to metformin to reduce BG and/or to address specific comorbidities (such as ASCVD, HF, CKD, obesity, NAFLD), independent of glucose-lowering effects. • For some recently diagnosed individuals with T2D and more severe hyperglycemia (A1C ≥7.5%), unlikely to attain the A1C target with a single agent, early combination pharmacotherapy should be considered, usually to include metformin plus another agent that does not cause hypoglycemia, especially a GLP-1 RA, SGLT2i, or dipeptidyl peptidase 4 (DPP-4) inhibitor. • For newly diagnosed persons with T2D and an entry A1C >9.0% and/or ≥1.5% above target, one should initiate, along with lifestyle modifications, dual- or possibly triple-combination pharmacotherapy usually including metformin. Basal insulin along with noninsulin therapy is recommended if there are significant signs or symptoms of hyperglycemia, especially including catabolism (e.g., weight loss) or a very high A1C >10% (86 mmol/mol) or BG levels (≥300 mg/dL [16.7 mmol/L]). • Clinicians should discuss with persons with T2D the likelihood that most persons with T2D ultimately require a combination of multiple complementary antihyperglycemic agents, in addition to lifestyle interventions, to attain and maintain optimal glycemic control. • The DM care team should assess medication adherence and safety and glycemic control in persons with T2D quarterly or more frequently as needed. Subsequent visits will depend upon the metabolic targets achieved and the stability of metabolic control. • Persons with T2D who start on metformin should continue it unless intolerance or contraindications occur. When intensification of antihyperglycemic treatment is needed, other agents should be added to metformin. • Most persons with T2D who require intensification of antihyperglycemic therapy with a GLP-1 RA or insulin should initially be prescribed a GLP-1 RA. If further intensification is required, one should prescribe a basal insulin or a switch to a fixed-ratio combination of a basal insulin and a GLP-1 RA (insulin glargine U100 + lixisenatide [GlarLixi] or insulin degludec + liraglutide [IdegLira]). • Insulin should be prescribed for persons with T2D when noninsulin antihyperglycemic therapy fails to achieve target glycemic control or when a person has symptomatic hyperglycemia. • Long-acting basal insulin analogs are the recommended initial choice of insulin therapy for persons with T2D. The insulin analogs glargine (U100 or U300), degludec (U100 or U200), or detemir are preferred over intermediate-acting Neutral Protamine Hagedorn (NPH) insulin because analog insulins have demonstrated less hypoglycemia in some studies. Glargine U300 and degludec can be associated with less hypoglycemia than glargine U100 or detemir. • Many persons with T2D receiving basal insulin and not at goal A1C can have significantly improved glycemia by the addition of a GLP-1 RA or being switched to a fixed-ratio combination basal insulin–GLP-1 RA (GlarLixi or IdegLira). One of these changes should be considered before adding a meal-time insulin for postprandial glycemic control. • When control of postprandial hyperglycemia is needed and a basal insulin and a GLP-1 RA are already being used, preference should be given to rapid-acting insulins (the analogs lispro, aspart, and glulisine or the rapid-acting inhaled human insulin powder) over regular human insulin. The former have a more

Clinical Guideline	Recommendation(s)
	consistent and a more rapid onset and offset of action with less risk of hypoglycemia. • Ultra-rapid-acting insulins (faster-acting insulin aspart, lispro aabc, and [human insulin] inhalation powder) may allow a decrease in the time between insulin administration and food intake and reduce the postprandial peak of PG as compared with rapid-acting insulins. The significance of this on long-term complications is unknown. • Basal-bolus insulin regimens or continuous subcutaneous insulin infusion (CSII) (i.e., insulin pump) allow for adjustment of insulin doses according to carbohydrate intake and activity levels and are recommended for intensive insulin therapy in persons with T2D. • Premixed insulin formulations (fixed combinations of shorter- and longer-acting components) of human or analog insulin may be considered for persons with T2D who have consistent dietary and exercise patterns and in whom adherence to more intensive insulin regimens is problematic. However, these preparations have reduced dosage flexibility and may increase the risk of hypoglycemia compared with basal insulin or basal-bolus regimens. • In persons with T2D who are treated with basal-bolus insulin therapy, adding a GLP-1 RA, or switching to a fixed-ratio combination of a GLP-1 RA and a basal insulin, or adding an SGLT2i or pramlintide (less commonly used) may be able to reduce postprandial hyperglycemia, A1C, and weight. GLP-1 RAs may also allow reduction or discontinuation of bolus insulin in some individuals. <u>How should insulin therapy be used for management of persons with type 1 diabetes?</u> • Insulin must be used to treat all persons with T1D. • Physiologic insulin replacement regimens, which provide both basal and prandial (meal-related or bolus) insulin, are recommended for most persons with T1D. • Achievement of glucose targets using either MDI of insulin or CSII, is needed to prevent development of life-threatening crises, such as acute hyperglycemic crises (DKA and hyperglycemic hyperosmolar state) and catabolic state. • A multi-component self-management DM education program is recommended for persons with T1D. Ideally, this is provided by a professional with expertise (i.e., certified diabetes care and education specialist) in the topics of healthy lifestyle, insulin technique including prandial insulin dosing guided by carbohydrate counting and diet adjustments for special situations, such as physical activity and prolonged fasting. Instruction is also needed in how to deal with sick days and prevention of DKA and hypoglycemia, and other relevant issues. Due to changes in DM self-management practices and each individual's medical history, personal and cultural background, and educational needs, specific education topics may need to be repeated at regular intervals. • The ideal insulin regimen should be personalized to an individual's needs and glycemic targets, attempting to better emulate physiological insulin replacement to maintain near normoglycemia, to prevent the development and progression of DM complications, while minimizing hypoglycemia and providing flexibility for specific daily life situations/scenarios such as: exercise, sleep, acute illness, psychological stress, etc. • Insulin regimens usually should involve the use of insulin analogs for most persons with T1D and include the following approaches: ○ MDI, which usually involve 1 to 2 subcutaneous injections daily of basal insulin to suppress ketogenesis and gluconeogenesis and to control glycemia between meals and overnight, and subcutaneous injections of prandial insulin or use of inhaled insulin before each meal to control meal-related glycemic excursions. CGM is the preferred method of glucose monitoring for all individuals with T1D.

Clinical Guideline	Recommendation(s)
	○ Insulin pump therapy (CSII) provides constant/continuous infusion of fast-acting insulin driven by mechanical force and delivered via a cannula inserted under the skin. CSII can improve (or enhance) glycemic control and should be an option for insulin delivery for appropriate persons with DM. Ideally, these individuals should also use CGM as stated in R13.6.a. ○ Automated insulin delivery systems (AIDs), which include an insulin pump, an integrated CGM, and computer software algorithm, aim to better emulate physiological insulin replacement and achieve glycemic targets. This technology is recommended for many persons with T1D since its use has been shown to increase TIR while often reducing hypoglycemia or at least without causing increased hypoglycemia. ○ Open-loop (use of a pump and sensor which do not communicate) and sensor-augmented pump (SAP) systems: (CGM communicates with pump facilitating needed adjustments to basal rate; temporary interruption of insulin delivery when glucose levels are low or forecast to be low within 30 min). Insulin pump with a CGM or an SAP is recommended to manage persons with DM treated with intensive insulin management who prefer not to use AIDs or have no access to them. How should diabetes mellitus in pregnancy be managed? • For women with GDM, the following treatment goals are recommended: preprandial glucose concentration ≤95 mg/dL and either a 1-h post-meal glucose ≤140 mg/dL or a 2-h post-meal glucose ≤120 mg/dL to decrease adverse fetal outcomes. • All women with preexisting DM (T1D, T2D, or previous GDM) need access to preconception care and counseling to ensure adequate nutrition, healthy weight, and glucose control before conception, during pregnancy, and in the postpartum period. • Rapid-acting insulin analogs (insulin-lispro, insulin-aspart) should be used to treat postprandial hyperglycemia in pregnant women. • Options for basal insulin include long-acting insulin (e.g., NPH, detemir, or glargine) or rapid-acting insulin via a CSII. Regular insulin, although not recommended as first-line therapy, is acceptable to use in managing pregnant women with DM when rapid-acting insulin analogs are not available. • Insulin is the preferred therapeutic choice for pregnant women with GDM or T2D, but metformin has been given a category B for pregnancy with accumulating clinical evidence of metformin's safety during the first trimester and beyond. Metformin has been shown to improve pregnancy and fetal outcomes except for increased rates of infants with SGA and later onset of obesity. The prescriber should discuss the potential risks and benefits of oral agent therapy during pregnancy as well as the need for longer-term outcome studies.
American Association of Clinical Endocrinologists/ American College of Endocrinology: **Consensus Statement on the Comprehensive Type 2 Diabetes Management Algorithm (2023)**[7]	Principles underlying the algorithm • Lifestyle modification underlies all therapy. • Maintain or achieve optimal weight. • Choice of antihyperglycemic therapy reflects glycemic targets, atherosclerotic cardiovascular disease (ASCVD), congestive heart failure (CHF), chronic kidney disease (CKD), overweight/obesity, and nonalcoholic fatty liver disease (NAFLD). • Choice of therapy includes ease of use and access. • Optimal hemoglobin A1c (A1C) is ≤6.5% or as close to normal as is safe and achievable for most patients. • Individualize all glycemic targets (A1C, glucose management indicator [GMI], time in range [TIR], fasting blood glucose [FBG], and PPG).

Clinical Guideline	Recommendation(s)
	• Get to goal as soon as possible (adjust ≤3 months). • Avoid hypoglycemia. Hypoglycemia, defined as blood glucose (BG) <70 mg/dL, is associated with an increased risk for adverse outcomes including mortality. • CGM is highly recommended to assist persons with diabetes in reaching goals safely. • Comorbidities must be managed for comprehensive care. Algorithm summative information • The algorithm is intended as a more concise document than the guideline, providing easily accessible, visual guidance for decision-making in the clinic setting. • In this 2023 algorithm, there continues to be an emphasis on lifestyle modification and treatment of overweight/obesity as key pillars of the management of prediabetes and DM. • The importance of appropriate management of the atherosclerotic risk factors of dyslipidemia and hypertension is highlighted. • One notable new theme is an obvious emphasis on a complication-centric approach, beyond glucose levels, to frame decisions regarding first-line pharmacologic choices for the treatment of persons with diabetes. • The algorithm is divided into discrete graphic sections that outline the principles for management of T2D and guide management of adiposity-based chronic disease (ABCD), prediabetes, and atherosclerotic risk factors of dyslipidemia and hypertension. In addition, the algorithms for antihyperglycemic agents include both complication-centric and glucose-centric approaches, and there is direction for insulin initiation and titration. Tables summarizing the benefits and risks of antihyperglycemic medications (updated) and weight-loss pharmacotherapy (new) are provided.

American Academy of Pediatrics: **Management of Newly Diagnosed Type 2 Diabetes Mellitus (T2DM) in Children and Adolescents (2013)[8]**	• Clinicians must ensure that insulin therapy is initiated for children and adolescents with T2DM who are ketotic or in diabetic ketoacidosis and in whom the distinction between types 1 and 2 diabetes mellitus is unclear and, in usual cases, should initiate insulin therapy for patients.
	  ○ Who have random venous or plasma blood glucose (BG) concentrations ≥250 mg/dL.
	  ○ Whose HbA_{1c} is >9%.
	• In all other instances, clinicians should initiate a lifestyle modification program, including nutrition and physical activity, and start metformin as first-line therapy for children and adolescents at the time of diagnosis of T2DM.
	• Monitoring of HbA_{1c} concentrations is recommended every three months and intensifying treatment is recommended if treatment goals for finger-stick BG and HbA_{1c} concentrations are not being met.
	• Advise patients to monitor finger-stick BG concentrations in patients who:
	  ○ Are taking insulin or other medications with a risk of hypoglycemia; or
	  ○ Are initiating or changing their diabetes treatment regimen; or
	  ○ Have not met treatment goals; or
	  ○ Have intercurrent illnesses.
	• Incorporate the Academy of Nutrition and Dietetics' *Pediatric Weight Management Evidence-Based Nutrition Practice Guidelines* in dietary or nutrition counseling of patients with T2DM at the time of diagnosis and as part of ongoing management.
	• Encourage children and adolescents with T2DM to engage in moderate-to-vigorous exercise for at least 60 minutes daily and to limit nonacademic "screen time" to less than two hours a day.

American Diabetes Association:	Blood Glucose Management: Monitoring and Treatment

Clinical Guideline	Recommendation(s)

Type 1 Diabetes in Children and Adolescents: A Position Statement by the American Diabetes Association (2018)[9]	• Most children with type 1 diabetes should be treated with intensive insulin regimens via either multiple daily injections of prandial insulin and basal insulin or continuous subcutaneous insulin infusion.
	• An HbA_{1c} target of <7.5% should be considered in most children and adolescents but should be individualized based on the needs and situation of the patient and family.
	• Children and adolescents with type 1 diabetes should have blood glucose levels monitored up to six to ten times/day including premeal, pre-bedtime, and as needed for safety (e.g., exercise, driving, illness, or the presence of symptoms of hypoglycemia).
	• Continuous blood glucose monitoring should be considered in all children and adolescents whether using insulin injections or an insulin pump.
	• In pediatric patients with type 1 diabetes automated insulin delivery systems can improve glycemic control and reduce hypoglycemia.
	
	<u>Lifestyle Management</u>
	• Individualized medical nutrition therapy is recommended for children and adolescents with type 1 diabetes.
	• Monitoring carbohydrate intake, whether by carbohydrate counting or experience-based estimation, is key to achieving optimal glycemic control.
	• Exercise if recommended for all children and adolescents with type 1 diabetes. The suggested goal is 60 minutes of moderate to vigorous aerobic activity daily with muscle-strengthening and bone-strengthening activities three times a week.
	• Children and adolescents with type 1 diabetes should be educated about prevention and management of potential hypoglycemia during and after exercise.
	• Strategies to prevent hypoglycemia during exercise, after exercise, and overnight following exercise include reducing prandial insulin dosing for the meal/snack preceding exercise, increasing carbohydrate intake, eating bedtime snacks, using continuous blood glucose monitoring, and/or reducing basal insulin doses.
	
	<u>Behavioral Aspects of Self-Management</u>
	• Children and adolescents with diabetes should be assessed for psychosocial issues and family stresses that could impact diabetes management at diagnosis and routine follow-up.
	• Consider including children in consent processes as early as cognitive development indicates understanding of health consequences of behavior.
	• Offer adolescents time by themselves with their care provider(s) starting at age 12 years, or when developmentally appropriate.
	
	<u>Complications and Comorbidities</u>
	• Diabetic Ketoacidosis
	  o All individuals with type 1 diabetes should have access to an uninterrupted supply of insulin. Lack of access and insulin omissions are major causes of diabetic ketoacidosis.
	  o Patients with type 1 diabetes should have continuous access to medical support for sick-day management.
	• Hypoglycemia
	  o The recommended treatment of hypoglycemia (blood glucose <70 mg/dL) in conscious patients is 15 g of glucose, although any form of carbohydrate can be used. If hypoglycemia continues after 15 minutes, treatment should be repeated. Once blood glucose has returned to normal patients should consider consuming a meal/snack and/or reduce insulin.
	  o All individuals with type 1 diabetes should be prescribed glucagon and families/caregivers should be educated on administration.

Clinical Guideline	Recommendation(s)
	○ Treatment regimens should be reevaluated in those with hypoglycemia unawareness or one or more episodes of severe hypoglycemia. • Diabetic Kidney Disease ○ Annual screening for albuminuria with a random spot urine sample for albumin-to-creatinine ratio should be considered at puberty or at age >10 years, whichever is earlier, once the child has had diabetes for 5 years. ○ An angiotensin-converting-enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB), titrated to normalization of albumin excretion, may be considered when elevated urinary albumin-to-creatinine ratio is documented. • Retinopathy ○ An initial dilated and comprehensive eye examination is recommended at age 10 years or after puberty has started, whichever is earlier, once the patient has had diabetes for three to five years. ○ Annual routine follow-up is recommended but may be given every two years based on the advice of an eye care professional. • Neuropathy ○ Consider an annual comprehensive foot exam for adolescents at the start of puberty or at age 10 years, whichever is earlier, once the patient has had type 1 diabetes for 5 years. • Hypertension ○ Children and adolescents with type 1 diabetes should have blood pressure monitored at each visit. Elevated blood pressure should be confirmed on three separate days. ○ Initial treatment of high-normal blood pressure should include dietary modification and increased exercise. Pharmacologic treatment should be considered if blood pressure is not controlled after three to six months. ○ In patients with conformed hypertension pharmacologic treatment should be added to lifestyle modification at diagnosis. ○ ACE inhibitors and ARBs should be considered for initial treatment. • Dyslipidemia ○ A fasting lipid profile should be taken in children ≥10 years of age or older after the diagnosis of diabetes. Obtain a fasting lipid profile in children 10 years of age or older as soon as convenient after the diagnosis of diabetes ○ If lipids are abnormal, initial therapy should consist of optimizing glucose control and medical nutrition therapy using a Step 2 American Heart Association diet that restricts saturated fat to 7% of total calories and dietary cholesterol to 200 mg/day. ○ If lipids remain abnormal after six months of lifestyle intervention, consider adding a statin in children at least 10 years of age.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the meglitinides are noted in Table 3.

Table 3. FDA-Approved Indications for the Meglitinides[1-3]

Indication	Single Entity Agents	
	Nateglinide	Repaglinide
Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus	✔	✔

IV. Pharmacokinetics

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

Table 4. Pharmacokinetic Parameters of the Meglitinides[2]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Single Entity Agents					
Nateglinide	72 to 75	97 to 99	Liver, extensive (% not reported)	Renal (13 to 14), Feces (10)	1.25 to 2.90
Repaglinide	56	>98	Liver, complete (% not reported)	Renal (8), Feces (90)	1

V. Drug Interactions

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

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

Generic Name(s)	Interaction	Mechanism
Meglitinides	Fluoroquinolone antibiotics	Concurrent use of fluoroquinolones and antidiabetic agents may result in changes in blood glucose and increased risk of hypoglycemia or hyperglycemia. Monitor blood glucose levels when starting or stopping antibiotic therapy and adjust the repaglinide dose as needed.
Meglitinides	Simeprevir	Concurrent use of meglitinides and simeprevir may result in increased exposure of meglitinides.
Repaglinide	Gemfibrozil	Gemfibrozil may inhibit repaglinide metabolism (cytochrome P450 2C8 isoenzyme) causing elevated repaglinide plasma concentrations and increasing the risk of severe and protracted hypoglycemia. Avoid coadministration of repaglinide and gemfibrozil and reduce the dose of repaglinide when used together.
Repaglinide	Itraconazole	Concurrent use of itraconazole and repaglinide may result in increased plasma concentrations of repaglinide.
Repaglinide	Clopidogrel	Concurrent use of clopidogrel and repaglinide may result in increased repaglinide exposure.
Repaglinide	Teriflunomide	Concurrent use of repaglinide and teriflunomide may result in increased repaglinide exposure.
Repaglinide	Atazanavir	Concurrent use of atazanavir and repaglinide may result in increased repaglinide exposure or loss of glycemic control.
Repaglinide	Abiraterone	Concurrent use of abiraterone and repaglinide may result in increased repaglinide plasma concentrations.

VI. Adverse Drug Events

The most common adverse drug events reported with the meglitinides are listed in Table 6.

Table 6. Adverse Drug Events (%) Reported with the Meglitinides[1-3]

Adverse Events	Nateglinide	Repaglinide
Cardiovascular		
Arrhythmia	-	≤1
Chest pain	-	<2
EEG abnormal	-	≤1
Hypertension	-	≤1
Myocardial infarction	-	≤1
Palpitations	-	≤1

Adverse Events	Nateglinide	Repaglinide
Central Nervous System		
Dizziness	4	-
Headache	-	9 to 11
Dermatologic		
Pruritus	✔	-
Rash	✔	-
Urticaria	✔	-
Endocrine/Metabolic		
Hypoglycemia	2	16 to 31
Gastrointestinal		
Constipation	-	2 to 3
Diarrhea	3.2	4 to 5
Dyspepsia	-	2 to 4
Nausea	-	3 to 5
Vomiting	-	2 to 3
Hepatic		
Hepatic dysfunction	-	✔
Hepatitis	✔	✔
Jaundice	✔	✔
Laboratory Test Abnormalities		
Hemolytic anemia	-	✔
Liver enzymes increased	✔	✔
Thrombocytopenia	-	✔
Uric acid increased	✔	-
Musculoskeletal		
Arthralgia	3	3 to 6
Back pain	4	5 to 6
Paresthesia	-	2 to 3
Respiratory		
Bronchitis	2.7	2 to 6
Coughing	2.4	-
Rhinitis	-	3 to 7
Sinusitis	-	3 to 6
Upper respiratory infection	11	10 to 16
Other		
Accidental trauma	2.9	-
Allergy	-	1 to 2
Alopecia	-	✔
Anaphylactic reaction	-	✔
Blurred vision	-	✔
Flu symptoms	4	-
Pancreatitis	-	✔
Stevens-Johnson Syndrome	-	✔
Tooth disorder	-	2
Urinary tract infection	-	2 to 3
Weight gain	✔	-

✔ Percent not specified.
-Event not reported.

VII. Dosing and Administration

The usual dosing regimens for the meglitinides are listed in Table 7.

Table 7. Usual Dosing Regimens for the Meglitinides[1-3]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Single Entity Agents			
Nateglinide	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus: Tablet: initial, 60 to 120 mg TID before meals; maintenance, 120 mg TID before meals	Safety and efficacy in children have not been established.	Tablet: 60 mg 120 mg
Repaglinide	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus: Tablet: initial, 0.5 to 2 mg with meals; maintenance, 0.5 to 4 mg with meals; maximum, 16 mg/day	Safety and efficacy in children have not been established.	Tablet: 0.5 mg 1 mg 2 mg

BID=twice daily, TID=three times daily

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the meglitinides are summarized in Table 8.

Table 8. Comparative Clinical Trials with the Meglitinides

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Type 2 Diabetes – Monotherapy				
Rosenstock et al.[10] (2004) Nateglinide 60 mg TID before each meal (titrated to a maximum of 360 mg daily) vs repaglinide 0.5 mg TID before each meal (titrated to a maximum of 16 mg daily)	MC, OL, PG, RCT Patients ≥18 years of age with type 2 diabetes for ≥3 months, BMI 24 to 42 kg/m^2, HbA_{1c} 7.0 to 12.0%, and drug naïve	N=150 16 weeks	Primary: Final HbA_{1c} and changes in HbA_{1c} from baseline Secondary: Changes in FPG from baseline	Primary: Mean baseline HbA_{1c} values were similar in both groups (8.9%). The changes in HbA_{1c} for repaglinide from baseline were -1.57 vs -1.04% for nateglinide (P=0.002). Final HbA_{1c} values were lower in the repaglinide group vs the nateglinide group (7.3 vs 7.9%, respectively). At the end of the study, 54% of the repaglinide-treated patients had HbA_{1c} values ≤7.0% vs 42% of nateglinide-treated patients (P=0.18). Secondary: The final FPG was 154.0±40.2 mg/dL for repaglinide and 188.0±62.2 mg/dL for nateglinide. The mean change from baseline in FPG was greater with repaglinide compared to nateglinide (-57 vs -18 mg/dL; P<0.001). There were no major hypoglycemic episodes (requiring the assistance of another person) in either treatment group. Mean weight gains from baseline to the study end point were 1.8 kg for repaglinide and 0.7 kg for nateglinide (incremental mean imputation method calculation P=0.04 and P=0.034 by last observed carried forward method calculation). The most common adverse events (3 to 10% of patients in both treatment groups) were upper respiratory tract infection, sinusitis, constipation, arthralgia, headache, and vomiting. There were no notable differences in the pattern of adverse events for the treatment groups.
Li et al.[11] (2007)	DB, DD, MC, RCT Chinese patients 35 to 65 years of age with type 2	N=223 12 weeks	Primary: FPG, HbA_{1c}, TG, TC, BMI, HOMA-IR, β-cell function indexes, plasma	Primary: Compared to baseline, FPG; 30-, 60-, and 120-minute PPG; and HbA_{1c} all decreased significantly with both repaglinide and nateglinide treatment (P<0.05). Effects on FPG and PPG of the two agents were not significantly different (P>0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Nateglinide 90 mg TID before each meal vs repaglinide 1 mg TID before each meal	diabetes, on a stable diet and exercise for 4 weeks, with fasting blood glucose ≥7.8 mmol/L and/or 2-hour PPG ≥11.1 mmol/L at least twice in 2 weeks, without a history of antidiabetic agents other than metformin (on stable dosage for 4 weeks)		insulin, C-peptide, PPG using the incremental AUC ($AUC_{0\text{-}120\ min}$) after a standard 800-kcal meal (55% carbohydrate, 25% fat and 20% protein) Secondary: Not reported	The HbA_{1c} levels at week 12 of the repaglinide group and the nateglinide group were not significantly different (6.27 vs 6.59%, respectively; P>0.05). However, an HbA_{1c} reduction at week 12 from baseline in the repaglinide group was significantly greater than an HbA_{1c} reduction in the nateglinide group (-1.21 vs -0.68%, respectively; P=0.0039). AUC of glucose significantly decreased in both repaglinide and nateglinide groups at week 12 to a similar extent (20.36±4.67 vs 20.54±4.83 mmol/L/h, respectively; P<0.0001 vs baseline; P>0.05 between the groups). AUC of insulin and C-peptide in both groups were increased at week 12 to a similar extent (P<0.05 vs baseline; P>0.05 between two groups). HOMA-IR in both groups were decreased significantly, and effects of repaglinide and nateglinide on insulin sensitivity were not different (2.44 vs 2.48, at week 12 respectively; P<0.05 vs baseline; P>0.05 between the groups). B-cell function indexes were increased in both groups, but the values were not significantly different between two groups after 12 weeks of treatment (P<0.05 vs baseline; P>0.05 between the groups). After the 12 weeks of treatment with repaglinide, TG level significantly decreased from baseline (no values reported; P<0.05). In both groups, TC level was decreased from baseline at week 12 (no values reported; P<0.05), and BMI was reduced slightly (P>0.05). Effects of both agents on TG, TC and BMI were not different (no values reported; P>0.05). Adverse events between the groups were reported to be similar (P>0.05). However, the rate of adverse reaction was reported to be 4.5% (hypoglycemic event, thrombocytopenia, elevation of liver enzymes) in the repaglinide group and 0.87% (thrombocytopenia) in the nateglinide group. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Not reported
Hollander et al.[12] (2003) Nateglinide 120 mg TID before each meal vs glyburide 5 mg to 10 mg QD vs placebo	DB, MC, PC, RCT Patients 32 to 75 years of age with type 2 diabetes ≥3 months prior to entry into the trial on diet modification alone for ≥4 weeks before initial visit, mean HbA_{1c} 6.8 to 11.0%, and a BMI 20 to 35 kg/m^2	N=152 8 weeks	Primary: Change from week 0 to week eight during liquid meal challenges in FPG, fasting insulin, fasting C-peptide, and fasting proinsulin Secondary: Not reported	Primary: At week eight, FPG was reduced more with glyburide compared to nateglinide (-1.9 mmol/L; P<0.001). Nateglinide treatment did not have significant changes from baseline with fasting levels of C-peptide, insulin, or proinsulin. Glyburide treatment increased fasting C-peptide vs placebo and nateglinide (P<0.001), fasting insulin vs placebo (P<0.001) and nateglinide (P<0.05), and proinsulin vs placebo (P<0.001) and nateglinide (P<0.025). Reduction of mealtime glucose excursions from nateglinide was approximately twice that from glyburide (-4.94±0.74 vs -2.71±0.71 mmol/hr/L; P<0.03). The insulin secretion reflected by the C-peptide AUCs was approximately twice that in the glyburide group than in the nateglinide group (1.83±0.24 vs 0.95±0.23 nmol/hr/L, respectively; P=0.063 vs nateglinide). Secondary: Not reported
Wolffenbuttel et al.[13] (1999) Repaglinide 0.5 to 4 mg TID before each meal vs glyburide 1.75 to 10.5 mg daily	DB, MC, PG, RCT Patients 40 to 75 years of age with type 2 diabetes who were being treated with oral blood glucose-lowering agents and/or diet, BMI 21 to 35 kg/m^2, and an HbA_{1c} >6.5% when treated with diet only and <12%	N=424 12 months	Primary: Change in HbA_{1c} and FPG from baseline to the final visit Secondary: Change in fasting insulin and lipid levels and four-point blood glucose levels (fasting, before lunch, before	Primary: Change in HbA_{1c} levels was not different between groups when compared to baseline. HbA_{1c} levels increased by 0.58% (95% CI, 0.41 to 0.76) in the repaglinide group and by 0.45% (95% CI, 0.22 to 0.69) in the glyburide group. In a subset of patients who were treated previously with diet only, HbA_{1c} decreased significantly more during glyburide treatment (–2.4%) vs repaglinide (–1%; P<0.05). The changes in HbA_{1c} in patients who were already being treated with oral agents were similar, 0.6% in the repaglinide group and 0.7% in the glyburide group. Changes in fasting plasma glucose from baseline showed a similar trend as the HbA_{1c}.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	when treated with diet plus oral blood glucose-lowering agents		supper, and at bedtime) from baseline to the final visit	Secondary: Mean fasting insulin levels decreased in the repaglinide group (–3 pmol/L) and increased in the glyburide group (+1 pmol/L). There was no treatment difference. Changes from baseline in four-point glucose levels were small for both treatment groups. Lipid levels (TC, HDL, and TG) did not change during the study.
Derosa et al.[14] (2003) Repaglinide 1 to 2.5 mg daily vs glimepiride 1 to 3 mg daily	DB, PC, RCT Patients with type 2 diabetes for ≥6 months, drug naïve, and HbA_{1c} >7.0% with diet and exercise	N=124 12 months	Primary: Changes from baseline in HbA_{1c}, FPG, PPG, fasting plasma insulin, lipoprotein(a), plasminogen activator inhibitor-1, homocysteine, body weight, BMI, postprandial insulin, BP, TC, LDL-C, HDL-C, TG, apolipoprotein A-1, apolipoprotein B, and fibrinogen Secondary: Not reported	Primary: Changes in HbA_{1c} and FPG from baseline were significant for both treatments (P<0.01). Changes in PPG were significant for repaglinide vs baseline (P<0.01) and compared to glimepiride (P<0.05). Changes in PPG from baseline for the glimepiride group was significant (P<0.05). Change in fasting plasma insulin from baseline was significant for repaglinide (P<0.05). Changes in lipoprotein(a) from baseline were significant for repaglinide (P<0.05) and glimepiride (P<0.01). Changes in plasminogen activator inhibitor-1 from baseline were significant for both treatment groups (P<0.05). Changes in homocysteine were significant from baseline for repaglinide (P<0.05) and glimepiride (P<0.01). Changes in homocysteine were significant for glimepiride vs repaglinide (P<0.05). There were no significant changes during the study from baseline at six or 12 months in the following parameters for either treatment group: body weight, BMI, postprandial insulin, BP, TC, LDL-C, HDL-C, TG, apolipoprotein A-1, apolipoprotein B, and fibrinogen. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Not reported
Cesur et al.[15] (2007) Repaglinide up to 4 mg QD vs glimepiride up to 8 mg QD vs insulin glargine up to 36 U QD	MC, OL, OS, PRO Patient 33 to 67 years of age with type 2 diabetes, HbA_{1c} 6.0 to 8.0% taking oral diabetes agents, who were willing to fast throughout Ramadan month	N=65 Duration not specified	Primary: FBG, PPG, HbA_{1c}, fructosamine, BMI, lipid metabolism and hypoglycemia in pre-Ramadan and post-Ramadan fasting Secondary: Not reported	Primary: In the fasting group, both FPG and PPG levels showed no significant changes at post-Ramadan and one-month post-Ramadan compared to pre-Ramadan. In the nonfasting group, FPG levels did not change significantly throughout the study, whereas PPG levels increased at post-Ramadan ($P<0.05$ and $P<0.01$, respectively). At post-Ramadan and one-month post-Ramadan, changes in PPG values in the fasting group were lower compared to the nonfasting group ($P<0.01$ for both time periods). There was no significant change in HbA_{1c} levels between the nonfasting and fasting groups. There was a significant increase in fructosamine levels in both fasting group and non-fasting group at one-month post-Ramadan ($P<0.01$ for both). BMI did not change during the study in fasting group but a gradual increase in BMI was seen in the nonfasting group ($P<0.05$ between pre-Ramadan and post-Ramadan in nonfasting group). TC, LDL-C, and TG did not change throughout the study period but HDL-C levels significantly increased at post-Ramadan in the fasting group ($P<0.01$). In nonfasting group, LDL-C and TG levels significantly increased at post-Ramadan ($P<0.05$ for both). At least one hypoglycemia episode was reported in 12.2% of patients in the fasting group and 12.5% of patients in the nonfasting group. Hypoglycemia was seen in 14.3% of patients in the glimepiride group, 11.1% in the repaglinide group and 10% in the insulin group. There was no significant difference between three drug groups regarding the rate of hypoglycemia. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Taki et al.[16] (2005) Nateglinide	OS Patients with type 2 diabetes, drug naïve, with FPG ≤150 mg/dL and had started to take nateglinide alone	N=547 12 weeks	Primary: HbA_{1c}, PPG, FPG, hypoglycemia Secondary: Not reported	Primary: In the nateglinide group, a reduction in HbA_{1c} was 0.82%, PPG was 59.4 to 158.0 mg/dL, and FPG was 11.7 to 122.4 mg/dL. Hypoglycemia was the most prevalent adverse event (2.1%). A total of nine of 11 episodes required no therapeutic intervention. Severe hypoglycemia was recognized in one case of diabetes complicated by serious renal dysfunction, for which nateglinide has been contraindicated in Japan. No patient experienced symptoms of nocturnal or prolonged hypoglycemia. Secondary: Not reported
Taki et al.[17] (2006) Nateglinide	OS Japanese patients with type 2 diabetes	N=1,014 15 months	Primary: PPG, FPG, HbA_{1c}, BMI Secondary: Not reported	Primary: In patients receiving nateglinide, there were reductions in PPG of -9.3 mg/dL (from 155.1±40.0 to 145.0±35.1 mg/dL) and HbA_{1c} of 0.68% (from 7.51±1.36 to 6.83±1.09%). In patients previously treated with sulfonylurea, a decrease in HbA_{1c} was not observed. No change in BMI was noted after 15 months of nateglinide treatment. Secondary: Not reported
Schwarz et al.[18] (2008) Nateglinide 120 mg TID before meals vs placebo	DB, MC, PC, PG, RCT Patients 65 to 90 years of age with type 2 diabetes for ≥4 weeks, oral antidiabetic agents, with FPG ≤240 mg/dL, BMI 22 to 40 mg/m^2, HbA_{1c} 7.0 to 9.5%, without	N=54 12 weeks	Primary: Change in baseline HbA_{1c} Secondary: FPG, PPG, proportion of patients achieved a target HbA_{1c} <7.0 or ≤6.5%, adverse events	Primary: Plasma HbA_{1c} decreased from 7.6±0.1 to 6.9±0.1% in patients receiving nateglinide (mean change, -0.7±0.1%; P<0.001) compared to a reduction of 7.7± 0.2 to 7.5±0.1% in patients receiving placebo (change, -0.2±0.2%; P=0.206). A significant difference between the two groups in HbA_{1c} change was reported (-0.5%; 95% CI, -1.0 to -0.2; P=0.004). Secondary: After 12 weeks of treatment, FPG decreased significantly from 164±6 to 141±7 mg/dL in patients receiving nateglinide (change, -23±7 mg/dL; P=0.003) compared to a reduction of 153±8 to 159±7 mg/dL in patients receiving placebo (change, 2±5 mg/dL; P=0.728). A significant difference

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	history of type 1 diabetes or secondary diabetes, significant symptomatic complications of diabetes, severe cardiac dysfunction, significant cardiovascular events within 6 months prior to randomization, and severe liver disease			between the two groups in FPG change was reported (-25 mg/dL; 95% CI, -40 to -3; P=0.022). Two-hour PPG decreased from 184±11 to 153±8 mg/dL in patients receiving nateglinide (change, -29±11 mg/dL; P=0.019) compared to a reduction of 192±14 to 188±15 mg/dL in patients receiving placebo (change, -7±17 mg/dL; P=0.687). A difference between two groups in Two-hour PPG change was significant (-36 mg/dL; 95% CI, -74 to -8; P=0.018). Sixty percent of patients in the nateglinide group achieved a target HbA_{1c} of <7.0% compared to 21% of patients in the placebo group (P=0.004). Significantly higher number of patients receiving nateglinide achieved a target HbA_{1c} ≤6.5% compared to placebo-treated patients (8/30 vs 1/24, respectively; P=0.028). Similar adverse-event profiles were reported between the two groups (15 patients in each group reported one or more adverse events). No serious adverse events, hypoglycemic events or deaths were reported.
Zhou et al.[19] (2013) Acarbose 50 mg TID nateglinide 120 mg TID	AC, ML, OL, PG, RCT Patients 18 to 75 years who were antihyperglycemic agent–naive with type 2 diabetes (HbA_{1c} 6.5 to 9.0%)	N=103 2 weeks	Primary: Incremental area under the curve of postprandial blood glucose (AUCpp) during continuous glucose monitoring (CGM) Secondary: Additional CGM measures, serum glycated albumin, safety	Primary: Both treatment groups showed a significant decrease in the AUCpp of treatment (vs baseline, P<0.001), but the decrease achieved by the two therapies was not significantly different (nateglinide vs acarbose, P=0.691). Secondary: No significant differences between treatment groups occurred for secondary efficacy outcomes, except for therapy-mediated effects on insulin levels. The insulin concentrations in the nateglinide group increased at 30 minutes (P<0.0001) and at 120 minutes (P=0.0012), with statistical differences between pretreatment and posttreatment. In contrast, compared with baseline, the insulin concentrations at the end point in the acarbose group decreased at 30 minutes and at 120 minutes with statistical differences between pretreatment and post-treatment (both P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Both treatments were well-tolerated.
Chisalita et al.[20] (2009) Repaglinide 4 mg TID before meals for 10 weeks vs insulin aspart 13 to 46 units/day (4 to 20 units at breakfast, 5 to 15 units at lunch and 4 to 15 units at dinner) for 10 weeks	XO Patients ≥60 years of age with type 2 diabetes	N=5 20 weeks	Primary: HbA_{1c}, blood glucose, C-peptide, free human insulin, free total (human and analogue) insulin, proinsulin, islet amyloid polypeptide, growth hormone binding protein, and plasma lipoprotein concentrations were measured Secondary: Not reported	Primary: The HbA_{1c} was 6.1% at the end of repaglinide therapy and 5.9% at the end of insulin aspart therapy (P value not significant). C-peptide concentrations were significantly higher during repaglinide treatment compared to insulin aspart treatment (AUC 2,453 vs 1,153; P=0.02). Free human insulin levels were significantly higher on repaglinide than on insulin aspart therapy (AUC: 215 vs 128; P<0.05). Proinsulin levels were higher when measured during repaglinide treatment than during treatment with insulin aspart. Islet amyloid polypeptide levels tended to be higher during repaglinide compared to insulin aspart treatment (P value not significant). Fasting plasma insulin like growth factor-I concentration was 220 ng/mL during treatment with insulin aspart and 226 ng/mL during treatment with repaglinide (P value not significant). Compared to fasting levels, the insulin like growth factor binding protein-1 levels were lower during repaglinide (P<0.05), but not during insulin aspart treatment (P value not significant). Repaglinide treatment increased plasma growth hormone binding protein concentration compared with insulin aspart (1,094 vs 942 pmol/L; P=0.02). Repaglinide treatment resulted in higher postprandial plasma TC, TG and apolipoprotein B concentrations compared with insulin aspart. There was no significant difference in LDL-C or HDL-C Secondary: Not reported
Lund et al.[21]	DD, XO	N=96	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2008) Repaglinide 2 mg TID for 4 months vs metformin 1,000 mg BID for 4 months	Non-obese (BMI ≤27 kg/m^2), insulin-naïve patients with type 2 diabetes mellitus	8 months with 1 month washout	Cardiovascular disease biomarkers and metabolic regulation Secondary: Not reported	Levels of tumor necrosis factor-alpha, plasminogen activator inhibitor-1 antigen, tissue-type plasminogen activator antigen, von Willebrand factor, soluble intercellular adhesion molecule-1 and soluble E-selectin were significantly lower during metformin treatment compared with repaglinide treatments. Amadori albumin and heart rate were higher during metformin compared with repaglinide. Both treatment groups experienced similar levels of interleukin-6, fibrinogen, soluble vascular cell adhesion molecule-1, asymmetric dimethylarginine and advanced glycation end products as well as glycemic levels and 24 hour BP. Secondary: Not reported
Lund et al.[22] (2008) Repaglinide 2 mg TID for 4 months vs metformin 1,000 mg BID for 4 months	DD, XO Non-obese (BMI ≤27 kg/m^2), insulin-naïve patients with type 2 diabetes mellitus	N=192 8 months with 1 month washout	Primary: Postprandial metabolism with blood sampling 0 to six hours postprandially Secondary: Not reported	Primary: Both treatment groups equally changed fasting levels and total AUC for plasma glucose, TG and FFA. The metformin treatment group obtained lower fasting levels and AUC of TC, LDL-C, and non-HDL-C and serum insulin compared with repaglinide. After adjusting for fasting levels, AUC differences still remained significant. Secondary: Not reported
Fang et al.[23] (2014) Repaglinide vs metformin	OL, PG, RCT Chinese drug-naive patients aged 20 to 90 years with newly diagnosed type 2 diabetes mellitus with a BMI of 18.5 to 30 kg/m^2 and	N=60 15 weeks	Primary: Change in HbA_{1c} from baseline Secondary: Changes in glycemic variability, insulin	Primary: At week 15, mean changes in HbA_{1c} from baseline were -1.8±1.5% in the repaglinide group (P<0.01) and -1.6±1.5% in the metformin group (P<0.01). No significant difference was found with regard to change in HbA_{1c} level between the two groups (P=0.739).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	with an HbA_{1c} <10.0%		sensitivity, β-cell function	Secondary: No significant differences in secondary outcomes were found between the groups.
Bolen et al.[24] (2007) Meglitinides vs biguanides vs TZDs vs α-glucosidase inhibitors vs second-generation sulfonylureas	MA (Analysis of 216 controlled trials and cohort studies, and 2 SRs) Patients with type 2 diabetes	N=136 (articles on intermediate outcomes) N=167 (articles on adverse events) N=68 (articles on micro-vascular outcomes and mortality) Duration varied	Primary: Intermediate outcomes: HbA_{1c}, body weight, BP, lipid panels, all-cause mortality, cardiovascular morbidity and mortality, microvascular outcomes Secondary: Adverse events: hypoglycemia, gastrointestinal problems, congestive heart failure, edema or hypervolemia, lactic acidosis, elevated liver enzymes, allergic reactions requiring hospitalization, other serious adverse events	Primary: Results from clinical trials showed that most oral agents including TZDs, metformin, and repaglinide improved glycemic control to the same degree as sulfonylureas (absolute decrease in HbA_{1c} level of about 1%). Nateglinide and α-glucosidase inhibitors have slightly weaker effects, on the basis of indirect comparisons of placebo-controlled trials. TZDs were the only class with beneficial effect on HDL-C (mean relative increase, 3 to 5 mg/dL) but a harmful effect on LDL-C (mean relative increase, 10 mg/dL) compared to other oral agents. Metformin decreased LDL-C levels by about 10 mg/dL, whereas other oral agents had no effects on LDL-C. TZDs, second-generation sulfonylureas, and metformin had similarly minimal effects on SBP. Most agents except metformin increased body weight by 1 to 5 kg. In the ADOPT (A Diabetes Outcome Progression Trial), the incidence of cardiovascular events was lower with glyburide compared to rosiglitazone or metformin (1.8, 3.4, and 3.2%, respectively; P<0.05). In the RECORD study (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of glycemia in Diabetes), rosiglitazone plus metformin or a sulfonylurea compared to metformin plus a sulfonylurea had a HR of 1.08 (95% CI, 0.89 to 1.31) for the primary end point of hospitalization or death from cardiovascular disease. The HR was driven by more congestive heart failure in the rosiglitazone plus metformin group compared to the control group of metformin plus sulfonylurea (absolute risk, 1.7 vs 0.8%, respectively). Too few comparisons were made to draw firm comparative conclusions on microvascular outcomes.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: According to several RCTs and some OS trials, sulfonylureas and repaglinide were associated with greater risk for hypoglycemia. In many RCTs, TZDs were associated with a higher risk for edema than sulfonylureas or metformin (absolute risk difference, 2 to 21%). In cohort studies, TZDs were associated with higher risk for congestive heart failure although absolute risks were small (1 to 3%) and higher risk for mild anemia yet produced similarly low rates of elevated aminotransferase levels (<1%) compared to sulfonylureas and metformin. In many trials and a few OS trials, metformin was associated with greater risk for gastrointestinal problems compared to other oral diabetes agents. According to a SR of 176 comparative trials, lactic acidosis events were similar between metformin and other oral diabetes agents.
Monami et al.[25] (2008) Metformin vs sulfonylureas, α-glucosidase inhibitors, TZDs, glinides, GLP-1 agonists	MA Patients with type 2 diabetes mellitus	N=7,890 (27 RCT) Variable duration	Primary: Reduction in HbA_{1c} at 16 to 36 months Secondary: Not reported	Primary: Combining the results of different placebo-controlled trials, sulfonylurea, α-glucosidase inhibitors, and TZDs led to a reduction in HbA_{1c} by -0.85% (95% CI, 0.78 to 0.94], -0.61% (95% CI, 0.55 to 0.67), and -0.42% (95% CI, 0.40 to 0.44), respectively when combined with metformin. In direct comparisons, sulfonylureas led to a greater reduction in HbA_{1c} (0.17%; 95% CI, 0.16 to 0.18; P<0.05) than TZDs. Differences between sulfonylureas and α-glucosidase inhibitors, and between α-glucosidase inhibitors and TZDs, were not statistically significant. Secondary: Not reported
Saenz et al.[26] (2005) Metformin monotherapy vs	MA (29 RCTs) Adult patients with type 2 diabetes	N=5,259 ≥3 months	Primary: Incidence of any diabetes-related outcomes (sudden death, death from hyperglycemia or hypoglycemia, fatal or nonfatal	Primary: Obese patients receiving metformin showed a greater benefit than chlorpropamide, glibenclamide*, or insulin for any diabetes-related outcomes (P=0.009) and for all-cause mortality (P=0.03). Obese patients receiving metformin showed a greater benefit than overweight patients on conventional treatment (diet) for any diabetes-

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo, sulfonylureas, TZDs, meglitinides, α-glucosidase inhibitors, diet, any other oral antidiabetic intervention, insulin			MI, angina, heart failure, stroke, renal failure, amputation [of at least one digit], vitreous hemorrhage, retinopathy requiring photocoagulation, blindness in one eye, or cataract extraction); diabetes-related death (death from MI, stroke, peripheral vascular disease, renal disease, hypo-glycemia or hyperglycemia, and sudden death); all-cause mortality Secondary: Changes in HbA_{1c}, FPG, quality of life, weight, BMI, lipids, insulin, C-peptide, BP, micro-albuminuria, glomerular filtration rate, renal plasma flow	related outcomes (P=0.004), diabetes-related death (P=0.03), all cause mortality (P=0.01), and MI (P=0.02). Secondary: Patients receiving metformin monotherapy showed a significant benefit for glycemic control, weight, dyslipidemia, and DBP. Metformin presents a strong benefit for HbA_{1c} when compared to diet and placebo. Additionally, metformin showed a moderate benefit for glycemic control, LDL-C, and BMI or weight when compared to sulfonylureas.
Gangji et al.[27] (2007)	MA (21 trials)	N=not reported	Primary: Hypoglycemia, glycemic control,	Primary: Glyburide was associated with a 52% higher risk of experiencing at least one episode of hypoglycemia compared to other secretagogues (RR, 1.52;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Glyburide vs sulfonylureas, meglitinides, insulin	Patients with type 2 diabetes	Duration varied	cardiovascular events, body weight, death Secondary: Not reported	95% CI, 1.21 to 1.92) and with an 83% higher risk compared to other sulfonylureas (RR, 1.83; 95% CI, 1.35 to 2.49). Glyburide was not associated with a higher risk of cardiovascular events (RR, 0.84; 95% CI, 0.56 to 1.26), death (RR, 0.87; 95% CI, 0.70 to 1.07), or end-of-trial weight (95% CI, -0.4 to 3.80) compared to other secretagogues. Secondary: Not reported
Richter et al.[28] (2007) Rosiglitazone monotherapy (10 trials) vs glyburide (2 trials), metformin (3 trials), pioglitazone (1 trial), placebo (5 trials), or repaglinide (1 trial) or rosiglitazone combination therapy vs a similar combination with another compound (8 trials) Some studies had more than 1 treatment arm.	MA of DB (11) or OL (5) RCTs (last search conducted in April 2007, included the ADOPT trial), PG Adults with type 2 diabetes, trial duration of at least 24 weeks	18 trials N=3,888 randomized to rosiglitazone treatment (total N not reported) 24 weeks to 4 years (median 26 weeks)	Primary: Patient-oriented outcomes including mortality, morbidity, adverse effects Secondary: Health-related quality of life, metabolic control (HbA_{1c})	Primary: No study included mortality as a primary or secondary end point. While not an initial primary or secondary study end point, the ADOPT trial reported that the all-cause mortality was 2.3% in the rosiglitazone group, 2.1% in the metformin group and 2.2% in the glyburide group (P values not reported in this reference). The ADOPT trial also reported comparable hospitalization rates for any cause between rosiglitazone (11.6%), metformin (11.8%), and glyburide (10.4%) groups (P values were not reported in this reference). Cardiovascular disease was increased in the rosiglitazone group compared to the glyburide group but not the metformin group with serious/total events reported in 3.4/4.3% and 1.8/2.8% of patients receiving rosiglitazone and glyburide, respectively (events were 3.2/4.0% with metformin; P values were not reported in this reference). Congestive heart failure was observed more frequently in patients receiving rosiglitazone (1.5%) than patients receiving glyburide (0.6%) but not metformin (1.3%; P values were not reported in this reference). The percentage of overall adverse events was comparable between the intervention and control groups (which included placebo arms); serious adverse events appeared to happen more often after rosiglitazone treatment (median of 6 vs 4% in the control groups; P value not reported). Median discontinuation rate following rosiglitazone administration was also higher than after control therapy (median of 7 vs 4%; P value not reported). Three studies reported a more pronounced (apparently dose-related) decrease of hemoglobin after rosiglitazone intake in comparison to other active

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				compounds or placebo; hemoglobin reductions ranged between 0.5 and 1.0 g/dL. Eleven studies evaluated body weight and observed an increase up to 5.0 kg after rosiglitazone treatment; four studies described a rise in body mass index up to 1.5 kg/m^2. Seven of the 18 included studies showed data on hypoglycemic episodes: compared to active monotherapy control, rosiglitazone treatment resulted in somewhat lower rates of hypoglycemia, especially when compared to sulfonylureas. Occurrence of edema was significantly raised when results of nine studies were pooled (OR, 2.27; 95% CI, 1.83 to 2.81; P<0.00001). The ADOPT trial reported a higher incidence of fractures in women receiving rosiglitazone (9.30%) than metformin (5.08%; P<0.01) or glyburide (3.47%; P<0.01). Secondary: No study investigated health-related quality of life. Active glucose-lowering compounds like metformin, glibenclamide* or glimepiride resulted in similar reductions of HbA_{1c} compared to rosiglitazone treatment.
Richter et al.[29] (2006) Pioglitazone monotherapy (16 trials) vs acarbose (1 trial), metformin (4 trials), placebo (4 trials), repaglinide (1 trial), rosiglitazone (1 trial), or a sulfonylurea (8 trials) or pioglitazone combination therapy	MA of DB (15) or OL (4) RCTs (last search conducted in August 2006, included PROactive Study), PG Adults with type 2 diabetes, trial duration of at least 24 weeks	22 trials N=6,200 randomized to pioglitazone treatment (total N not reported) 24 weeks to 34.5 months	Primary: Patient-oriented outcomes including mortality, morbidity, adverse effects Secondary: Health-related quality of life, HbA_{1c}	Primary: Only one trial (PROactive Study) evaluated mortality and morbidity as an end point. The primary composite end point (time from randomization to all-cause mortality, nonfatal MI, stroke, acute coronary syndrome, endovascular or surgical intervention on the coronary or leg arteries, or amputation above the ankle) did not show statistically significant differences between the pioglitazone and placebo group (HR, 0.90; 95% CI, 0.80 to 1.02; P=0.095). Time to the first event of the composite end point of death from any cause, MI and stroke indicated a statistically significant difference between pioglitazone and placebo (HR, 0.84; 95% CI, 0.72 to 0.98; P=0.027). The individual components of the primary composite end point did not disclose statistically significant differences between the intervention and control groups. Significantly more patients developed heart failure requiring hospitalization following administration of pioglitazone (6 vs 4% on placebo; P=0.007).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs a similar combination with another compound (9 trials including 2 trials vs rosiglitazone) Some studies had more than 1 treatment arm.				The percentage of overall and serious adverse events was comparable between the intervention and control groups. Six trials reported a more pronounced (sometimes dose-related) decrease of hemoglobin after pioglitazone intake in comparison to other active compounds or placebo; hemoglobin reductions ranged between -0.50 and- 0.75 g/dL. Fifteen trials evaluated body weight and observed an increase up to 3.9 kg after pioglitazone treatment; seven trials described a rise in body mass index up to 1.5 kg/m^2. Eleven of the 22 included trials showed data on hypoglycemic episodes: compared to the active monotherapy control, pioglitazone treatment resulted in somewhat lower rates of hypoglycemia (P value not reported). The RR for development of edema with pioglitazone compared to the control was 2.86 (95% CI, 2.14 to 3.18; P<0.00001) when results from 18 trials were pooled. Secondary: No study investigated health-related quality of life. Active glucose-lowering compounds like metformin, glibenclamide*, gliclazide† or glimepiride resulted in similar reductions of HbA_{1c} compared to pioglitazone treatment (P values not reported).
Kheirbek et al.[30] (2013) Hypoglycemic medications (metformin, glyburide, glipizide, rosiglitazone, acarbose, chlorpropamide, glimepiride, pioglitazone, tolazamide, repaglinide, troglitazone, insulin, and DPP-4 inhibitors)	OS, RETRO Veterans with diabetes cared for at a Veterans Administration Capital area medical center	N=17,773 Variable duration	Primary: All-cause mortality Secondary: Not reported	Primary: After adjustments were made for severity of illness and patient demographics, the remaining variance in mortality was explained by exposure to five medications, listed in order of impact on risk-adjusted mortality: glipizide (OR=1.566), glyburide (OR=1.804), rosiglitazone (OR=1.805), insulin (OR=2.382), and chlorpropamide (OR=3.026). None of the other medications (metformin, acarbose, glimepiride, pioglitazone, tolazamide, repaglinide, troglitazone, and DPP-4 inhibitors) were associated with excess mortality beyond what could be expected from the patients' severity of illness or demographic characteristics. Insulin, glyburide, glipizide, and rosiglitazone continued to be associated with statistically significant increased mortality after controlling for possible drug interactions. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
*Defined as any use of the medication independent of dose or days of use				
Type 2 Diabetes – Combination Therapy				
Raskin et al.[31] (2003) Nateglinide 120 mg TID before meals and metformin 1,000 mg BID vs repaglinide 1 to 4 mg TID before meals and metformin 1,000 mg BID	MC, OL, PG, RCT Patients ≥18 years of age with type 2 diabetes for ≥3 months, BMI 24 to 42 kg/m^2, HbA_{1c} 7.0 to 12.0% on previous monotherapy with a sulfonylurea, metformin, or low dose glyburide plus metformin	N=192 16 weeks	Primary: Final HbA_{1c} values and changes in HbA_{1c} from baseline Secondary: Changes in FPG and assessment of glucose area under the time concentration curves from 0 to 240 minutes ($AUC_{0\text{-}240\ min}$), insulin $AUC_{0\text{-}240\ min}$, and glucagon $AUC_{0\text{-}240\ min}$ after a liquid test meal at baseline and at study end point	Primary: Mean HbA_{1c} changes from baseline were significantly greater in the repaglinide group compared to the nateglinide group (-1.28 vs -0.67%; P<0.001). The final HbA_{1c} at 16 weeks was 7.1±1.1% for the repaglinide group and 7.5±1.4% for the nateglinide group. The percent of patients who achieved final HbA_{1c} values ≤7.0% was 59% for the repaglinide group and 47% for the nateglinide group (P value not reported). Secondary: FPG values were significantly different between the two treatment groups with one week of therapy. Mean changes in FPG values from baseline were significantly greater for the repaglinide group (-39 vs -21 mg/dL for nateglinide group; P=0.002). The final FPG at 16 weeks was 150.0±45.1 mg/dL for the repaglinide group and 170±52 mg/dL for the nateglinide group. At the end of the 16 week maintenance study, 48% of the repaglinide group had reductions of FPG values >40 mg/dL and 26% of the nateglinide group had a response of this magnitude. Mean end point reductions in PPG levels from baseline were not significantly different between the groups (glucose $AUC_{0\text{-}240\ min}$). The treatments were also similar for changes in insulin $AUC_{0\text{-}240\ min}$ and glucagon $AUC_{0\text{-}240\ min}$ during the study (P values not reported). There were no patients in either group who experienced major hypoglycemic episodes (requiring the assistance of another person).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The most frequent adverse event in both groups was upper respiratory infection (12 vs 21%). Adverse events that occurred from 3 to 8% included nausea, viral infection, accidental injury, sinusitis, diarrhea, and headache. The repaglinide group had 5% incidence of chest pain and arthralgia, as compared to 1% for each in the nateglinide groups. Mean changes from baseline in weight were small for both groups, 0.6 kg gain for repaglinide compared to 0.5 kg loss with nateglinide.
Horton et al.[32] (2000) Nateglinide 120 mg TID before each meal and metformin 500 mg TID immediately after the start of each meal vs nateglinide 120 mg TID before each meal vs metformin 500 mg TID immediately after the start of each meal vs placebo	DB, PC, PRO, RCT Patients ≥30 years of age with type 2 diabetes for ≥3 months with a BMI 20 to 35 kg/m^2, and all patients needed to have been treated with diet alone with an HbA_{1c} 6.8 to 11.0% and FPG level ≤15 mmol/L	N=701 24 weeks	Primary: Change in HbA_{1c}, FPG, glucose AUC after Sustacal challenge from baseline Secondary: Not reported	Primary: Adjusted mean change from baseline in HbA_{1c}, FPG, and glucose AUC after Sustacal challenge were significantly reduced from baseline (P≤0.0001) in patients receiving active treatment. HbA_{1c}, FPG, and glucose AUC were all significantly reduced compared to placebo (P≤0.001), except from glucose AUC with metformin monotherapy. The decrease in HbA_{1c} was greater for metformin compared to nateglinide, the between group difference was small (0.3% difference; P≤0.01). The decrease in FPG was greater with the metformin group compared to the nateglinide group, the between group difference was 0.9 mmol/L (P<0.001). The combination of nateglinide plus metformin was additive (HbA_{1c}, -1.4% and FPG, -2.4 mmol/L; P≤0.01 vs either monotherapy). After a Sustacal challenge, there was a greater reduction in mealtime glucose with nateglinide compared to metformin or placebo ($AUC_{0\text{-}130\ min}$, -2.1, -1.1, and 0.6 mmol/hr/L, respectively; P≤0.0001). A greater reduction was seen with nateglinide plus metformin ($AUC_{0\text{-}130\ min}$, -2.5 mmol/hr/L; P≤0.0001 vs metformin and placebo). Secondary: Not reported
Marre et al.[33] (2002)	DB, MC, PG, RCT	N=467 24 weeks	Primary: Change in HbA_{1c} from baseline	Primary: Mean HbA_{1c} was reduced significantly from baseline when compared to the placebo group for the nateglinide 60 mg group (-0.36%; 95% CI, -0.59

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Nateglinide 60 to 120 mg TID before meals and metformin 1,000 mg BID vs metformin 1,000 mg BID and placebo	Patients ≥30 years of age with type 2 diabetes for ≥6 months with HbA_{1c} 6.8 to 11.0%, BMI 20 to 35 kg/m^2, and were treated with metformin for a minimum of 3 months and stabilized at a dose of ≥1,500 mg/day for ≥4 weeks prior to study entry		Secondary: Change in FPG, body weight, and lipid profile (TC, fasting TGs, LDL-C, HDL-C)	to -0.13; P=0.003) and for the nateglinide 120 mg group (-0.51%; 95% CI, -0.82 to -0.36; P<0.001) at end point. Dose-dependent reduction in HbA_{1c} was seen with nateglinide irrespective of baseline parameters, with larger mean reductions seen with nateglinide 120 mg. There was little or no change in HbA_{1c} at end point in the placebo group. Secondary: There were modest changes from baseline in FBG in the nateglinide groups and an increase was seen in the placebo group, the difference compared to baseline was significant in both the nateglinide 60 and 120 mg groups (P=0.044 and P=0.003, respectively). There were no notable changes in body weight at end point in the patients that received placebo (0.1 kg) or nateglinide 60 mg (0.4 kg). There was a significant increase (P<0.001) in mean weight of 0.9 kg in the nateglinide 120 mg group as compared to baseline. Fasting TGs were significantly reduced in the nateglinide 120 mg group as compared to the placebo group at end point (P=0.042). The mean changes in TC, LDL-C, and HDL-C remained almost unchanged throughout the study.
Gerich et al.[34] (2003) Nateglinide 120 mg TID before meals and metformin 500 to 2,000 mg daily vs glyburide 1.25 to 10 mg daily and metformin 500 to 2,000 mg daily	DB, MC, RCT (PRESERVE-β Study) Men and women aged 18 to 77 years with type 2 diabetes, drug naïve, HbA_{1c} 7.0 to 11.0%, FPG ≤15 mmol/L, BMI of 22 to 45 kg/m^2 and inadequately	N=428 104 weeks	Primary: Change in HbA_{1c} from baseline (average of weeks -2 and 0) to week 104 Secondary: Change from baseline to week 104 in FPG, and body weight	Primary: Both treatments maintained similar reductions in HbA_{1c}. The mean change in HbA_{1c} from baseline to week 104 in the nateglinide plus metformin group (–1.2 ±0.1%) was similar (P=0.1730) to that in the glyburide plus metformin group (–1.5 ±0.1%). The changes in HbA_{1c} were significant for both groups as compared to baseline (P<0.0001) after one and two years of treatment and there was no significant difference between the groups. Secondary: Mean change in FPG was –1.6±0.2 mmol/L in patients in the nateglinide plus metformin group (P<0.0001 vs baseline) and –2.4±0.2 mmol/L in patients in the glyburide plus metformin group (P<0.0001 vs baseline; P=0.0078 vs nateglinide plus metformin).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	controlled on diet and exercise			Body weight decreased in the nateglinide plus metformin group (–0.4 kg±0.4 kg) and increased in the glyburide plus metformin group (0.8 kg±0.5 kg). The change from baseline was significant for the glyburide plus metformin group (P=0.0011) only (P=0.8413 for the nateglinide plus metformin group). The difference between groups was statistically significant (P=0.0115).
Schwarz et al.[35] (2008) Nateglinide 120 mg TID before meals and metformin 2,000 mg QD vs glyburide 10 mg QD and metformin 2,000 mg QD	AC, DB, MC, RCT (PRESERVE-β Study – subgroup analysis) Men and women ≥65 years of age with type 2 diabetes, drug naïve, HbA_{1c} 7.0 to 11.0%, FPG ≤15 mmol/L, BMI 22 to 45 kg/m^2	N=69 104 weeks	Primary: Change in HbA_{1c} from baseline Secondary: Change from baseline to week 104 in FPG, two-hour PPG using the incremental AUC ($AUC_{0\text{-}120\ min}$) of glucose during oral glucose tolerance tests, the proportion of patients achieving a target HbA_{1c} <7.0 or ≤6.5%, adverse events	Primary: Similar reductions in HbA_{1c} were seen with both treatments. The average change in HbA_{1c} from baseline to week 104 in the nateglinide plus metformin group (–1.2±0.2%) was similar (P=0.310) to that in the glyburide plus metformin group (–1.2±0.1%). The changes in HbA_{1c} were significant for both groups as compared to baseline (P<0.001) after two years of treatment and there was no significant difference between the groups. Secondary: Mean change in FPG was –26±6 mg/dL in patients receiving nateglinide plus metformin (P<0.001 vs baseline) and –36±6 mg/dL in patients receiving glyburide plus metformin (P<0.001 vs baseline) (P=0.234 between the groups). A non-significant reduction in two-hour PPG from baseline was reported in both the nateglinide plus metformin and glyburide plus metformin groups (–15±7 mg/dL; P=0.071 and –8±8 mg/dL; P=0.385, respectively). The proportion of patients who achieved a target HbA_{1c} <7.0% in the nateglinide plus metformin group was not significantly different compared to the glyburide plus metformin group (70 vs 65%, respectively; P=0.736). Similar proportions of patients in the nateglinide plus metformin group and the glyburide plus metformin group maintained a target HbA_{1c} ≤6.5% (40 and 60%, respectively; P=0.206). Approximately 94% of patients in the nateglinide plus metformin group and 88% of patients in the glyburide plus metformin group reported one or more adverse events. One mild hypoglycemic event occurred with

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				nateglinide plus metformin treatment vs eight mild-to-severe hypoglycemic events with glyburide plus metformin treatment (P<0.023).
Fonseca et al.[36] (2003) Nateglinide 120 mg before each meal and rosiglitazone 8 mg QD vs rosiglitazone 8 mg QD and placebo	DB, MC, PC, RCT Patients ≥21 years of age with type 2 diabetes for ≥6 months previously and treated with rosiglitazone 8 mg/day, diet, and exercise for ≥3 months, had a BMI 22 to 40 kg/m^2, FPG 6.1 to 13.3 mmol/L, and HbA_{1c} 7.0 to 11.0%	N=402 24 weeks	Primary: Change in baseline HbA_{1c} Secondary: FPG, two-hour postprandial insulin, TC, LDL-C, HDL-C, TG, body weight, four-hour AUC for glucose, insulin during meal challenges	Primary: HbA_{1c} did not change significantly from baseline in the placebo group, but did change significantly in the nateglinide group. The change from baseline to end point was -0.8±0.1% (P<0.0001 vs baseline or placebo). Secondary: Change in FPG decreased significantly from a baseline of 9.8 to 9.0 mmol/L in the nateglinide group (P<0.001). FPG did not change significantly from the baseline (10 mmol/L) in patients receiving placebo. Two-hour postprandial insulin in the nateglinide group decreased from 14.0 to 11.4 mmol/L (P<0.0001). The group receiving placebo had an increase in two-hour postprandial insulin from 14.4 to 14.8 mmol/L (P<0.0001 vs nateglinide). Total and incremental glucose $AUCs_{(0\text{-}4\ hours)}$ were significantly reduced in the nateglinide group (-8.6±0.8 and -6.2±0.5 mmol/L/hr, respectively; P<0.0001 vs baseline or placebo for both total and incremental AUCs). This represents a 16% reduction in the total and a 49% reduction in the incremental glucose AUC. Total and incremental insulin $AUCs_{(0\text{-}4\ hour)}$ were increased in the nateglinide group (425 and 395 pmol/L/hr, respectively; P<0.0001 vs baseline or placebo plus for both total and incremental AUCs). This represents a 46% increase in the total and 69% increase in the incremental insulin AUC. There were no significant changes in TC, LDL-C, or TG in either group. There was a small, but significant increase from baseline in HDL-C observed in patients receiving nateglinide (P<0.025) and in patients receiving placebo (P<0.005). Body weight increased in both groups. The mean change from baseline in patients receiving nateglinide (3.1±0.3 kg) was significantly greater compared to patients receiving placebo (1.1±0.3 kg; P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Meal challenges were performed at week 0 and at end point. The glucose and insulin profiles were similar in the two groups at baseline, and PPG and insulin concentrations were unchanged at end point relative to baseline in patients receiving placebo.
Moses et al.[37] (1999) Repaglinide 0.5 to 4 mg TID before each meal and metformin 1,000 to 3,000 mg daily vs repaglinide 0.5 to 4 mg TID before each meal vs metformin 1,000 to 3,000 mg daily	DB, MC, PG, RCT Patients 40 to 75 years of age with type 2 diabetes treated with metformin alone (1 to 3 g/day) for >6 months and had not achieved optimal glycemic control (HbA_{1c} >7.0%) and BMI ≥21 kg/m^2	N=83 3 months	Primary: Change in baseline HbA_{1c} and FPG Secondary: Change in fasting insulin, C-peptide levels, fasting TG, TC, HDL-C, LDL-C, free fatty acids, body weight	Primary: Patients in the metformin plus repaglinide group had a significant decrease in HbA_{1c} from 8.3 to 6.9% (P=0.0016) and FPG from 10.2 to 8.0 mmol/L (P=0.0003) compared to baseline. There were no significant changes in HbA_{1c} or FPG for patients receiving metformin alone and repaglinide alone. The HbA_{1c} and FPG changes from baseline for metformin plus repaglinide vs metformin alone and metformin plus repaglinide vs repaglinide were significant (P<0.05 for all). Secondary: Fasting insulin and C-peptide levels increased significantly from baseline in both groups receiving repaglinide (P<0.05 for both). Lipid levels (TC, HDL-C, LDL-C, TG, FFA) did not change significantly from baseline in the metformin plus repaglinide group. No significant differences were found between the metformin plus repaglinide group and the monotherapy groups. In both groups receiving repaglinide there was an increase in body weight which was significant compared to baseline (P<0.05 for both).
Raskin et al.[38] (2004) Repaglinide 0.5 to 4 mg TID before meals and rosiglitazone 2 to 4 mg BID vs	MC, OL, PG, RCT Patients ≥18 years of age with type 2 diabetes for ≥12 months with an HbA_{1c} >7.0 to ≤12.0% during previous monotherapy with sulfonylurea or metformin for ≥3	N=252 24 weeks	Primary: Change in baseline HbA_{1c} Secondary: Change in baseline FPG	Primary: Mean change in HbA_{1c} from baseline with repaglinide was -0.17% and -0.56% with rosiglitazone. The mean change in HbA_{1c} from baseline with combination therapy was -1.43 (P≤0.001 vs either monotherapy). The reduction in HbA_{1c} from baseline was greater with combination therapy compared to the sum of the responses for monotherapy (P<0.01). Secondary: Mean FPG change from baseline with repaglinide was -3 mmol/L and -3.7 mmol/L with rosiglitazone. Mean FPG change from baseline with combination therapy was -5.2 mmol/L (P≤0.001 vs either monotherapy).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
repaglinide 0.5 to 4 mg TID before meals vs rosiglitazone 2 to 4 mg BID	months with a BMI ≤45 kg/m^2			
Ozbek et al.[39] (2006) Repaglinide 4.5 mg QD vs placebo All patients were also receiving insulin.	RCT Patients with type 2 diabetes who had been initially treated with oral antidiabetic agents without a satisfactory response (HbA_{1c} <7.0%), hospitalized in a single center for glycemic control with intensive insulin therapy involving multiple daily subcutaneous injections	N=50 3 months	Primary: Exogenous insulin requirements, HbA_{1c}, hypoglycemia Secondary: Not reported	Primary: A significant reduction in daily total exogenous insulin requirements was seen in the repaglinide group. The daily total insulin requirements were 57.4±14.8 and 28.8±13.8 units before and after the three month study period, respectively (P<0.01). Serum HbA_{1c} levels were 7.3±0.3 and 6.4±0.3% before and after the three month period in the repaglinide group (P<0.01). None of the patients experienced symptomatic hypoglycemia episode. Secondary: Not reported
Civera et al.[40] (2008) Repaglinide 2mg TID before meals, metformin 850mg BID, and NPH insulin before dinner vs	OL, PG Patients with poorly controlled type 2 diabetes despite being on two or more oral antidiabetic drugs	N=37 24 weeks	Primary: HbA_{1c}, hypoglycemia, body weight Secondary: Not reported	Primary: The HbA_{1c} was lower in the repaglinide triple therapy group (7.2%) compared to the metformin plus NPH insulin group (8.8%; P=0.02) and the NPH insulin group (8.4%; P=0.02). The absolute reduction in HbA_{1c} was -2.4% in the repaglinide triple therapy group compared to -0.7% (P=0.01) in the metformin plus NPH insulin group and -1.4% in the insulin NPH group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
metformin 850mg BID and NPH insulin before dinner vs NPH insulin BID				Lower PPG values were seen with the repaglinide triple therapy group compared to the other two treatment groups (P<0.01). Significant differences in weight gain and hypoglycemia were not seen. Secondary: Not reported
Wang et al.[41] (abstract) Repaglinide 1 mg TID, titrated up to 4 mg TID vs repaglinide 1 mg TID plus metformin 500 mg TID, titrated up to 4 mg TID and 500 mg TID	AC, OL, PG, RCT Patients 18 to 75 years of age with type 2 diabetes, HbA_{1c} >8.5%, BMI ≤35 kg/m^2, and who were naïve to oral antidiabetic agents,	N=432 16 weeks	Primary: Change in baseline HbA_{1c} Secondary: FPG, two-hour PPG, seven-point plasma glucose, safety	Primary: Mean HbA_{1c} reduction was 4.51±1.64% with combination therapy and 4.05±1.59% with repaglinide. Estimated mean treatment difference for combination therapy vs repaglinide was -0.30% (95% CI, -0.49 to -0.11; P< 0.01). Secondary: Combination therapy demonstrated significant improvements compared to repaglinide in FPG, seven-point plasma glucose, and lunchtime and dinnertime two-hour PPG (P<0.05 for all). Hypoglycemia rates were 2.04 events/patient-year with combination therapy compared to 1.35 events/patient-year with repaglinide (P=0.058). Adverse events were comparable between the two treatments.
Derosa et al.[42] (2009) Nateglinide 60 mg TID and metformin 1,500 to 3,000 mg daily vs glyburide 7.5 to 12.5 mg daily and metformin 1,500 to 3,000 mg daily	DB, MC, PG, RCT Patients ≥18 years of age with type 2 diabetes mellitus, HbA_{1c} >7.0%), BMI 25 to 28 kg/m^2, and hypertensive (SBP/DBP, >130/≥85 mmHg)	N=248 12 months	Primary: Changes in BMI, FPG and PPG, HbA_{1c}, fasting and postprandial plasma insulin, HOMA index, and lipid profile [TC, LDL-C, HDL-C, TG, apolipoprotein A-I, and apolipoprotein B, SBP, and DBP Secondary:	Primary: BMI did not show any significant change during the study. A significant reduction in HbA_{1c} was shown after nine months (P<0.05) and 12 months (P<0.01) in the nateglinide group compared to the baseline value. A significant reduction in HbA_{1c} was seen with glyburide after 12 months (P<0.05) compared to baseline. The HbA_{1c} at 12 months was 6.4% in the nateglinide group compared to 7.3% in the glyburide group (P<0.05). After nine and 12 months, mean FPG levels were significantly decreased in the nateglinide and glyburide groups (P<0.05 and P<0.01, respectively) compared to baseline.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Not reported	Significant changes in PPG were found at nine months (P<0.05) in the nateglinide group and after 12 months in glyburide and nateglinide groups (P<0.05 and P<0.01, respectively) compared to baseline. Fasting plasma insulin and postprandial insulin did not show any significant change after three, six, nine and 12 months in both groups compared to the baseline. HOMA index decrease was obtained only at 12 months (P<0.05) compared to the baseline value in both groups, No significant change was observed in TC, LDL-C, HDL-C, TG, apolipoprotein A-I, apolipoprotein B, SBP, DBP and heart rate in either group after three, six, nine and 12 months. Secondary: Not reported
Swinnen et al.[43] (2010) Continuation of secretagogues (sulfonylureas or meglitinides) vs discontinuation of secretagogues (sulfonylureas or meglitinides) All patients received existing metformin regimens and initiated insulin therapy.	PRO Patients 40 to 75 years of age with type 2 diabetes, HbA_{1c} 7.0 to 10.5% receiving oral glucose-lowering drugs	N=865 24 weeks	Primary: Change in HbA_{1c} Secondary: Hypoglycemia, body weight, insulin dose	Primary: In patients continuing secretagogue treatment, HbA_{1c} decreased to 7.0±0.8% at week 12 compared to 7.4±0.9% in patients discontinuing their secretagogues. Endpoint HbA_{1c} level was 7.2±0.9% in both treatment groups. The difference in mean HbA_{1c} reduction during the trial was not significant (-1.59±1.08% for patients continuing secretagogues and -1.30±1.14% for patients discontinuing secretagogues; P=0.382). Secondary: Compared to patients who discontinued secretagogues, patients who continued secretagogues experienced significantly more hypoglycemia (40.0 vs 24.5%; P<0.001) and gained significantly more weight (1.44±3.04 vs 0.43±3.00 kg; P<0.001). End of trial insulin doses, were significantly lower in patients who continued secretagogues compared to patients who discontinued secretagogues (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Black et al.[44] (2007) Meglitinide vs meglitinide and metformin vs meglitinide and insulin vs metformin vs placebo	MA (15 trials) Patients with type 2 diabetes	N=3,781 Duration varied	Primary: Mortality and morbidity Secondary: Change in HbA_{1c}, weight or BMI, hypoglycemia, adverse effects, quality of life	Primary: No trials reported the effect of meglitinides on mortality and morbidity. Secondary: In the 11 trials comparing meglitinides to placebo, both repaglinide and nateglinide resulted in reductions in HbA_{1c} (0.1 to 2.1% and 0.2 to 0.6%, respectively). In two trials comparing repaglinide to nateglinide, reduction in HbA_{1c} was similar. When compared to metformin, both repaglinide and nateglinide showed similar or slightly smaller reduction in HbA_{1c} compared to metformin. The combination therapy of metformin plus a meglitinide showed a clinically significant reduction in HbA_{1c} compared to metformin. Weight gain was generally greater in patients receiving meglitinides compared to patients receiving metformin. Evidence from the meglitinide trials with metformin suggests that both repaglinide and nateglinide had fewer gastrointestinal adverse events including diarrhea. There was no evidence of serious adverse events associated with meglitinides. There were more reports of hypoglycemia episodes in patients receiving meglitinides compared to patients receiving placebo. In the two head-to-head trials of repaglinide and nateglinide, fewer patients receiving nateglinide reported hypoglycemia symptoms (2 vs 7%). When compared to metformin, patients receiving meglitinides reported more hypoglycemia episodes. There were two trials that assessed quality of life in patients receiving repaglinide vs placebo and in patients receiving repaglinide plus insulin vs metformin plus insulin. There were no substantial changes in quality of life using a variety of validated diseases specific and nonspecific tools. Treatment satisfaction using the World Health Organization DTSQ improved significantly in patients receiving repaglinide compared to patients receiving placebo.
Mearns et al.[45] (2015)	Network MA (62 RCTs)	N=32,185	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Hypoglycemic medications (Alpha-glucosidase inhibitors, DPP-4 inhibitors, colesevelam, meglitinides, GLP-1 analogs, long-acting, once-daily basal insulin, SGLT2 inhibitors, sulfonylureas, TZDs, and combinations of the above agents)	Patients with inadequately controlled type 2 diabetes on metformin alone	3 to 12 months	Changes in HbA_{1c}, body weight, and SBP; risk of developing hypoglycemia and urinary and genital tract infection Secondary: Not reported	All agents significantly reduced HbA_{1c} vs placebo; although, not to the same extent (range, 0.43% for miglitol to 1.29% for glibenclamide). Glargine, sulfonylureas, and nateglinide were associated with increased hypoglycemia risk vs placebo. SGLT2 inhibitors, GLP-1 analogs, miglitol, and empagliflozin/linagliptin significantly reduced body weight (range, 1.15 to 2.26 kg) whereas sulfonylureas, TZDs, glargine, and alogliptin/pioglitazone caused weight gain (range, 1.19 to 2.44 kg). SGLT2 inhibitors, empagliflozin/linagliptin, liraglutide, and sitagliptin decreased SBP (range, 1.88 to 5.43 mmHg). No therapy increased UTI risk vs placebo; however, SGLT2 inhibitors were associated with an increased risk of genital tract infection (RR range, 2.16 to 8.03). Secondary: Not reported

*Synonym for glyburide.
†Product not available in the United States.
Drug regimen abbreviations: BID=twice daily, QD=once daily, TID=three times daily
Study abbreviations: AC=active-comparator, DB=double-blind, DD=double-blind, MA=meta-analysis, MC=multicenter, OL=open-label, OS=observational, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, SR=systematic review, XO=cross-over
Miscellaneous abbreviations: AUC=area under the curve, BMI=body mass index, BP=blood pressure, CI=confidence interval, DBP=diastolic blood pressure, DTSQ=Diabetes Treatment Satisfaction Questionnaire, FFA=free fatty acid, FPG=fasting plasma glucose, GLP-1=Glucagon-like peptide-1, HbA_{1c}=glycosylated hemoglobin, HDL-C=high density lipoprotein cholesterol, HOMA-IR=homeostasis model assessment-estimated insulin resistance, HR=hazard ratio, LDL-C=low density lipoprotein cholesterol, MI=myocardial infarction, NPH=neutral protamine Hagedorn, OR=odds ratio, PPG=postprandial plasma glucose, RR=relative risk, SBP=systolic blood pressure, TC=total cholesterol, TG=triglyceride, TZD=thiazolidinedione

Additional Evidence

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

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

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

IX. Cost

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

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

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

Rx=prescription

Table 9. Relative Cost of the Meglitinides

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Single Entity Agents				
Nateglinide	tablet	N/A	N/A	$$
Repaglinide	tablet	N/A	N/A	$

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

X. Conclusions

The meglitinides are approved for use as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.[1-3] All of the agents are available in a generic formulation.

The goal of treatment for type 2 diabetes is to control hyperglycemia and reduce the risk of long-term complications. A notable new theme in diabetes treatment guidelines is an emphasis on a complication-centric approach, beyond glucose levels, to frame decisions regarding first-line pharmacologic choices for the treatment of persons with diabetes. Pharmacologic therapy should be guided by person-centered treatment factors, including comorbidities and treatment goals. In adults with type 2 diabetes and established/high risk of atherosclerotic cardiovascular disease, heart failure, and/or chronic kidney disease, the treatment regimen should include agents that reduce cardiorenal risk. Pharmacologic approaches that provide adequate efficacy to achieve and maintain treatment goals should be considered, such as metformin or other agents, including combination therapy.[4-7]

Clinical guidelines note that meglitinides are associated with a limited HbA_{1c}-lowering ability, weight gain, and a greater risk of inducing hypoglycemia compared to other available antidiabetic medications. The American Association of Clinical Endocrinologists recommend that the meglitinides be considered as alternative therapy but should be used with caution due to the adverse event profile.[6,7] Among clinical guidelines, preference of one meglitinide over another is not stated.[4-9]

The meglitinides have been evaluated in a variety of clinical trials. Three studies have directly compared nateglinide and repaglinide, either as monotherapy or in combination with metformin. In all three studies, the mean change in HbA_{1c} from baseline was greater with repaglinide compared to nateglinide.[10-11,31] The meglitinides have also been compared to sulfonylureas in monotherapy studies. Glyburide was found to be more effective than nateglinide in one study, whereas glyburide and repaglinide were found to be equally efficacious in another study.[12-13] The combination of nateglinide and metformin was shown to be as effective, or more effective, than the combination of glyburide and metformin in two studies.[34,42] Several studies evaluated the efficacy of meglitinides in dual therapy regimens compared to monotherapy regimens. In these studies, the more aggressive treatment regimens improved glycemic parameters to a greater extent than the less-intensive treatment regimens.[32-33,36-39]

There is insufficient evidence to support that one brand meglitinide is safer or more efficacious than another within its given indication. Since the meglitinides are not recommended as first-line therapy for the treatment of type 2 diabetes mellitus, formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand products 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 meglitinide 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 Sodium-glucose Cotransport 1 Inhibitors
AHFS Class 682017
November 8, 2023

I. Overview

Currently there are no prescription medications classified by American Hospital Formulary Service (AHFS) as Sodium-glucose Cotransport 1 Inhibitors.

II. Conclusions

There are no prescription medications available in the sodium-glucose cotransport 1 inhibitors class (AHFS Class 682017).

III. Recommendations

No sodium-glucose cotransport 1 inhibitor is recommended for preferred status. Alabama Medicaid should continue to include AHFS Class 682017 in the Preferred Drug List screening process. If new prescription sodium-glucose cotransport 1 inhibitors are added, it is recommended that this class be re-reviewed.

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Sodium-glucose Cotransport 2 Inhibitors
AHFS Class 682018
November 8, 2023

I. Overview

Diabetes mellitus is a chronic condition which results in hyperglycemia. It is differentiated into four main classes: 1) type 1 diabetes; 2) type 2 diabetes; 3) gestational diabetes; and 4) other types (drug- or chemical-induced, genetic defects in β-cell function or insulin action, and diseases of the exocrine pancreas). Type 2 diabetes is the most prevalent form of the disease in the United States. Inadequate glycemic control may lead to both acute and long-term complications, including microvascular and macrovascular events. There are a variety of oral and injectable antidiabetic agents currently available to treat diabetes. The antidiabetic agents are categorized into 12 different American Hospital Formulary Service (AHFS) classes, which differ with regards to their mechanism of action, efficacy, safety profiles, tolerability, and ease of use.

Sodium-glucose cotransport 2 (SGLT2) inhibitors are a novel class of oral antidiabetic agents initially approved by the Food and Drug Association (FDA) in 2013. The kidneys play a pivotal role in controlling plasma glucose concentration, reabsorbing nearly all plasma glucose in the proximal tubules and preventing glucose excretion in patients with normal glucose-tolerance. Approximately 90% of the filtered renal glucose is reabsorbed in the early convoluted segment of the proximal tubule and is facilitated by the SGLT2 transporter. The remaining 10% of filtered glucose is reabsorbed in the distal straight segment of the proximal tube by the SGLT1 transporter. In diabetic patients, the SGLT transporter system is often overwhelmed and unable to reabsorb all filtered plasma glucose due to hyperglycemic conditions. Once this threshold capacity is reached and surpassed, excess glucose that is not reabsorbed is excreted into the urine. In addition, a chronic elevated plasma glucose concentration provides the stimulus that ultimately leads to increased SGLT2 expression by the renal proximal tubular cells, resulting in an undesirable increase in renal capacity and threshold to reabsorb filtered glucose in both type 1 and type 2 diabetic patients.[1,2]

SGLT2 inhibitors improve glycemic control by producing glucosuria. This is accomplished by inhibiting SGLT2 and increasing urinary glucose excretion. The net effect is an increase excretion of glucose from the body and normalizing plasma glucose levels. SGLT2 inhibitors reduce reabsorption of filtered glucose and lower the renal threshold for glucose, and thereby increasing urinary glucose excretion. They also have beneficial nonglycemic effects, including weight loss and small decreases in systolic and diastolic blood pressure as observed during clinical trials.[1-16]

The sodium-glucose cotransport 2 inhibitors 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 November 2021.

Table 1. Sodium-glucose Cotransport 2 Inhibitors Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Single Entity Agents			
Canagliflozin	tablet	Invokana®	Invokana®
Dapagliflozin	tablet	Farxiga®	Farxiga®
Empagliflozin	tablet	Jardiance®	Jardiance®
Ertugliflozin	tablet	Steglatro®	none
Combination Products			
Canagliflozin and Metformin	extended-release tablet, tablet	Invokamet®, Invokamet XR®	Invokamet®
Dapagliflozin and Metformin	extended-release tablet	Xigduo XR®	Xigduo XR®
Dapagliflozin and Saxagliptin	tablet	Qtern®	none

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Empagliflozin and Linagliptin	tablet	Glyxambi®	none
Empagliflozin and Metformin	extended-release tablet, tablet	Synjardy®, Synjardy XR®	Synjardy®, Synjardy XR®
Empagliflozin, Linagliptin, and Metformin	extended-release tablet	Trijardy XR®	none
Ertugliflozin and Metformin	tablet	Segluromet®	none
Ertugliflozin and Sitagliptin	tablet	Steglujan®	none

PDL=Preferred Drug List

II. Evidence- Based Medicine and Current Treatment Guidelines

Current clinical guidelines are summarized in Table 2. Please note that guidelines addressing the treatment of type 2 diabetes are presented globally, addressing the role of various medication classes.

Table 2. Treatment Guidelines Using the Sodium-glucose Cotransport 2 Inhibitors

Clinical Guideline	Recommendation(s)
American Diabetes Association: **Standards of Care in Diabetes (2023)**[17]	Current criteria for the diagnosis of diabetes • The following are the criteria for a diagnosis of diabetes: glycosylated hemoglobin (HbA_{1c}) ≥6.5%, or a fasting plasma glucose (FPG) ≥126 mg/dL, or a two-hour plasma glucose ≥200 mg/dL during an oral glucose tolerance test or patients with classic symptoms of hyperglycemia, or classic symptoms of hyperglycemia or hyperglycemic crisis (random plasma glucose ≥200 mg/dL). Prevention or delay of type 2 diabetes • Refer adults with overweight/obesity at high risk of type 2 diabetes, as typified by the Diabetes Prevention Program (DPP), to an intensive lifestyle behavior change program to achieve and maintain a weight reduction of at least 7% of initial body weight through healthy reduced-calorie diet and ≥150 minutes/week of moderate-intensity physical activity. • A variety of eating patterns can be considered to prevent diabetes in individuals with prediabetes. • Metformin therapy for prevention of type 2 diabetes should be considered in adults at high risk of type 2 diabetes, as typified by the DPP, especially those aged 25 to 59 years with BMI ≥35 kg/m^2, higher FPG) (e.g., ≥110 mg/dL), and higher A1C (e.g., ≥6.0%), and in individuals with prior gestational diabetes mellitus (GDM). • Long-term use of metformin may be associated with biochemical vitamin B12 deficiency; consider periodic measurement of vitamin B12 levels in metformin-treated individuals, especially in those with anemia or peripheral neuropathy. Glycemic goals in adults • An A1C goal for many nonpregnant adults of <7% (53 mmol/mol) without significant hypoglycemia is appropriate. • If using ambulatory glucose profile (AGP)/glucose management indicator (GMI) to assess glycemia, a parallel goal for many nonpregnant adults is time in range (TIR) of >70% with time below range (TBR) <4% and time <54 mg/dL <1%. For those with frailty or at high risk of hypoglycemia, a target of >50% TIR with <1% TBR is recommended. • On the basis of health care provider judgment and patient preference, achievement of lower A1C levels than the goal of 7% may be acceptable and

Clinical Guideline	Recommendation(s)
	even beneficial if it can be achieved safely without significant hypoglycemia or other adverse effects of treatment. • Less stringent A1C goals (such as <8% [64 mmol/mol]) may be appropriate for patients with limited life expectancy or where the harms of treatment are greater than the benefits. HCPs should consider deintensification of therapy if appropriate to reduce the risk of hypoglycemia in patients with inappropriate stringent A1C targets. Pharmacologic therapy for type 1 diabetes • Most individuals with type 1 diabetes should be treated with multiple dose insulin injections (three to four injections per day of basal and pre-prandial insulin) or continuous subcutaneous (SC) insulin infusion therapy. • Most patients should use rapid-acting insulin analogs to reduce hypoglycemia risk. • Patients with type 1 diabetes should receive education on how to match prandial insulin doses to carbohydrate intake, premeal blood glucose, and anticipated physical activity. Pharmacologic therapy for type 2 diabetes • Healthy lifestyle behaviors, diabetes self-management education and support, avoidance of clinical inertia, and social determinants of health should be considered in the glucose-lowering management of type 2 diabetes. Pharmacologic therapy should be guided by person-centered treatment factors, including comorbidities and treatment goals. • In adults with type 2 diabetes and established/high risk of atherosclerotic cardiovascular disease, heart failure, and/or chronic kidney disease, the treatment regimen should include agents that reduce cardiorenal risk. • Pharmacologic approaches that provide adequate efficacy to achieve and maintain treatment goals should be considered, such as metformin or other agents, including combination therapy. • Weight management is an impactful component of glucose-lowering management in type 2 diabetes. The glucose-lowering treatment regimen should consider approaches that support weight management goals. • Metformin should be continued upon initiation of insulin therapy (unless contraindicated or not tolerated) for ongoing glycemic and metabolic benefits. • Early combination therapy can be considered in some individuals at treatment initiation to extend the time to treatment failure. • The early introduction of insulin should be considered if there is evidence of ongoing catabolism (weight loss), if symptoms of hyperglycemia are present, or when A1C levels (>10% [86 mmol/mol]) or blood glucose levels (≥300 mg/dL [16.7 mmol/L]) are very high. • A person-centered approach should guide the choice of pharmacologic agents. Consider the effects on cardiovascular and renal comorbidities, efficacy, hypoglycemia risk, impact on weight, cost and access, risk for side effects, and individual preferences. • Among individuals with type 2 diabetes who have established atherosclerotic cardiovascular disease or indicators of high cardiovascular risk, established kidney disease, or heart failure, a sodium–glucose cotransporter 2 inhibitor and/or glucagon-like peptide 1 receptor agonist with demonstrated cardiovascular disease benefit is recommended as part of the glucose-lowering regimen and comprehensive cardiovascular risk reduction, independent of A1C and in consideration of person-specific factors. • In adults with type 2 diabetes, a glucagon-like peptide 1 receptor agonist is preferred to insulin when possible.

Clinical Guideline	Recommendation(s)
	• If insulin is used, combination therapy with a glucagon-like peptide 1 receptor agonist is recommended for greater efficacy, durability of treatment effect, and weight and hypoglycemia benefit. • Recommendation for treatment intensification for individuals not meeting treatment goals should not be delayed. • Medication regimen and medication-taking behavior should be reevaluated at regular intervals (every three to six months) and adjusted as needed to incorporate specific factors that impact choice of treatment. • Clinicians should be aware of the potential for over-basalization with insulin therapy. Clinical signals that may prompt evaluation of over-basalization include basal dose more than ~0.5 units/kg/day, high bedtime–morning or post-preprandial glucose differential, hypoglycemia (aware or unaware), and high glycemic variability. Indication of over-basalization should prompt reevaluation to further individualize therapy.
American Diabetes Association/ European Association for the Study of Diabetes: **Management of Hyperglycemia in Type 2 Diabetes. A consensus report by the American Diabetes Association and the European Association for the Study of Diabetes (2022)**[18]	Consensus recommendations • All people with type 2 diabetes should be offered access to ongoing diabetes self-management education and support programs. • Providers and health care systems should prioritize the delivery of person-centered care. • Optimizing medication adherence should be specifically considered when selecting glucose-lowering medications. • Medical nutrition therapy focused on identifying healthy dietary habits that are feasible and sustainable is recommended in support of reaching metabolic and weight goals. • Physical activity improves glycemic control and should be an essential component of type 2 diabetes management. • Adults with type 2 diabetes should engage in physical activity regularly (>150 min/week of moderate- to vigorous-intensity aerobic activity) and be encouraged to reduce sedentary time and break up sitting time with frequent activity breaks. • Aerobic activity should be supplemented with two to three resistance, flexibility, and/or balance training sessions/week. Balance training sessions are particularly encouraged for older individuals or those with limited mobility/poor physical function. • Metabolic surgery should be considered as a treatment option in adults with type 2 diabetes who are appropriate surgical candidates with a BMI ≥40.0 kg/m^2 (BMI ≥37.5 kg/m^2 in people of Asian ancestry) or a BMI of 35.0 to 39.9 kg/m^2 (32.5 to 37.4 kg/m^2 in people of Asian ancestry) who do not achieve durable weight loss and improvement in comorbidities (including hyperglycemia) with nonsurgical methods. • In people with established CVD, a GLP-1 RA with proven benefit should be used to reduce MACE, or an SGLT2i with proven benefit should be used to reduce MACE and HF and improve kidney outcomes. • In people with CKD and an eGFR ≥20 ml/min per 1.73 m^2 and a urinary albumin/creatinine ratio >3.0 mg/mmol (>30 mg/g), an SGLT2i with proven benefit should be initiated to reduce MACE and HF and improve kidney outcomes. Indications and eGFR thresholds may vary by region. If such treatment is not tolerated or is contraindicated, a GLP-1 RA with proven cardiovascular outcome benefit could be considered to reduce MACE and should be continued until kidney replacement therapy is indicated. • In people with HF, SGLT2i should be used because they improve HF and kidney outcomes. • In individuals without established CVD but with multiple cardiovascular risk factors (such as age ≥55 years, obesity, hypertension, smoking, dyslipidemia, or albuminuria), a GLP-1 RA with proven benefit could be used to reduce MACE,

Clinical Guideline	Recommendation(s)
	or an SGLT2i with proven benefit could be used to reduce MACE and HF and improve kidney outcomes. • In people with HF, CKD, established CVD, or multiple risk factors for CVD, the decision to use a GLP-1 RA or SGLT2i with proven benefit should be independent of background use of metformin. • SGLT2i and GLP-1 RA reduce MACE, which is likely to be independent of baseline HbA1c. In people with HF, CKD, established CVD, or multiple risk factors for CVD, the decision to use a GLP-1 RA or an SGLT2i with proven benefit should be independent of baseline HbA1c. • In general, selection of medications to improve cardiovascular and kidney outcomes should not differ for older people. • In younger people with diabetes (<40 years), consider early combination therapy. • In women with reproductive potential, counseling regarding contraception and taking care to avoid exposure to medications that may adversely affect a fetus are important.
American Association of Clinical Endocrinologists/ American College of Endocrinology: **Clinical Practice Guidelines for Developing a Diabetes Mellitus Comprehensive Care Plan (2022)**[19]	Antihyperglycemic Pharmacotherapy for Persons with Type 2 Diabetes • Individualized pharmacotherapy for persons with T2D should be prescribed based on evidence for benefit that includes glucose lowering, avoidance of hypoglycemia and weight gain, and reduction of cardio-renal risk. • Persons with T2D and their health care professionals should use patient-centered shared decision-making to agree on therapy targets and treatments as well as a regimen for glucose monitoring (i.e., BGM, structured BGM, or CGM). • Glycemic targets include A1C, BGM, and, for those using CGM, achievement of CGM targets such as time in range (TIR), percentage in low and very low range, time above range, and glycemic variability. Nonglycemic targets include avoidance of hypoglycemia, control of BP, lipids, other CVD risk factors, and achieving and maintaining a healthy body weight. • Independent of glycemic control, targets, or treatment, if there is established or high risk for ASCVD, HF, and/or CKD, clinicians should prescribe a GLP-1 RA or an SGLT2i with proven efficacy for the specific condition(s) of the person with T2D being treated. • DM therapy should be individualized based on level of glycemia and the presence of comorbidities, complications, and access. Metformin is often the preferred initial therapy. Other agents may be appropriate as first line or in addition to metformin to reduce BG and/or to address specific comorbidities (such as ASCVD, HF, CKD, obesity, NAFLD), independent of glucose-lowering effects. • For some recently diagnosed individuals with T2D and more severe hyperglycemia (A1C ≥7.5%), unlikely to attain the A1C target with a single agent, early combination pharmacotherapy should be considered, usually to include metformin plus another agent that does not cause hypoglycemia, especially a GLP-1 RA, SGLT2i, or dipeptidyl peptidase 4 (DPP-4) inhibitor. • For newly diagnosed persons with T2D and an entry A1C >9.0% and/or ≥1.5% above target, one should initiate, along with lifestyle modifications, dual- or possibly triple-combination pharmacotherapy usually including metformin. Basal insulin along with noninsulin therapy is recommended if there are significant signs or symptoms of hyperglycemia, especially including catabolism (e.g., weight loss) or a very high A1C >10% (86 mmol/mol) or BG levels (≥300 mg/dL [16.7 mmol/L]). • Clinicians should discuss with persons with T2D the likelihood that most persons with T2D ultimately require a combination of multiple complementary antihyperglycemic agents, in addition to lifestyle interventions, to attain and maintain optimal glycemic control.

Clinical Guideline	Recommendation(s)
	• The DM care team should assess medication adherence and safety and glycemic control in persons with T2D quarterly or more frequently as needed. Subsequent visits will depend upon the metabolic targets achieved and the stability of metabolic control. • Persons with T2D who start on metformin should continue it unless intolerance or contraindications occur. When intensification of antihyperglycemic treatment is needed, other agents should be added to metformin. • Most persons with T2D who require intensification of antihyperglycemic therapy with a GLP-1 RA or insulin should initially be prescribed a GLP-1 RA. If further intensification is required, one should prescribe a basal insulin or a switch to a fixed-ratio combination of a basal insulin and a GLP-1 RA (insulin glargine U100 + lixisenatide [GlarLixi] or insulin degludec + liraglutide [IdegLira]). • Insulin should be prescribed for persons with T2D when noninsulin antihyperglycemic therapy fails to achieve target glycemic control or when a person has symptomatic hyperglycemia. • Long-acting basal insulin analogs are the recommended initial choice of insulin therapy for persons with T2D. The insulin analogs glargine (U100 or U300), degludec (U100 or U200), or detemir are preferred over intermediate-acting Neutral Protamine Hagedorn (NPH) insulin because analog insulins have demonstrated less hypoglycemia in some studies. Glargine U300 and degludec can be associated with less hypoglycemia than glargine U100 or detemir. • Many persons with T2D receiving basal insulin and not at goal A1C can have significantly improved glycemia by the addition of a GLP-1 RA or being switched to a fixed-ratio combination basal insulin–GLP-1 RA (GlarLixi or IdegLira). One of these changes should be considered before adding a meal-time insulin for postprandial glycemic control. • When control of postprandial hyperglycemia is needed and a basal insulin and a GLP-1 RA are already being used, preference should be given to rapid-acting insulins (the analogs lispro, aspart, and glulisine or the rapid-acting inhaled human insulin powder) over regular human insulin. The former have a more consistent and a more rapid onset and offset of action with less risk of hypoglycemia. • Ultra-rapid-acting insulins (faster-acting insulin aspart, lispro aabc, and [human insulin] inhalation powder) may allow a decrease in the time between insulin administration and food intake and reduce the postprandial peak of PG as compared with rapid-acting insulins. The significance of this on long-term complications is unknown. • Basal-bolus insulin regimens or continuous subcutaneous insulin infusion (CSII) (i.e., insulin pump) allow for adjustment of insulin doses according to carbohydrate intake and activity levels and are recommended for intensive insulin therapy in persons with T2D. • Premixed insulin formulations (fixed combinations of shorter- and longer-acting components) of human or analog insulin may be considered for persons with T2D who have consistent dietary and exercise patterns and in whom adherence to more intensive insulin regimens is problematic. However, these preparations have reduced dosage flexibility and may increase the risk of hypoglycemia compared with basal insulin or basal-bolus regimens. • In persons with T2D who are treated with basal-bolus insulin therapy, adding a GLP-1 RA, or switching to a fixed-ratio combination of a GLP-1 RA and a basal insulin, or adding an SGLT2i or pramlintide (less commonly used) may be able to reduce postprandial hyperglycemia, A1C, and weight. GLP-1 RAs may also allow reduction or discontinuation of bolus insulin in some individuals. How should insulin therapy be used for management of persons with type 1 diabetes?

Clinical Guideline	Recommendation(s)
	• Insulin must be used to treat all persons with T1D. • Physiologic insulin replacement regimens, which provide both basal and prandial (meal-related or bolus) insulin, are recommended for most persons with T1D. • Achievement of glucose targets using either MDI of insulin or CSII, is needed to prevent development of life-threatening crises, such as acute hyperglycemic crises (DKA and hyperglycemic hyperosmolar state) and catabolic state. • A multi-component self-management DM education program is recommended for persons with T1D. Ideally, this is provided by a professional with expertise (i.e., certified diabetes care and education specialist) in the topics of healthy lifestyle, insulin technique including prandial insulin dosing guided by carbohydrate counting and diet adjustments for special situations, such as physical activity and prolonged fasting. Instruction is also needed in how to deal with sick days and prevention of DKA and hypoglycemia, and other relevant issues. Due to changes in DM self-management practices and each individual's medical history, personal and cultural background, and educational needs, specific education topics may need to be repeated at regular intervals. • The ideal insulin regimen should be personalized to an individual's needs and glycemic targets, attempting to better emulate physiological insulin replacement to maintain near normoglycemia, to prevent the development and progression of DM complications, while minimizing hypoglycemia and providing flexibility for specific daily life situations/scenarios such as: exercise, sleep, acute illness, psychological stress, etc. • Insulin regimens usually should involve the use of insulin analogs for most persons with T1D and include the following approaches: o MDI, which usually involve 1 to 2 subcutaneous injections daily of basal insulin to suppress ketogenesis and gluconeogenesis and to control glycemia between meals and overnight, and subcutaneous injections of prandial insulin or use of inhaled insulin before each meal to control meal-related glycemic excursions. CGM is the preferred method of glucose monitoring for all individuals with T1D. o Insulin pump therapy (CSII) provides constant/continuous infusion of fast-acting insulin driven by mechanical force and delivered via a cannula inserted under the skin. CSII can improve (or enhance) glycemic control and should be an option for insulin delivery for appropriate persons with DM. Ideally, these individuals should also use CGM as stated in R13.6.a. o Automated insulin delivery systems (AIDs), which include an insulin pump, an integrated CGM, and computer software algorithm, aim to better emulate physiological insulin replacement and achieve glycemic targets. This technology is recommended for many persons with T1D since its use has been shown to increase TIR while often reducing hypoglycemia or at least without causing increased hypoglycemia. o Open-loop (use of a pump and sensor which do not communicate) and sensor-augmented pump (SAP) systems: (CGM communicates with pump facilitating needed adjustments to basal rate; temporary interruption of insulin delivery when glucose levels are low or forecast to be low within 30 min). Insulin pump with a CGM or an SAP is recommended to manage persons with DM treated with intensive insulin management who prefer not to use AIDs or have no access to them. <u>How should diabetes mellitus in pregnancy be managed?</u> • For women with GDM, the following treatment goals are recommended: preprandial glucose concentration ≤95 mg/dL and either a 1-h post-meal glucose ≤140 mg/dL or a 2-h post-meal glucose ≤120 mg/dL to decrease adverse fetal outcomes.

Clinical Guideline	Recommendation(s)
	• All women with preexisting DM (T1D, T2D, or previous GDM) need access to preconception care and counseling to ensure adequate nutrition, healthy weight, and glucose control before conception, during pregnancy, and in the postpartum period. • Rapid-acting insulin analogs (insulin-lispro, insulin-aspart) should be used to treat postprandial hyperglycemia in pregnant women. • Options for basal insulin include long-acting insulin (e.g., NPH, detemir, or glargine) or rapid-acting insulin via a CSII. Regular insulin, although not recommended as first-line therapy, is acceptable to use in managing pregnant women with DM when rapid-acting insulin analogs are not available. • Insulin is the preferred therapeutic choice for pregnant women with GDM or T2D, but metformin has been given a category B for pregnancy with accumulating clinical evidence of metformin's safety during the first trimester and beyond. Metformin has been shown to improve pregnancy and fetal outcomes except for increased rates of infants with SGA and later onset of obesity. The prescriber should discuss the potential risks and benefits of oral agent therapy during pregnancy as well as the need for longer-term outcome studies.
American Association of Clinical Endocrinologists/ American College of Endocrinology: **Consensus Statement on the Comprehensive Type 2 Diabetes Management Algorithm (2023)**[20]	<u>Principles underlying the algorithm</u> • Lifestyle modification underlies all therapy. • Maintain or achieve optimal weight. • Choice of antihyperglycemic therapy reflects glycemic targets, atherosclerotic cardiovascular disease (ASCVD), congestive heart failure (CHF), chronic kidney disease (CKD), overweight/obesity, and nonalcoholic fatty liver disease (NAFLD). • Choice of therapy includes ease of use and access. • Optimal hemoglobin A1c (A1C) is ≤6.5% or as close to normal as is safe and achievable for most patients. • Individualize all glycemic targets (A1C, glucose management indicator [GMI], time in range [TIR], fasting blood glucose [FBG], and PPG). • Get to goal as soon as possible (adjust ≤3 months). • Avoid hypoglycemia. Hypoglycemia, defined as blood glucose (BG) <70 mg/dL, is associated with an increased risk for adverse outcomes including mortality. • CGM is highly recommended to assist persons with diabetes in reaching goals safely. • Comorbidities must be managed for comprehensive care. <u>Algorithm summative information</u> • The algorithm is intended as a more concise document than the guideline, providing easily accessible, visual guidance for decision-making in the clinic setting. • In this 2023 algorithm, there continues to be an emphasis on lifestyle modification and treatment of overweight/obesity as key pillars of the management of prediabetes and DM. • The importance of appropriate management of the atherosclerotic risk factors of dyslipidemia and hypertension is highlighted. • One notable new theme is an obvious emphasis on a complication-centric approach, beyond glucose levels, to frame decisions regarding first-line pharmacologic choices for the treatment of persons with diabetes. • The algorithm is divided into discrete graphic sections that outline the principles for management of T2D and guide management of adiposity-based chronic disease (ABCD), prediabetes, and atherosclerotic risk factors of dyslipidemia and hypertension. In addition, the algorithms for antihyperglycemic agents include both complication-centric and glucose-centric approaches, and there is direction

Clinical Guideline	Recommendation(s)
	for insulin initiation and titration. Tables summarizing the benefits and risks of antihyperglycemic medications (updated) and weight-loss pharmacotherapy (new) are provided.

American Academy of Pediatrics: **Management of Newly Diagnosed Type 2 Diabetes Mellitus (T2DM) in Children and Adolescents (2013)**[21]	• Clinicians must ensure that insulin therapy is initiated for children and adolescents with T2DM who are ketotic or in diabetic ketoacidosis and in whom the distinction between types 1 and 2 diabetes mellitus is unclear and, in usual cases, should initiate insulin therapy for patients.
	  ○ Who have random venous or plasma blood glucose (BG) concentrations ≥250 mg/dL.
	  ○ Whose HbA_{1c} is >9%.
	• In all other instances, clinicians should initiate a lifestyle modification program, including nutrition and physical activity, and start metformin as first-line therapy for children and adolescents at the time of diagnosis of T2DM.
	• Monitoring of HbA_{1c} concentrations is recommended every three months and intensifying treatment is recommended if treatment goals for finger-stick BG and HbA_{1c} concentrations are not being met.
	• Advise patients to monitor finger-stick BG concentrations in patients who:
	  ○ Are taking insulin or other medications with a risk of hypoglycemia; or
	  ○ Are initiating or changing their diabetes treatment regimen; or
	  ○ Have not met treatment goals; or
	  ○ Have intercurrent illnesses.
	• Incorporate the Academy of Nutrition and Dietetics' *Pediatric Weight Management Evidence-Based Nutrition Practice Guidelines* in dietary or nutrition counseling of patients with T2DM at the time of diagnosis and as part of ongoing management.
	• Encourage children and adolescents with T2DM to engage in moderate-to-vigorous exercise for at least 60 minutes daily and to limit nonacademic "screen time" to less than two hours a day.

American Diabetes Association: **Type 1 Diabetes in Children and Adolescents: A Position Statement by the American Diabetes Association (2018)**[22]	<u>Blood Glucose Management: Monitoring and Treatment</u> • Most children with type 1 diabetes should be treated with intensive insulin regimens via either multiple daily injections of prandial insulin and basal insulin or continuous subcutaneous insulin infusion. • An HbA_{1c} target of <7.5% should be considered in most children and adolescents but should be individualized based on the needs and situation of the patient and family. • Children and adolescents with type 1 diabetes should have blood glucose levels monitored up to six to ten times/day including premeal, pre-bedtime, and as needed for safety (e.g., exercise, driving, illness, or the presence of symptoms of hypoglycemia). • Continuous blood glucose monitoring should be considered in all children and adolescents whether using insulin injections or an insulin pump. • In pediatric patients with type 1 diabetes automated insulin delivery systems can improve glycemic control and reduce hypoglycemia. <u>Lifestyle Management</u> • Individualized medical nutrition therapy is recommended for children and adolescents with type 1 diabetes. • Monitoring carbohydrate intake, whether by carbohydrate counting or experience-based estimation, is key to achieving optimal glycemic control. • Exercise if recommended for all children and adolescents with type 1 diabetes. The suggested goal is 60 minutes of moderate to vigorous aerobic activity daily with muscle-strengthening and bone-strengthening activities three times a week. • Children and adolescents with type 1 diabetes should be educated about prevention and management of potential hypoglycemia during and after exercise.

Clinical Guideline	Recommendation(s)
	• Strategies to prevent hypoglycemia during exercise, after exercise, and overnight following exercise include reducing prandial insulin dosing for the meal/snack preceding exercise, increasing carbohydrate intake, eating bedtime snacks, using continuous blood glucose monitoring, and/or reducing basal insulin doses. <u>Behavioral Aspects of Self-Management</u> • Children and adolescents with diabetes should be assessed for psychosocial issues and family stresses that could impact diabetes management at diagnosis and routine follow-up. • Consider including children in consent processes as early as cognitive development indicates understanding of health consequences of behavior. • Offer adolescents time by themselves with their care provider(s) starting at age 12 years, or when developmentally appropriate. <u>Complications and Comorbidities</u> • Diabetic Ketoacidosis o All individuals with type 1 diabetes should have access to an uninterrupted supply of insulin. Lack of access and insulin omissions are major causes of diabetic ketoacidosis. o Patients with type 1 diabetes should have continuous access to medical support for sick-day management. • Hypoglycemia o The recommended treatment of hypoglycemia (blood glucose <70 mg/dL) in conscious patients is 15 g of glucose, although any form of carbohydrate can be used. If hypoglycemia continues after 15 minutes, treatment should be repeated. Once blood glucose has returned to normal patients should consider consuming a meal/snack and/or reduce insulin. o All individuals with type 1 diabetes should be prescribed glucagon and families/caregivers should be educated on administration. o Treatment regimens should be reevaluated in those with hypoglycemia unawareness or one or more episodes of severe hypoglycemia. • Diabetic Kidney Disease o Annual screening for albuminuria with a random spot urine sample for albumin-to-creatinine ratio should be considered at puberty or at age >10 years, whichever is earlier, once the child has had diabetes for 5 years. o An angiotensin-converting-enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB), titrated to normalization of albumin excretion, may be considered when elevated urinary albumin-to-creatinine ratio is documented. • Retinopathy o An initial dilated and comprehensive eye examination is recommended at age 10 years or after puberty has started, whichever is earlier, once the patient has had diabetes for three to five years. o Annual routine follow-up is recommended but may be given every two years based on the advice of an eye care professional. • Neuropathy o Consider an annual comprehensive foot exam for adolescents at the start of puberty or at age 10 years, whichever is earlier, once the patient has had type 1 diabetes for 5 years. • Hypertension o Children and adolescents with type 1 diabetes should have blood pressure monitored at each visit. Elevated blood pressure should be confirmed on three separate days. o Initial treatment of high-normal blood pressure should include dietary modification and increased exercise. Pharmacologic treatment should be considered if blood pressure is not controlled after three to six months.

Clinical Guideline	Recommendation(s)
	○ In patients with conformed hypertension pharmacologic treatment should be added to lifestyle modification at diagnosis. ○ ACE inhibitors and ARBs should be considered for initial treatment. • Dyslipidemia ○ A fasting lipid profile should be taken in children ≥10 years of age or older after the diagnosis of diabetes. Obtain a fasting lipid profile in children 10 years of age or older as soon as convenient after the diagnosis of diabetes ○ If lipids are abnormal, initial therapy should consist of optimizing glucose control and medical nutrition therapy using a Step 2 American Heart Association diet that restricts saturated fat to 7% of total calories and dietary cholesterol to 200 mg/day. ○ If lipids remain abnormal after six months of lifestyle intervention, consider adding a statin in children at least 10 years of age.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the sodium-glucose cotransport 2 inhibitors are noted in Table 3.

Table 3. FDA-Approved Indications for the Single-Entity Sodium-glucose Cotransport 2 Inhibitors[3-16]

Indication	Canagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin
Type 2 diabetes mellitus, an adjunct to diet and exercise to improve glycemic control	✔	✔	✔	✔
To reduce the risk of cardiovascular death in adult patients with type 2 diabetes mellitus and established cardiovascular disease			✔	
To reduce the risk of cardiovascular death and hospitalization for heart failure in adults with heart failure			✔	
To reduce the risk of cardiovascular death, hospitalization for heart failure, and urgent heart failure visit in adults with heart failure		✔		
To reduce the risk of hospitalization for heart failure in adults with type 2 diabetes mellitus and either established cardiovascular disease or multiple cardiovascular risk factors		✔		
To reduce the risk of major adverse cardiovascular events (cardiovascular death, nonfatal myocardial infarction and nonfatal stroke) in adults with type 2 diabetes mellitus and established cardiovascular disease	✔			
To reduce the risk of end-stage kidney disease, doubling of serum creatinine, cardiovascular death, and hospitalization for heart failure in adults with type 2 diabetes mellitus and diabetic nephropathy with albuminuria >300 mg/day	✔			

Indication	Canagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin
To reduce the risk of sustained eGFR decline, end stage kidney disease cardiovascular death, and hospitalization for heart failure in adults with chronic kidney disease at risk of progression		✔		

Table 4. FDA-Approved Indications for the Combination Sodium-glucose Cotransport 2 Inhibitors[3-16]

See the individual prescribing information for additional indications based on the single-entity components.

Indication	Canagliflozin and Metformin	Dapagliflozin and Metformin	Dapagliflozin and Saxagliptin	Empagliflozin and Linagliptin	Empagliflozin and Metformin	Empagliflozin, Linagliptin, and Metformin	Ertugliflozin and Metformin	Ertugliflozin and Sitagliptin
Type 2 diabetes mellitus, as an adjunct to diet and exercise to improve glycemic control	✔	✔	✔	✔	✔	✔	✔	✔

IV. Pharmacokinetics

The pharmacokinetic parameters of the sodium-glucose cotransport 2 inhibitors are listed in Table 5.

Table 5. Pharmacokinetic Parameters of the Sodium-glucose Cotransport 2 Inhibitors[3]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Single Entity Agents					
Canagliflozin	65	99 (primarily albumin)	Liver (extensive)	Urine (33) Feces (41.5)	10.6 to 13.1
Dapagliflozin	78	91	Liver (extensive)	Urine (75) Feces (21)	8 to 12.9
Empagliflozin	Not reported	86.2	Glucuronidation	Urine (54.4) Feces (41.2)	12.4
Ertugliflozin	100	93.6	Glucuronidation	Urine (50.2) Feces (40.9)	16.6
Combination Products					
Canagliflozin and Metformin	65/ 50 to 60	99 (primarily albumin)/ Negligible (% not reported)	Liver (extensive)/ None	Urine (33) Feces (41.5)/ Renal (90)	10.6 to 13.1/ 6.2
Dapagliflozin and Metformin	78/ 50 to 60	91/ Negligible (% not reported)	Liver (extensive)/ None	Urine (75) Feces (21)/ Renal (90)	8 to 12.9/ 6.2
Dapagliflozin and Saxagliptin	78/ Not reported	91/ Negligible (% not reported)	Liver (extensive)/ Liver (% not reported)	Urine (75) Feces (21)/ Urine (60) Feces (22)	8 to 12.9/ 2.5
Empagliflozin and Linagliptin	Not reported/ 30	86.2/ 70 to 99	Glucuronidation/ Limited	Urine (54.4) Feces (41.2)/ Urine (5 to 7) Bile (80)	12.4/ >100
Empagliflozin and Metformin	Not reported/ 50 to 60	86.2/	Glucuronidation/ None	Urine (54.4) Feces (41.2)/	12.4/ 6.2

		Negligible (% not reported)		Renal (90)	
Empagliflozin, Linagliptin, and Metformin	Not reported/ 30/ 50 to 60	86.2/ 70 to 99/ Negligible (% not reported)	Glucuronidation/ Limited/ None	Urine (54.4) Feces (41.2)/ Urine (5 to 7) Bile (80)/ Renal (90)	12.4/ >100/ 6.2
Ertugliflozin and Metformin	100/ 50 to 60	93.6/ Negligible (% not reported)	Glucuronidation/ None	Urine (50.2) Feces (40.9)/ Renal (90)	16.6/ 6.2
Ertugliflozin and Sitagliptin	100/ 87	93.6/ 38	Glucuronidation/ Minimal	Urine (50.2) Feces (40.9)/ Urine (87) Feces (13)	16.6/ 12.4

V. Drug Interactions

Concurrent use of lithium and sodium-glucose cotransporter 2 inhibitors may result in reduced lithium exposure..[3,4] Coadministration of canagliflozin with UDP-glucuronosyltransferase inducers, such as rifampin, may decrease the exposure to canagliflozin and therefore decrease efficacy.[5] Additionally, Coadministration of canagliflozin with digoxin may increase digoxin exposure. Use caution if concomitant use is required and monitor digoxin levels. Consider advising the patient to report signs or symptoms of digoxin toxicity.[5]

VI. Adverse Drug Events

The most common adverse drug events reported with the sodium-glucose cotransport 2 inhibitors are listed in Tables 6 and 7. The boxed warnings for metformin-containing products are listed in Table 8.

Table 6. Adverse Drug Events (%) Reported with the Single-Entity SGLT2 Inhibitors[4]

Adverse Event	Canagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin
Central Nervous System				
Fatigue	2.0 to 2.2	-	-	-
Headache	-	-	-	3 to 4
Gastrointestinal				
Abdominal pain	1.7 to 1.8	-	-	-
Constipation	1.8 to 2.3	2	-	-
Nausea	2.2 to 2.3	3	2	-
Genitourinary				
Dysuria	-	2	-	-
Fungal vaginosis†	-	7 to 8	-	-
Genitourinary fungal infection‡	10.4 to 11.4 (female) 3.7 to 4.2 (male)	7 to 8 (female) 3 (male)	5 to 6 (female) 2 to 3 (male)	9 to 12 (female) 4 (male)
Increased urination§	4.6 to 5.3	3 to 4	3	2 to 3
Urinary tract infection§§	4.3 to 5.9	4 to 6	9	✔
Vulvovaginal pruritus	1.6 to 3	-	-	2 to 3
Endocrine and metabolic				
Dyslipidemia	-	2 to 3	4	-
Hypovolemia*	2 to 3	1	✔	2 to 4
Increased LDL cholesterol	✔	✔	5 to 7	-
Increased serum phosphate	✔	2	-	-
Weight loss	-	-	-	2
Renal				
Acute renal failure	✔	✔	✔	✔
Decreased estimated GFR	✔	✔	✔	✔
Increased serum creatinine	✔	✔	✔	✔

Adverse Event	Canagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin
Other				
Back pain	-	3 to 4	-	3
Hypersensitivity reaction	3.8 to 4.2	✔	-	-
Hypoglycemia	4	-	-	3
Increased hematocrit	-	1	3 to 4	-
Increased hemoglobin	✔	-	-	✔
Influenza	-	2 to 3	-	-
Ketoacidosis	-	-	✔	✔
Limb pain	-	2	-	-
Nasopharyngitis	-	6 to 7	-	3
Thirst	2.3 to 2.8	-	2	1 to 3
Urticaria	-	✔	✔	-

*Hypovolemia includes: dehydration, hypovolemia, orthostatic hypotension, and hypotension.
†Fungal vaginosis includes: vulvovaginal mycotic infection, vaginal infection, vulvovaginal candidiasis, vulvovaginitis, genital infection, genital candidiasis, fungal genital infection, vulvitis, genitourinary tract infection, vulval abscess, vaginitis bacterial.
‡Genitourinary fungal infections include: balanitis, fungal genital infection, balanitis candida, genital candidiasis, genital infection male, penile infection, balanoposthitis, balanoposthitis infective, genital infection, posthitis.
§Increased urination includes: polyuria, pollakiuria, urine output increased, micturition urgency, and nocturia.
§§Urinary tract infection includes: urinary tract infection, cystitis, kidney infection, and urosepsis.
-Incidence not reported or <1%.
✔ Incidence not specified.

Table 7. Adverse Drug Events (%) Reported with the Combination Product SGLT2 Inhibitors[4]

Adverse Event	Canagliflozin and Metformin#	Dapagliflozin and Saxagliptin	Dapagliflozin and Metformin	Empagliflozin and Linagliptin	Empagliflozin and Metformin	Empagliflozin Linagliptin, and Metformin	Ertugliflozin and Metformin#	Ertugliflozin and Sitagliptin#
Central Nervous System								
Dizziness	-	-	3	-	-	-	-	-
Fatigue	2.0 to 2.2	-	-	-	-	-	-	-
Headache	-	4	5	-	-	5	3 to 4	3 to 4
Gastrointestinal								
Abdominal pain	1.7 to 1.8	-	-	-	-	-	-	-
Constipation	1.8 to 2.3	-	3	-	-	5 to 6	-	-
Diarrhea	-	4	-	-	-	2 to 7	-	-
Gastroenteritis	-	-	-	-	-	3 to 6	-	-
Nausea	2.2 to 2.3	-	3 to 4	2	2	-	-	-
Genitourinary								
Dysuria	-	-	2	-	-	-	-	-
Fungal vaginosis†	-	-	-	-	-	-	-	-
Genitourinary fungal infection‡	10.4 to 11.4 (female) 3.7 to 4.2 (male)	3	9 (female) 4 (male)	5 to 6 (female) 2 to 3 (male)	5 to 6 (female) 2 to 3 (male)	-	9 to 12 (female) 4 (male)	9 to 12 (female) 4 (male)
Increased urination§	4.6 to 5.3	-	2 to 3	3	3	-	2 to 3	2 to 3
Urinary tract infection§§	4.3 to 5.9	6	6	11 to 13	9	10	✔	✔
Vulvovaginal pruritus	1.6 to 3	-	-	-	-	-	2 to 3	2 to 3
Endocrine and metabolic								
Dyslipidemia	-	5	2 to 3	4	4	-	-	-
Hypoglycemia	4	2	-	-	-	✔	3	3
Hypovolemia*	2 to 3	✔	-	✔	✔	-	2 to 4	2 to 4
Increased LDL cholesterol	✔	-	-	✔	5 to 7	-	-	-
Increased serum phosphate	✔	-	-	-	-	-	-	-
Renal								
Decreased estimated GFR	✔	-	-	✔	✔	-	✔	✔

Adverse Event	Canagliflozin and Metformin[#]	Dapagliflozin and Saxagliptin	Dapagliflozin and Metformin	Empagliflozin and Linagliptin	Empagliflozin and Metformin	Empagliflozin Linagliptin, and Metformin	Ertugliflozin and Metformin[#]	Ertugliflozin and Sitagliptin[#]
Increased serum creatinine	✔	-	-	✔	✔	-	✔	✔
Renal insufficiency	-	2	-	-	-	-	-	-
Other								
Arthralgia	-	2	-	-	-	-	-	-
Back pain	-	3	-	-	-	-	3	3
Cough	-	-	3	-	-	-	-	-
Hypersensitivity reaction	3.8 to 4.2	-	-	-	-	-	-	-
Increased hematocrit	-	-	-	✔	3 to 4	-	-	-
Increased hemoglobin	✔	-	-	-	-	-	✔	✔
Influenza	-	-	3 to 4	-	-	-	-	-
Ketoacidosis	-	-	✔	✔	✔	-	✔	✔
Limb pain	-	-	-	-	-	-	-	-
Nasopharyngitis	-	-	-	6 to 7	-	6 to 8	3	3
Pharyngitis	-	-	2 to 3	-	-	-	-	-
Thirst	2.3 to 2.8	-	-	2	2	-	1 to 3	1 to 3
Upper respiratory tract infection	-	14	-	7	-	8 to 10	-	-
Urticaria	-	-	-	-	-	-	-	-

*Hypovolemia includes: dehydration, hypovolemia, orthostatic hypotension, and hypotension.
[†]Fungal vaginosis includes: vulvovaginal mycotic infection, vaginal infection, vulvovaginal candidiasis, vulvovaginitis, genital infection, genital candidiasis, fungal genital infection, vulvitis, genitourinary tract infection, vulval abscess, vaginitis bacterial.
[‡]Genitourinary fungal infections include: balanitis, fungal genital infection, balanitis candida, genital candidiasis, genital infection male, penile infection, balanoposthitis, balanoposthitis infective, genital infection, posthitis.
§Increased urination includes: polyuria, pollakiuria, urine output increased, micturition urgency, and nocturia.
§§Urinary tract infection includes: urinary tract infection, cystitis, kidney infection, and urosepsis.
-Incidence not reported or <1%.
✔ Incidence not specified.
[#]The incidence and type of adverse reactions for the combinations canagliflozin/metformin, ertugliflozin/metformin, and ertugliflozin/sitagliptin were similar to the adverse reactions of the SGLT2 inhibitor alone.

Table 8. Boxed Warning for the Metformin-Containing Combination Products[4]

WARNING
Lactic Acidosis: • Postmarketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias. The onset of metformin-associated lactic acidosis is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, somnolence, and abdominal pain. Metformin-associated lactic acidosis was characterized by elevated blood lactate levels (>5 mmol/Liter), anion gap acidosis (without evidence of ketonuria or ketonemia), an increased lactate/pyruvate ratio; and metformin plasma levels generally >5 mcg/mL. • Risk factors for metformin-associated lactic acidosis include renal impairment, concomitant use of certain drugs (e.g., carbonic anhydrase inhibitors such as topiramate), age 65 years old or greater, having a radiological study with contrast, surgery and other procedures, hypoxic states (e.g., acute congestive heart failure), excessive alcohol intake, and hepatic impairment. • Steps to reduce the risk of and manage metformin-associated lactic acidosis in these high risk groups are provided in the full prescribing information. • If metformin-associated lactic acidosis is suspected, immediately discontinue metformin-containing products and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended.

VII. Dosing and Administration

The usual dosing regimens for the sodium-glucose cotransport 2 inhibitors are listed in Table 9.

Table 9. Usual Dosing Regimens for the Sodium-glucose Cotransport 2 Inhibitors[3-16]

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
Single Entity Agents			
Canagliflozin	Type 2 diabetes mellitus, to reduce the risk of major adverse cardiovascular events (cardiovascular death, nonfatal myocardial infarction and nonfatal stroke) in adults with type 2 diabetes mellitus and established cardiovascular disease, to reduce the risk of end-stage kidney disease, doubling of serum creatinine, cardiovascular death, and hospitalization for heart failure in adults with type 2 diabetes mellitus and diabetic nephropathy with albuminuria: Tablet: eGFR ≥ 60 mL/min/1.73 m^2, 100 mg orally once daily, taken before the first meal of the day, dose can be increased to 300 mg once daily for additional glycemic control; eGFR 30 to <60 mL/min/1.73 m^2, 100 mg once daily; eGFR <30 mL/min/1.73 m^2, initiation is not recommended, however patients with albuminuria >300 mg/day may continue 100 mg once daily to reduce the risk of ESKD, doubling of serum creatinine, CV death, and hospitalization for heart failure	Safety and efficacy in children have not been established.	Tablet: 100 mg 300 mg
Dapagliflozin	Type 2 diabetes mellitus, to reduce the risk of cardiovascular death and hospitalization for heart failure in adults with heart failure (NYHA class II-IV), to reduce the risk of hospitalization for heart failure in adults with type 2 diabetes mellitus and either established cardiovascular disease or multiple cardiovascular risk factors, to reduce the risk of sustained eGFR decline, end stage kidney disease cardiovascular death and hospitalization for heart failure in adults with chronic kidney disease at risk of progression: Tablet: eGFR ≥45 mL/min/1.73 m^2, to improve glycemic control, the recommended starting dose is 5 mg orally once daily, dose can be increased to 10 mg orally once daily for additional glycemic control*. For all other indications, the recommended starting dose is 10 mg orally once daily; eGFR 25 to <45 mL/min/1.73 m^2, 10 mg orally once daily; eGFR <25 mL/min/1.73 m^2, initiation is not recommended, however patients may continue 10 mg orally once daily to reduce the risk of eGFR decline, ESKD, CV death and hospitalization for HF	Safety and efficacy in children have not been established.	Tablet: 5 mg 10 mg
Empagliflozin	Type 2 diabetes mellitus, to reduce the risk of cardiovascular death in adult patients with type 2 diabetes mellitus and established cardiovascular disease; to reduce the risk of cardiovascular death plus hospitalization for heart failure in adults with heart failure: Tablet: 10 mg once daily in the morning; in patients tolerating empagliflozin who require additional glycemic control, the dose can be increased to 25 mg once daily	Type 2 diabetes mellitus in patients ≥10 years of age: Tablet: 10 mg once daily in the morning; in patients tolerating empagliflozin who require additional glycemic	Tablet: 10 mg 25 mg

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
		control, the dose can be increased to 25 mg once daily	
Ertugliflozin	Type 2 diabetes mellitus: Tablet: initial, 5 mg once daily in the morning; in patients tolerating ertugliflozin 5 mg once daily, the dose may be increased to a maximum recommended dose of 15 mg once daily if additional glycemic control is needed	Safety and efficacy in children have not been established.	Tablet: 5 mg 15 mg
Combination Products			
Canagliflozin and Metformin	Type 2 diabetes mellitus: Extended-release tablet: initial, based on current regimen once daily in the morning with food; adjust to a maximum of 300-2,000 mg Tablet: initial, based on current regimen start canagliflozin 50 mg and/or metformin 500 mg twice daily with meals	Safety and efficacy in children have not been established.	Extended-release tablet: 50-500 mg 50-1,000 mg 150-500 mg 150-1,000 mg Tablet: 50-500 mg 50-1,000 mg 150-500 mg 150-1,000 mg
Dapagliflozin and Metformin	Type 2 diabetes mellitus: Extended-release tablet: initial, based on current regimen once daily in the morning with food; adjust to a maximum of 10-2,000 mg	Safety and efficacy in children have not been established.	Extended-release tablet: 2.5-1,000 mg 5-500 mg 5-1,000 mg 10-500 mg 10-1,000 mg
Dapagliflozin and Saxagliptin	Type 2 diabetes mellitus: Tablet: initial, 5-5 mg once daily in the morning with or without food; in patients tolerating initial dose, may increase to 10-5 mg	Safety and efficacy in children have not been established.	Tablet: 5-5 mg 10-5 mg
Empagliflozin and Linagliptin	Type 2 diabetes mellitus: Tablet: initial, 10-5 mg once daily in the morning with or without food; in patients tolerating initial dose, may increase to 20-5 mg	Safety and efficacy in children have not been established.	Tablet: 10-5 mg 25-5 mg
Empagliflozin and Metformin	Type 2 diabetes mellitus: Extended-release tablet: initial, based on current regimen once daily with a meal in the morning; adjust to a maximum of 25-2,000 mg Tablet: initial, based on current regimen twice daily with meals; adjust to a maximum of 25-2,000 mg	Type 2 diabetes mellitus in patients ≥10 years of age: Tablet: initial, based on current regimen twice daily with meals; adjust to a maximum of 25-2,000 mg	Extended-release tablet: 5-1,000 mg 10-1,000 mg 12.5-1,000 mg 25-1,000 mg Tablet: 5-500 mg 5-1,000 mg 12.5-500 mg 12.5-1,000 mg

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
Empagliflozin, Linagliptin, and Metformin	Type 2 diabetes mellitus: Extended-release tablet: initial, based on current regimen once daily with a meal in the morning; adjust to a maximum of two tablets a day	Safety and efficacy in children have not been established.	Extended-release tablet: 5-2.5-1,000 mg 10-5-1,000 mg 12.5-2.5-1,000 mg 25-5-1,000 mg
Ertugliflozin and Metformin	Type 2 diabetes mellitus: Tablet: initial, based on current regimen twice daily with meals; adjust to a maximum of 15-2,000 mg	Safety and efficacy in children have not been established.	Tablet: 2.5-500 mg 2.5-1,000 mg 7.5-500 mg 7.5-1,000 mg
Ertugliflozin and Sitagliptin	Type 2 diabetes mellitus: Tablet: initial, 5-100 mg once daily in the morning with or without food; in patients tolerating initial dose, may increase to 15-100 mg	Safety and efficacy in children have not been established.	Tablet: 5-100 mg 15-100 mg

*Dapagliflozin is not recommended for use to improve glycemic control in adults with type 2 diabetes mellitus with an eGFR <45 mL/min/1.73 m^2. Dapagliflozin is likely to be ineffective in this setting based upon its mechanism of action.

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the sodium-glucose cotransport 2 inhibitors are summarized in Table 10.

Table 10. Comparative Clinical Trials with the Sodium-glucose Cotransport 2 Inhibitors

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Chronic Kidney Disease				
Heerspink et al.[23] (2020) DAPA-CKD Dapagliflozin 10 mg once daily vs placebo	DB, MC, RCT Adults with eGFR 25 to 75 mL/min and a urinary albumin-to-creatinine ratio of 200 to 5000 who were receiving a stable dose of an ACE inhibitor or ARB (unless unable to take ACE/ARBs)	N=4,304 Median of 2.4 years	Primary: First occurrence of any of the following: a decline of at least 50% in the eGFR (confirmed by a second serum creatinine measurement after ≥28 days), the onset of end-stage kidney disease (defined as maintenance dialysis for ≥28 days, kidney transplantation, or an eGFR of <15 mL/min confirmed by a second measurement after ≥28 days), or death from renal or cardiovascular causes Secondary: Hierarchical evaluation of ach outcome	Primary: The independent data monitoring committee recommended that the trial be discontinued because of clear efficacy, on the basis of 408 primary outcome events. The primary composite outcome occurred in 197 participants (9.2%) in the dapagliflozin group and 312 participants (14.5%) in the placebo group (HR, 0.61; 95% CI, 0.51 to 0.72; P<0.001). Secondary: The incidence of each secondary outcome was lower in the dapagliflozin group than in the placebo group. The hazard ratio for the kidney composite of a sustained decline in the eGFR of at least 50%, end-stage kidney disease, or death from renal causes was 0.56 (95% CI, 0.45 to 0.68; P<0.001). The hazard ratio for the composite of death from cardiovascular causes or hospitalization for heart failure was 0.71 (95% CI, 0.55 to 0.92; P=0.009). There were 101 deaths (4.7%) from any cause in the dapagliflozin group and 146 (6.8%) in the placebo group (HR, 0.69; 95% CI, 0.53 to 0.88; P=0.004).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Heart Failure				
McMurray et al.[24] (2019) DAPA-HF Dapagliflozin 10 mg once daily vs placebo in addition to recommended therapy	DB, MC, RCT Patients ≥18 years of age with NYHA class II, III, or IV HF and an EF of 40% or less	N=4,744 Median of 18.2 months	Primary: Composite of worsening HF (hospitalization or an urgent visit resulting in intravenous therapy for HF) or cardiovascular death Secondary: Composite of hospitalization for HF or cardiovascular death	Primary: The primary outcome occurred in 16.3% of patients in the dapagliflozin group and in 21.2% of patients in the placebo group (HR, 0.74; 95% CI, 0.65 to 0.85; P<0.001). Secondary: The incidence of the secondary composite outcome was lower in the dapagliflozin group than in the placebo group (HR, 0.75; 95% CI, 0.65 to 0.85; P<0.001).
Solomon et al.[25] (2022) DELIVER Dapagliflozin 10 mg once daily vs placebo in addition to usual therapy	DB, MC, PG, RCT Patients ≥40 years of age with chronic heart failure and a left ventricular ejection fraction >40%	N=6,263 Median of 2.3 years	Primary: Composite of worsening heart failure (which was defined as either an unplanned hospitalization for heart failure or an urgent visit for heart failure) or cardiovascular death Secondary: Total number of worsening heart failure events and cardiovascular deaths, the change	Primary: The primary outcome occurred in 16.4% of patients in the dapagliflozin group and in 19.5% of patients in the placebo group (hazard ratio, 0.82; 95% CI, 0.73 to 0.92; P<0.001). Secondary: The number of cardiovascular deaths and first and recurrent worsening heart failure events was lower in the dapagliflozin group than in the placebo group in the overall population (rate ratio, 0.77; 95% CI, 0.67 to 0.89; P<0.001) and among the patients with a left ventricular ejection fraction of less than 60% (rate ratio, 0.77; 95% CI, 0.65 to 0.90; P=0.002). The change from baseline to month 8 in the KCCQ total symptom score indicated a benefit with dapagliflozin as compared with placebo with respect to symptoms of heart failure (win ratio, 1.11; 95% CI, 1.03 to 1.21; P=0.009; mean placebo-corrected difference between baseline and month 8 among survivors, 2.4 points; 95% CI, 1.5 to 3.4). The incidence of the components of the primary outcome favored the dapagliflozin group both in the overall population and among those with a left ventricular ejection fraction of less than 60%, including worsening heart failure (hazard ratio

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			from baseline in the total symptom score on the Kansas City Cardiomyopathy Questionnaire (KCCQ; scores range from 0 to 100, with higher scores indicating fewer symptoms and physical limitations) at month 8, cardiovascular death, and death from any cause	in the overall population, 0.79; 95% CI, 0.69 to 0.91) and cardiovascular death (hazard ratio, 0.88; 95% CI, 0.74 to 1.05), as well as death from any cause (hazard ratio, 0.94; 95% CI, 0.83 to 1.07).
Packer et al.[26] (2020) EMPEROR-Reduced Empagliflozin 10 mg once daily vs placebo in addition to recommended therapy	DB, MC, RCT Patients ≥18 years of age with NYHA class II, III, or IV HF and an EF of 40% or less	N=3,730 Median of 16 months	Primary: Composite of adjudicated cardiovascular death or hospitalization for HF, analyzed as the time to the first event Secondary: Occurrence of all adjudicated hospitalizations for HF, including first and recurrent events; rate of the decline in the eGFR	Primary: The primary composite outcome occurred in 361 patients (19.4%) in the empagliflozin group and in 462 patients (24.7%) in the placebo group (HR, 0.75; 95% CI, 0.65 to 0.86; P<0.001). The hazard ratios for the effect of empagliflozin on cardiovascular death and on the first hospitalization for heart failure were 0.92 (95% CI, 0.75 to 1.12) and 0.69 (95% CI, 0.59 to 0.81), respectively. During the trial period, the number of patients who would need to have been treated with empagliflozin to prevent one primary event was 19 (95% CI, 13 to 37). Secondary: The total number of hospitalizations for HF was lower in the empagliflozin group than in the placebo group, with 388 events and 553 events, respectively (HR, 0.70; 95% CI, 0.58 to 0.85; P<0.001). The rate of the decline in the eGFR over the duration of the double-blind treatment period was slower in the empagliflozin group than in the placebo group (–0.55 mL/min/1.73 m^2 per year vs. –2.28 mL/min/1.73 m^2 per year), for a between-group difference of 1.73 mL/min/1.73 m^2 per year (95% CI, 1.10 to 2.37; P<0.001).
Anker et al.[27]	DB, PC, PG, RCT	N=5,988	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2021) EMPEROR-Reduced Empagliflozin 10 mg once daily vs placebo in addition to usual therapy	Adults with class II-IV heart failure and an ejection fraction >40%	Median of 26.2 months	Composite of cardiovascular death or hospitalization for heart failure Secondary: Occurrence of all adjudicated hospitalizations for heart failure, including first and recurrent events; rate of decline in the eGFR	A primary outcome event occurred in 13.8% of patients in the empagliflozin group and in 17.1% of patients in the placebo group (hazard ratio, 0.79; 95% CI, 0.69 to 0.90; P<0.001). Secondary: The total number of hospitalizations for heart failure was lower with empagliflozin than with placebo (hazard ratio, 0.73; 95% CI, 0.61 to 0.88; P<0.001). The rate of decline in the eGFR was slower in the empagliflozin group than in the placebo group (–1.25 vs –2.62 ml per minute per 1.73 m^2 per year; P<0.001).
Type 2 Diabetes – Monotherapy				
Stenlof et al.[28] (2013) DIA3005 Canagliflozin 100 mg QD vs canagliflozin 300 mg QD vs placebo Patients received metformin rescue if FPG was >270 mg/dL after day 1 to week 6; >240 mg/dL	AC, DB, MC, PC, RCT Patients ≥18 and <80 years of age with T2DM, FPG <270 mg/dL and no antihyperglycemic therapy and an HbA_{1c} ≥7.0 and <10.0% or prior metformin plus sulfonylurea combination therapy and an HbA_{1c} ≥6.5 and <9.5%	N=584 (N=91 enrolled in the hyper-glycemic substudy) 26 weeks followed by a 26 week ES using active control (sitagliptin)	Primary: Change in HbA_{1c} level from baseline to week 26 Secondary: Proportion of patients with HbA_{1c} <7.0%, change in FPG, PPG and systolic blood pressure, percent change in body weight, triglyceride level, HDL-C, apolipoprotein B and safety endpoints	Primary: At the end of treatment, the 100 and 300 mg QD doses resulted in a statistically significant improvement in HbA_{1c} (-1.03 and -0.77 vs 0.14%, respectively; P<0.001 for both doses) compared to placebo. Secondary: Both doses also resulted in a greater proportion of patients achieving an HbA_{1c} <7.0% (45 and 62 vs 21%, respectively; P<0.01), significant reductions of FPG (-27 and -35 vs 8 mg/dL, respectively; P<0.01), significant reductions of PPG (-43 and -59 vs 5 mg/dL, respectively; P<0.01), and in percent body weight reduction compared to placebo (-2.8 and -3.9 kg, respectively; P<0.01). From baseline, with the 100 and 300 mg doses, there were decreases in systolic blood pressure (-3.7 and -5.4 mm Hg, respectively) and increases in HDL-C (11.2 and 10.6 vs 4.5 mg/dL, respectively; P<0.01) relative to placebo. There was also a significantly smaller increase from baseline in triglycerides, including a decrease with the 300 mg dose (2.5 and -2.3 vs 7.9 mg/dL, respectively; P<0.01).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
after week 6 to week 12; or >200 mg/dL after week 12 to week 26. A substudy was conducted for patients with hyperglycemia. These patients were not allowed to receive placebo. Following completion of the study, patients randomized to receive placebo were transitioned to therapy with sitagliptin.				In a subset of patients with samples sufficient for analysis (n=349), greater increases in apolipoprotein B levels were seen with canagliflozin 100 (1.2%) and 300 mg (3.5%) than with placebo (0.9%). Urinary tract infections, genital mycotic infections, and adverse events related to osmotic diuresis and reduced intravascular volume occurred at higher rates with both doses of canagliflozin than with placebo. The incidence of documented hypoglycemic episodes prior to rescue therapy was similar between the treatment groups (canagliflozin 100 mg, 3.6%; canagliflozin 300 mg, 3.0%; placebo, 2.6%), and no severe hypoglycemic episodes were reported. Efficacy was maintained throughout the 52 week study period and the adverse event profile was similar through the 26 week extension period of the study.
Bode et al.[29] (abstract) (2013) Canagliflozin 100 mg QD vs canagliflozin 300 mg QD vs placebo	DB, MC, PC, RCT Patients 55 to 80 years of age with T2DM, an HbA_{1c} ≥7.0 and <10% despite treatment with blood glucose lowering therapy	N=716 26 weeks	Primary: Change in HbA_{1c} level from baseline to week 26 Secondary: Proportion of patients with HbA_{1c} <7.0%, change in FPG, and systolic blood pressure, percent change in body weight, triglyceride level, and HDL-C	Primary: At 26 weeks, significant reductions in HbA_{1c} were observed in all canagliflozin treatment groups compared placebo (-0.60 and -0.73% for canagliflozin 100 and 300 mg QD respectively vs -0.03% for placebo; P<0.001 for all doses). Secondary: At 26 weeks, a greater proportion of patients achieved an HbA_{1c} <7.0% with canagliflozin compared to placebo (percent not reported; P<0.001) At week 26, greater reductions in FPG, systolic blood pressure, and increased HDL-C levels were observed with canagliflozin vs placebo (P< 0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Ferranini et al.[30] (2010) Dapagliflozin 2.5 mg QD vs dapagliflozin 5 mg QD vs dapagliflozin 10 mg QD vs placebo Patients were divided into QAM and QPM dosing cohorts. In addition, those with HbA_{1c} >10.0 and ≤12.0% were evaluated separately in a high HBA_{1c} cohort. The QAM dosing cohort was used for evaluation of primary and secondary endpoints.	DB, MC, PC, PG, RCT Patients with T2DM, 18 to 77 years of age, who were treatment naïve with inadequately controlled blood sugar, BMI ≤45 kg/m^2 and fasting C-peptide ≥1.0 ng/mL	N=485 24 weeks	Primary: Change from baseline in HBA_{1c} Secondary: Change from baseline in FPG and body weight and safety assessments	Primary: At week 24, dapagliflozin 5 and 10 mg QAM provided significant improvements in HbA_{1c} compared to placebo (0.8%, -0.9% vs -0.2%, respectively; P<0.05 for 5 and 10 mg comparisons). Secondary: Change in FPG (-24.1 and -28.8 vs -4.1 mg/dL, respectively) from baseline was also significantly greater in the 5 and 10 mg QAM comparison compared to placebo (P<0.05 for both comparisons). Changes in HbA_{1c} and FPG for the 2.5 mg arm and changes in weight for all three comparisons also favored the treatment arm; however differences were not considered significant. In both exploratory cohorts (QAM dosing and high HbA_{1c}), dapagliflozin had greater reductions in primary and secondary analyses compared to placebo. However, in the high HbA_{1c} cohort the reduction compared to placebo was considered numerically greater. Treatment with dapagliflozin did not result in any clinically meaningful changes from baseline in serum electrolytes, serum albumin or renal function. Signs, symptoms, and other reports suggestive of urinary tract infections and genital infection were more frequently noted in the dapagliflozin arms. There were no major episodes of hypoglycemia.
Bailey et al.[31] (2012)	DB, MC, PC, PG, RCT	N=282	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Dapagliflozin 1 mg QD vs dapagliflozin 2.5 mg QD vs dapagliflozin 5 mg QD vs placebo	Patients with T2DM, 18 to 77 years of age, who were treatment naïve with inadequately controlled blood sugar, BMI ≤45 kg/m^2 and fasting C-peptide ≥0.34 ng/mL	24 weeks	Change from baseline in HbA_{1c} Secondary: Change from baseline in FPG and body weight, glucose after two hour liquid meal, percentage of patients with HbA_{1c} <7.0% and safety assessments	At week 24, dapagliflozin 1, 2.5 and 5 mg QD provided significant improvements in HbA_{1c} compared to placebo (-0.7%, -0.7%, -0.8% vs 0.2%, respectively; P<0.05 for all comparisons). Secondary: Changes in FPG and body weight and glucose after two hour liquid meal were significantly lower in the dapagliflozin arms compared to placebo (P<0.05 for all comparisons). The change in percentage of patients with HbA_{1c} <7.0% was greater in the dapagliflozin arms; however only the 1 mg QD arm was considered significantly greater than placebo (53.6 vs 24.6%, respectively; P<0.05). No major episodes of hypoglycemia were reported during the study, and frequency of minor episodes was similar for dapagliflozin and placebo groups. No clinically meaningful changes were observed in serum electrolytes, serum albumin, or renal function parameters.
Bailey et al.[32] (2015) Dapagliflozin 2.5 mg QD vs dapagliflozin 5 mg QD vs dapagliflozin 10 mg QD vs placebo	DB, PC, RCT Patients with type 2 diabetes 18 to 77 years of age and inadequate glycemic control on diet and exercise (HbA_{1c} 7.0 to 10.0%)	N=274 102 weeks	Primary: Change from baseline in HbA_{1c} over 102 weeks, FPG, body weight, percentage of patients achieving HbA_{1c} <7.0% Secondary: Not reported	Primary: At 102 weeks, significant differences vs placebo+low-dose metformin with dapagliflozin 5 and 10 mg were observed for HbA_{1c} (−5.8 mmol/mol [−0.53%], P=0.018; and −4.8 mmol/mol [−0.44%], P=0.048), respectively); and for FPG (−0.69 mmol/L, P=0.044; and −1.12 mmol/l, P=0.001, respectively). For body weight, the difference between the dapagliflozin 10-mg group and the placebo+low-dose metformin group was significant (−2.60 kg; P=0.016). Hypoglycemic events were uncommon, with rates of 5.3% for placebo+low-dose metformin group and 0 to 4.6% for the dapagliflozin groups. Genital infections and urinary tract infections were more common in the dapagliflozin groups than in the placebo+low-dose metformin group. The proportion of participants who achieved a level of HbA_{1c} <7% at 102 weeks was greater in the dapagliflozin 5 mg (33.2%) than in the placebo+low-dose metformin group (18.5%), resulting in a dapagliflozin 5 mg vs placebo+low-dose metformin group difference of 14.8% (95% CI, 0.3 to 29.2). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
After 24 weeks, low-dose double-blind metformin 500 mg/day was added to the placebo group regimen.				
Henry et al.[33] (2012) Dapagliflozin 5 or 10 mg QD vs metformin extended-release titrated to 2,000 mg daily vs dapagliflozin 5 or 10 mg QD and metformin titrated to 2,000 mg daily Dapagliflozin was dosed at 5 mg QD and 10 mg QD in the first and second trials, respectively.	AC, DB, MC, PG, RCT Patients with T2DM, 18 to 77 years of age, who were treatment naïve with inadequately controlled blood sugar, BMI ≤45 kg/m^2 and fasting C-peptide ≥0.34 ng/mL	N=598 for Study 1, N=638 for Study 2 2 trials each 24 weeks in duration	Primary: Change from baseline in HbA_{1c} Secondary: Change from baseline in FPG and body weight, glucose after two hour liquid meal, percentage of patients with HbA_{1c} <7.0% and safety assessments	Primary: Combination therapy led to significantly greater reductions in HbA_{1c} compared to either monotherapy (dapagliflozin and metformin) in the first study (-2.0 vs -1.2 and -1.4%, respectively; P<0.0001) and second study (-2.0 vs -1.5 and -1.4%, respectively; P<0.0001). In Study 2, treatment with dapagliflozin 10 mg (as monotherapy) was also non-inferior to metformin (as monotherapy) for reduction of HbA_{1c}. Secondary: Combination therapy was statistically superior to monotherapy in reduction of FPG (P<0.0001 for both studies); combination therapy was more effective than metformin for weight reduction (P<0.0001). Events suggestive of genital infection were reported in 6.7, 6.9 and 2.0% (Study 1) and 8.5, 12.8 and 2.4% (Study 2) of patients in combination, dapagliflozin and metformin groups; events suggestive of urinary tract infection were reported in 7.7, 7.9 and 7.5% (Study 1) and 7.6, 11.0 and 4.3% (Study 2) of patients in the respective groups. No major hypoglycemia was reported.
Roden et al.[34] (2013) Empagliflozin 10 mg QD	AC, DB, MC, PC, RCT Patients with type 2 DM and HbA_{1c} of ≥7% to <10%	N=986 24 weeks	Primary: HbA_{1c} Secondary:	Primary: At week 24, empagliflozin 10 mg or 25 mg daily provided statistically significant reductions in HbA_{1c} compared to placebo (-0.7% and -0.8% vs 0.1%, respectively; P<0.0001 for both comparisons).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs empagliflozin 25 mg QD vs sitagliptin 100 mg QD vs placebo			FPG, body weight, SBP and safety evaluations	In the active comparator analysis, adjusted mean difference in change from baseline HbA_{1c} at week 24 was -0.73% (95% CI, -0.88 to -0.59; P<0.0001) for sitagliptin compared to placebo. Secondary: At week 24, empagliflozin 10 mg or 25 mg daily provided statistically significant reductions in FPG (-19 mg/dL and -25 mg/dL vs 12 mg/dL, respectively; P values not reported) and body weight (-2.8 kg and -3.2 kg vs -0.4 kg, respectively; P values not reported) compared with placebo. SBP was statistically significantly reduced compared to placebo by -2.6 mmHg (placebo-adjusted, P=0.0231) in patients randomized to 10 mg of empagliflozin and by -3.4 mmHg (placebo-corrected, P=0.0028) in patients randomized to 25 mg of empagliflozin. There were 140 (61%) patients in the placebo group that reported adverse events (four [2%] severe and six [3%] serious), as did 123 (55%) patients in the empagliflozin 10 mg group (eight [4%] severe and eight [4%] serious), 135 (60%) patients in the empagliflozin 25 mg group (seven [3%] severe and five [2%] serious), and 119 (53%) patients in the sitagliptin group (five [2%] severe and six [3%] serious).
Barnett et al.[35] (2014) Empagliflozin 10 mg QD vs empagliflozin 25 mg QD vs placebo	DB, MC, PC, PG, RCT Patients with type 2 DM, HbA_{1c} of ≥7% to <10%, BMI ≤45 kg/m^2 and a baseline eGFR <90 mL/min/1.73 m^2	N=738; 290 with mild renal impairment ([eGFR ≥60 to <90 mL/min/1.73 m^2], 374 with moderate renal impairment [eGFR ≥30 to <60 mL/min/1.73 m^2], and 74 with severe renal	Primary: HbA_{1c} Secondary: FPG, body weight, SBP and safety evaluations	Primary: At week 24, empagliflozin 25 mg provided statistically significant reduction in HbA_{1c} relative to placebo in patients with mild to moderate renal impairment (-0.5% placebo-corrected comparison; P<0.0001). The glucose lowering efficacy decreased with decreasing level of renal function in the mild to moderate range. For patients with severe renal impairment, the analyses of changes in HbA_{1c} and FPG showed no discernible treatment effect compared to placebo. Secondary: At week 24, empagliflozin 10 mg or 25 mg QD provided statistically significant reductions in FPG in the mild renal impairment group (-13.86 mg/dL and –18 mg/dL vs 5.58 mg/dL, respectively; P<0.0001) and moderate renal impairment group (-9 mg/dL vs 10.8 mg/dL, respectively; P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Patients with Stage III chronic kidney disease (eGFR ≥ <60 mL/min/1.73 m^2) were only assigned to the empagliflozin 25 mg QD arm.		impairment [eGFR <30 mL/min/1.73 m^2]). 52 weeks		Significant body weight and SBP decreases were noted in most treatment comparisons. Adverse events included UTI and genital mycotic infections.
Terra et al.[36] (2017) VERTIS MONO Ertugliflozin 5 mg QD vs ertugliflozin 15 mg QD vs placebo Glycemic recue therapy with open-label metformin was prescribed for subjects who exceeded certain hyperglycemia thresholds.	DB, MC, PC, PG, RCT Patients ≥18 years of age with type 2 DM and HbA_{1c} ≥7.0% to ≤10.5% despite diet and exercise	N=461 52 weeks (two 26 week phases)	Primary: Change in HbA_{1c} from baseline to week 26 Secondary: Change from baseline at week 26 in FPG level, body weight, 2-hour PPG, systemic blood pressure, diastolic blood pressure and the proportion of subjects with HbA_{1c} <7.0% at week 26	Primary: The placebo-adjusted least squares mean HbA_{1c} changes from baseline at week 26 were -0.99% and -1.16% for the ertugliflozin 5 and 15 mg doses, respectively (P< 0.001 for both doses). Secondary: Both doses of ertugliflozin significantly lowered FPG and 2-hour PPG levels and body weight (P<0.001 for all). The placebo-adjusted least-squares mean FPG changes from baseline were -1.92 mmol/L (95% CI, -2.37 to -1.46) and -2.44 (95% CI, -2.90 to -1.98), body weight changes from baseline were -1.76 kg (95% CI, -2.57 to -0.95) and -2.16 kg (95% CI, -2.98 to -1.34) and 2-hour PPG level changes from baseline were -3.83 mmol/L (95% CI, -4.62 to -3.04) and -3.74 (95% CI, -4.54 to -2.94) for ertugliflozin 5 and 15 mg, respectively . The placebo-adjusted differences in changes from baseline in SBP were not statistically significant; as a result, testing for changes in diastolic blood pressure was not performed. The proportions of subjects with HbA_{1c} <7.0% were 28.2% and 35.8% in the ertugliflozin 5 and 15 mg groups, respectively, compared with 13.1% in the placebo group.
Type 2 Diabetes – Combination Therapy				
Rosenstock et al.[37] (2012)	DB, MC, PC, RCT Patients 18 to 65 years of age with	N=451 12 weeks	Primary: Change in HbA_{1c} level from baseline to week 12	Primary: At 12 weeks, significant reductions in HbA_{1c} were observed in all canagliflozin treatment groups compared placebo (-0.79, -0.76, -0.70, -

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Canagliflozin 50 mg QD vs canagliflozin 100 mg QD vs canagliflozin 200 mg QD vs canagliflozin 300 mg QD vs canagliflozin 300 mg BID vs sitagliptin 100 mg QD vs placebo	T2DM, an HbA_{1c} ≥7.0 and <10.5%, were on metformin monotherapy at a stable (≥3 months) dose of ≥1,500 mg/day, had a stable body weight and BMI 25 to 45 kg/m^2 (24 to 45 kg/m^2 for those of Asian descent), and had serum creatinine <1.5 mg/dL for men and <1.4 mg/dL for women		Secondary: Change in FPG, change in body weight, and overnight urinary glucose -to-creatinine ratio	0.92, -0, and -0.95% for canagliflozin 50, 100, 200, and 300 mg QD and 300 mg BID, respectively, vs -0.22% for placebo; P<0.001 for all doses). At 12 weeks, significant reductions in HbA_{1c} were observed with sitagliptin 100 mg compared to placebo (-0.74 vs -0.22%; P<0.001). Secondary: At 12 weeks, a greater proportion of patients achieved the target HbA_{1c} <7.0% with canagliflozin doses of 100 mg QD and above (53 to 72%) and with sitagliptin (65%) compared to placebo (34%; P<0.05 for canagliflozin and sitagliptin). Significantly greater reductions in FPG were observed at 12 weeks with all canagliflozin doses (-16.2 to -27.0 mg/dL) compared to an increase observed with placebo (3.6 mg/dL; P<0.001 for all doses). FPG reductions were maximized with the 200 mg QD dose. Sitagliptin reduced FPG -12.6 mg/dL (P value compared to placebo not reported). Significant weight reductions were observed in canagliflozin groups relative to placebo, -2.3 to -3.4% (-2.0 to -2.9 kg; P<0.001 for all doses) at week 12. Reductions observed in the placebo and sitagliptin treatment groups were -1.1% (-0.8 kg) and -0.6% (-0.4 kg) from baseline, respectively. All doses of canagliflozin increased the overnight urinary glucose-to-urinary creatinine ratio (35.4 to 61.6 mg/mg) as compared to placebo (1.9 mg/mg; P<0.001 for all doses). Sitagliptin reduced urinary glucose-to-urinary creatinine ratio -1.9 mg/mg (P value compared to placebo not reported).
Lavalle-González et al.[38] (2013) canagliflozin 100 mg	DB, PG, RCT Patients with type 2 diabetes aged ≥18 and ≤80 years who	N=1,284 2 week placebo run-in, 26 week placebo- and	Primary: Change from baseline in HbA_{1c} at week 26 Secondary:	Primary: At week 26, canagliflozin 100 mg and 300 mg significantly reduced HbA_{1c} from baseline compared with placebo (P<0.001 for both). Secondary:

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vs canagliflozin 300 mg vs sitagliptin 100 mg vs placebo	had inadequate glycemic control (HbA_{1c} ≥7.0% and ≤10.5%) on metformin therapy	active-control treatment period (period I), followed by a 26 week active-control treatment period (period II), and a 4 week follow-up period	Changes in HbA_{1c} (week 52) and FPG, body weight, and systolic blood pressure (BP; weeks 26 and 52), adverse events	At week 26, a greater proportion of participants treated with canagliflozin 100 mg and 300 mg achieved HbA_{1c} <7.0% than with placebo (45.5, 57.8, and 29.8%, respectively; P=0.000 for both); 54.5% of sitagliptin-treated participants achieved HbA_{1c} <7.0%. Both canagliflozin doses significantly reduced FPG and 2-hour PPG at week 26 vs placebo (P<0.001 for all); FPG and 2-hour PPG were also reduced from baseline with sitagliptin. At 52 weeks, canagliflozin 100 mg and 300 mg demonstrated non-inferiority to sitagliptin 100 mg in HbA_{1c}-lowering effect. Canagliflozin 300 mg demonstrated statistical superiority to sitagliptin in HbA_{1c}-lowering effect. Canagliflozin 100 mg and 300 mg significantly reduced body weight compared with sitagliptin. Canagliflozin 100 mg and 300 mg significantly decreased systolic BP relative to sitagliptin at 52 weeks. The change in diastolic BP from baseline was −1.8 mmHg with both canagliflozin doses and −0.3 mmHg with sitagliptin. Overall incidences of adverse events and adverse event-related discontinuations were generally comparable across groups over 52 weeks. Canagliflozin was associated with a higher incidence of genital mycotic infections in men and women. These were generally mild or moderate in intensity and led to few discontinuations.
Neal et al.[39] (2015) CANVAS Canagliflozin 100 mg vs canagliflozin 300 mg vs placebo	DB, MC, PC, RCT Patients with type 2 diabetes who have inadequate glycemic control (HbA_{1c} ≥7.0% and ≤10.5%), despite current management with glucose-lowering strategies, and are at an elevated risk of cardiovascular disease	N=2,074 52 weeks	Primary: Change in HbA_{1c} from baseline at week 18 Secondary: Body weight, FPG, blood pressure, lipids at 18 and 52 weeks	Primary: Both doses of canagliflozin significantly reduced the primary outcome of HbA_{1c} relative to placebo at week 18 (both P<0.001), with comparable reductions also seen at week 52. Secondary: There were also reductions in the secondary outcomes of body weight and FPG (all P<0.001) and increases in the proportion of patients achieving HbA_{1c} <7.0% (both P<0.001) with both canagliflozin doses versus placebo at week 18. Similar effects were seen for all outcomes at week 52. Canagliflozin 100 and 300 mg also provided dose-dependent reductions in systolic blood pressure compared with placebo at both time points. The higher dose of canagliflozin raised HDL cholesterol levels compared with placebo at both 18 and 52 weeks, but the lower dose raised levels only at 52 weeks. Canagliflozin 100 and 300 mg caused an elevation in LDL cholesterol at 18 and 52 weeks, but there was no detectable change in the

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used in addition to insulin therapy at a dose of ≥20 IU/day				ratio of LDL cholesterol to HDL cholesterol at either time point for either dose.
Neal et al.[40] (2017) CANVAS Canagliflozin 100 mg vs canagliflozin 300 mg vs placebo All groups used in addition to insulin therapy at a dose of ≥20 IU/day	DB, MC, PC, RCT Patients with type 2 diabetes who have inadequate glycemic control (HbA_{1c} ≥7.0% and ≤10.5%), despite current management with glucose-lowering strategies, and are at an elevated risk of cardiovascular disease	N=10,142 Mean follow-up of 188.2 weeks	Primary: Composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke Secondary: Death from any cause, death from cardiovascular causes, progression of albuminuria, and the composite of death from cardiovascular causes and hospitalization for heart failure	Primary: Fewer participants in the canagliflozin group than in the placebo group had a primary outcome event (the composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke): 26.9 vs. 31.5 participants with an event per 1000 patient-years (HR, 0.86; 95% CI, 0.75 to 0.97; P<0.001 for noninferiority; P=0.02 for superiority). Secondary: Superiority was not shown for the first secondary outcome in the testing sequence (death from any cause; P=0.24), and hypothesis testing was discontinued. Although on the basis of the prespecified hypothesis testing sequence the renal outcomes are not viewed as statistically significant, the results showed a possible benefit of canagliflozin with respect to the progression of albuminuria (HR, 0.73; 95% CI, 0.67 to 0.79) and the composite outcome of a sustained 40% reduction in the estimated glomerular filtration rate, the need for renal-replacement therapy, or death from renal causes (HR, 0.60; 95% CI, 0.47 to 0.77).
Mahaffey et al.[41] (2019) CREDENCE Canagliflozin 100 mg daily vs placebo Patients on a background of	DB, MC, RCT Patients ≥30 years of age with type 2 diabetes mellitus with HbA_{1c} between 6.5 and 12% and chronic kidney disease, stratified by previous cardiovascular disease status (primary vs	N=4,401 Median follow-up of 2.62 years	Primary: Composite of end-stage kidney disease (dialysis, transplantation, or a sustained estimated GFR of <15 ml per minute per 1.73 m^2), a doubling of the serum creatinine level, or death from renal or	Primary: Primary prevention participants (n=2181, 49.6%) were younger (61 versus 65 years), were more often female (37% versus 31%), and had shorter duration of diabetes mellitus (15 years versus 16 years) compared with secondary prevention participants (n=2220, 50.4%). In placebo-treated patients, the risk of the primary end point (composite of end-stage kidney disease, doubling serum creatinine, or renal or cardiovascular death) was comparable between the secondary prevention group and the primary prevention group (16.4% versus 14.5%; HR, 1.11; 95% CI, 0.89 to 1.37). Canagliflozin reduced renal outcomes, with no evidence of heterogeneity in the primary and secondary prevention groups. All interaction P values were not significant.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
optimized standard of care	secondary prevention)		cardiovascular causes Secondary: Cardiovascular outcomes	 Secondary: Canagliflozin reduced the risk of major cardiovascular events overall (HR, 0.80; 95% CI, 0.67 to 0.95; P=0.01), with consistent reductions in both the primary (HR, 0.68; 95% CI, 0.49 to 0.94) and secondary (HR, 0.85; 95% CI, 0.69 to 1.06) prevention groups (P for interaction=0.25). Effects were also similar for the components of the composite including cardiovascular death (HR, 0.78; 95% CI, 0.61 to 1.00), nonfatal myocardial infarction (HR, 0.81; 95% CI, 0.59 to 1.10), and nonfatal stroke (HR, 0.80; 95% CI, 0.56 to 1.15). The risk of the primary composite renal outcome and the composite of cardiovascular death or hospitalization for heart failure were also consistently reduced in both the primary and secondary prevention groups (P for interaction >0.5 for each outcome).
Perkovic et al.[42] (2019) CREDENCE Canagliflozin 100 mg daily vs placebo Patients on a background of optimized standard of care	DB, MC, RCT Patients ≥30 years of age with type 2 diabetes mellitus with HbA_{1c} between 6.5 and 12% and chronic kidney disease	N=4,401 Median follow-up of 2.62 years	Primary: Composite of end-stage kidney disease (dialysis, transplantation, or a sustained estimated GFR of <15 ml per minute per 1.73 m^2), a doubling of the serum creatinine level, or death from renal or cardiovascular causes Secondary: Not reported	Primary: The trial was stopped early after a planned interim analysis on the recommendation of the data and safety monitoring committee. At that time, 4,401 patients had undergone randomization, with a median follow-up of 2.62 years. The relative risk of the primary outcome was 30% lower in the canagliflozin group than in the placebo group, with event rates of 43.2 and 61.2 per 1000 patient-years, respectively (HR, 0.70; 95% CI, 0.59 to 0.82; P=0.00001). The relative risk of the renal-specific composite of end-stage kidney disease, a doubling of the creatinine level, or death from renal causes was lower by 34% (HR, 0.66; 95% CI, 0.53 to 0.81; P<0.001), and the relative risk of end-stage kidney disease was lower by 32% (HR, 0.68; 95% CI, 0.54 to 0.86; P=0.002). The canagliflozin group also had a lower risk of cardiovascular death, myocardial infarction, or stroke (HR, 0.80; 95% CI, 0.67 to 0.95; P=0.01) and hospitalization for heart failure (HR, 0.61; 95% CI, 0.47 to 0.80; P<0.001). There were no significant differences in rates of amputation or fracture. Secondary: Not reported
Cefalu et al.[43] CANTATA-SU (2013)	AC, DB, NI, RCT Patients aged 18 to 80 years with type 2 diabetes and an	N=1,450 52 weeks	Primary: Change in HbA_{1c} from baseline Secondary:	Primary: Both canagliflozin doses were non-inferior to glimepiride for lowering of HbA_{1c}, and canagliflozin 300 mg was superior to glimepiride for HbA_{1c} reduction. The least squares mean change from baseline was -0.81, -0.82,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Canagliflozin 100 mg vs canagliflozin 300 mg vs glimepiride titrated to a maximum of 6 or 8 mg/day	HbA_{1c} between 7.0 and 9.5% receiving stable metformin therapy		Percentage change from baseline in bodyweight, proportion of patients with documented hypoglycemic episodes	and -0.93% in the glimepiride, canagliflozin 100 mg, and canagliflozin 300 mg, respectively. Secondary: The proportion of patients with documented hypoglycemic episodes was significantly lower with canagliflozin 100 mg and 300 mg than with glimepiride (P<0.0001 for both). The frequency of severe hypoglycemia was also lower with canagliflozin 100 mg (two [<1%] patients) and 300 mg (three [<1%]) than with glimepiride (15 [3%]). Both canagliflozin doses significantly reduced bodyweight at week 52, whereas a slight increase occurred with glimepiride (P<0.0001 for both canagliflozin doses vs glimepiride).
Leiter et al.[44] (2015) Canagliflozin 100 mg vs canagliflozin 300 mg vs glimepiride (titrated up to 6 or 8 mg/day)	DB, MC, RCT Patients ≥18 and ≤80 years of age with type 2 diabetes and HbA_{1c} ≥7.0% and ≤9.5% whose conditions were stable while receiving metformin therapy (≥2,000 mg/day, or ≥1,500 mg/day if unable to tolerate a higher dose) for ≥10 weeks	N=1,450 104 weeks	Primary: Change in HbA_{1c} from baseline to week 52 Secondary: Change in HbA_{1c}. FPG, blood pressure, body weight, and lipids at week 104	Primary: Both canagliflozin doses were non-inferior to glimepiride for lowering of HbA_{1c}, and canagliflozin 300 mg was superior to glimepiride for HbA_{1c} reduction. Secondary: Over 104 weeks, canagliflozin 100 and 300 mg and glimepiride reduced HbA_{1c} from mean baseline values of 7.78, 7.79, and 7.83% (62 mmol/mol for all), respectively, with changes from baseline to week 104 of −0.65, −0.74, and −0.55% (−7.1, −8.1, and −6.0 mmol/mol), respectively. Reductions in body weight (−4.1, −4.2, and 0.9%, respectively) and systolic blood pressure (−2.0, −3.1, and 1.7 mmHg, respectively) were seen with canagliflozin 100 and 300 mg compared with glimepiride at week 104. The overall adverse event incidence was 73.3, 77.9, and 78.4% with canagliflozin 100 and 300 mg and glimepiride; the incidence of adverse event-related discontinuations was low across groups (6.2, 9.5, and 7.3%, respectively). Incidences of genital mycotic infections, urinary tract infections, and osmotic diuresis–related adverse events were higher with canagliflozin than glimepiride; these were generally mild to moderate in intensity and led to few discontinuations. Fewer patients had hypoglycemia episodes with canagliflozin 100 and 300 mg than glimepiride (6.8, 8.2, and 40.9%). Mild decreases in estimated glomerular

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				filtration rate occurred initially with canagliflozin; these attenuated over 104 weeks.
Rosenstock et al.[45] (2016) Canagliflozin 100 mg and metformin XR vs Canagliflozin 300 mg and metformin XR vs Canagliflozin 100 mg vs Canagliflozin 300 mg vs metformin XR (Metformin XR doses were titrated)	DB, RCT Patients with drug-naïve type 2 diabetes from 18 to 75 years of age	N=1,186 26 weeks	Primary: Change in baseline HbA_{1c} Secondary: Noninferiority in HbA_{1c} lowering with canagliflozin monotherapy versus metformin; changes in FPG, body weight, and SBP; and proportion of patients achieving HbA_{1c} <7.0%	Primary: At week 26, reductions from baseline in HbA_{1c} were seen with CANA100/MET, CANA300/MET, CANA100, CANA300, and MET (–1.77, −1.78, –1.37, –1.42, and –1.30%, respectively), resulting in final mean HbA_{1c} values of 7.0, 7.0, 7.4, 7.3, and 7.4%, respectively. Reductions in HbA_{1c} with CANA100/MET and CANA300/MET were statistically significant versus MET (LS mean differences of –0.46% and –0.48%, respectively; P=0.001 for both) and versus CANA100 and CANA300 (LS mean differences of –0.40% and –0.36%, respectively; P=0.001 for both). Secondary: Noninferiority of HbA_{1c} lowering was also demonstrated with CANA100 and CANA300 versus MET (LS mean differences of –0.06% and –0.11%, respectively; noninferiority P=0.001 for both). At week 26, significant differences in the proportion of patients who achieved HbA1c <7.0% were observed with CANA100/MET and CANA300/MET versus MET (P=0.027 and P=0.016, respectively); 49.6%, 56.8%, 38.8%, 42.8%, and 43.0% of patients achieved HbA1c <7.0% with CANA100/MET, CANA300/MET, CANA100, CANA300, and MET, respectively. Dose-related reductions in FPG were observed with CANA100/MET and CANA300/MET that were greater compared with their respective monotherapies. At week 26, reductions in body weight from baseline were observed across groups (–3.2, –3.9, –2.8, –3.7, and –1.9 kg [−3.5%, –4.2%, –3.0%, –3.9%, and –2.1%] with CANA100/MET, CANA300/MET, CANA100, CANA300, and MET, respectively). CANA100/MET, CANA300/MET, CANA100, and CANA300 provided modest reductions in SBP compared with MET (–2.2, –1.7, –2.2, –2.4, and –0.3 mmHg, respectively). Reductions in SBP with CANA100/MET and CANA300/MET were not statistically significant versus MET (LS mean differences of –1.9 and –1.3 mmHg, respectively).
Lingvay et al.[46] (2019) SUSTAIN 8	DB, MC, RCT	N=788 52 weeks	Primary: Change in	Primary: Treatment with semaglutide led to greater reductions in HbA_{1c} compared with those with canagliflozin, with an estimated change from baseline to

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Canagliflozin 300 mg orally once daily vs semaglutide 1.0 mg subcutaneous once weekly	Adults with uncontrolled type 2 diabetes (HbA_{1c} 7.0 to 10.5%) on stable daily metformin therapy		HbA_{1c} from baseline Secondary: Change in body weight from baseline	week 52 of −1.5 percentage points (standard error [SE], 0.06; −16.0 mmol/mol, SE 0.65) with semaglutide and −1.0 percentage points (0.06; −10.7 mmol/mol, 0.61) with canagliflozin. The estimated treatment difference (ETD) was −0.49 percentage points (95% CI, −0.65 to −0.33; −5.34 mmol/mol, 95% CI −7.10 to −3.57; P<0.0001). Greater proportions of patients achieved prespecified HbA_{1c} targets with semaglutide than with canagliflozin (66% vs 45% achieved HbA_{1c} <7.0% [<53 mmol/mol], OR, 2.77; 95% CI, 1.98 to 3.85; P<0.0001; 53% vs 24% achieved HbA_{1c} ≤6.5% [≤48 mmol/mol], 4.19, 2.97 to 5.92; P<0.0001). Secondary: From an overall mean baseline of 90.2 kg, estimated change in bodyweight was −5.3 kg with semaglutide and −4.2 kg with canagliflozin (ETD, −1.06 kg; 95% CI, −1.76 to −0.36; P=0.0029).
Schernthaner et al.[47] (2013) (abstract) Canagliflozin 300 mg QD vs sitagliptin 100 mg QD vs placebo	AC, DB, RCT Patients with T2DM, receiving a stable dose of metformin and a sulfonylurea	N=755 52 weeks	Primary: Change in HbA_{1c} level from baseline to week 52 Secondary: Change in FPG, systolic blood pressure, body weight, triglycerides, and HDL-C	Primary: At the end of the 52 treatment period, canagliflozin 300 mg once daily was considered non-inferior to and produced significant reductions in HbA_{1c} compared to sitagliptin 100 mg QD (-1.03 and -0.66%; difference, 0.37%; 95% CI, -0.50 to -0.25). Secondary: At week 52, greater reductions in FPG, body weight, and systolic blood pressure were observed with canagliflozin vs sitagliptin (P<0.001).
Jabbour et al.[48] (2018) DURATION-8 extension Exenatide 2 mg once weekly by subcutaneous	DB, MC, RCT Adults (≥18 years of age) with type 2 diabetes and inadequate glycemic control (HbA_{1c} 8.0 to 12.0%) despite	N=695 52 weeks	Primary: Glycemic parameters Secondary: Safety and tolerability	Primary: Treatment with exenatide once weekly plus dapagliflozin resulted in greater mean reductions in HbA_{1c} from baseline to week 28, which were maintained through week 52 (least squares mean change from baseline, −1.75%) compared with exenatide once weekly plus placebo (−1.38%; P=0.006) or dapagliflozin plus placebo (−1.23%; P<0.001). At week 52, mean HbA_{1c} was 6.87% with exenatide once weekly plus dapagliflozin, 7.21% with exenatide once weekly plus placebo, and 7.36% with

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injection plus dapagliflozin 10 mg oral tablets daily vs exenatide once weekly with dapagliflozin-matched oral placebo daily vs dapagliflozin daily with exenatide once weekly–matched placebo injections	stable metformin monotherapy (≥1,500 mg/day)			dapagliflozin plus placebo. The proportions of patients who achieved glycemic goals with exenatide once weekly plus dapagliflozin were generally similar at 28 and 52 weeks. At 52 weeks, more patients achieved an HbA_{1c} level of <7.0% or ≤6.5%, respectively, with exenatide once weekly plus dapagliflozin (37.7% and 26.3%) than with exenatide once weekly plus placebo (30.0% and 17.2%) or dapagliflozin plus placebo (16.5% and 8.7%). Secondary: Exenatide once weekly plus dapagliflozin was well tolerated; similar proportions of patients experienced an adverse event over 52 weeks across all treatment groups. The most common adverse events reported with exenatide once weekly plus dapagliflozin were injection-site nodule, urinary tract infection, headache, and nausea. Most adverse events were mild or moderate in intensity. Patients who received exenatide once weekly plus dapagliflozin and exenatide once weekly plus placebo experienced more gastrointestinal or injection site–related adverse events than those who received dapagliflozin plus placebo.
Müller-Wieland et al.[49] (2018) Dapagliflozin 10 mg vs dapagliflozin 10 mg plus saxagliptin 5 mg vs glimepiride 1 to 6 mg (titrated) Patients on metformin	DB, MC, RCT Patients with type 2 diabetes 18 to ≥75 years of age on stable metformin (≥1500 mg/day) for ≥8 weeks and HbA_{1c} concentration of 7.5 to 10.5%	N=939 52 weeks	Primary: Absolute change from baseline in HbA_{1c} Secondary: Proportion of patients reporting confirmed hypoglycemic episodes during the 52-week treatment period, changes from baseline in total body weight and FPG at week 52, and the time to rescue during the treatment period	Primary: Adjusted mean change from baseline in HbA_{1c} at 52 weeks was −0.82% for dapagliflozin alone and −1.20% for dapagliflozin plus saxagliptin, compared with −0.99% for glimepiride when added to baseline metformin monotherapy. Non-inferiority, based on a prespecified margin of 0.3%, was demonstrated for both dapagliflozin-containing treatment groups, relative to glimepiride, at Week 52. The change in HbA_{1c} from baseline was statistically significantly greater (P=0.001) with dapagliflozin plus saxagliptin than with glimepiride. Secondary: The proportion of patients experiencing at least one episode of confirmed hypoglycemia was low across all groups (<5%) and was significantly lower in both dapagliflozin-containing treatment groups than in the glimepiride group (P<0.001, both comparisons). Total body weight decreased from baseline in both dapagliflozin-containing treatment groups, whereas it increased in the glimepiride group. Reductions in FPG from baseline were statistically significantly greater with dapagliflozin plus saxagliptin than with glimepiride as add-on therapy, and dapagliflozin

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monotherapy (≥1500 mg/day)				was non-inferior to glimepiride as add-on therapy. The proportions of patients who met rescue criteria during the treatment period were 18.6%, 8.3% and 21.4% in the dapagliflozin, dapagliflozin plus saxagliptin and glimepiride add-on to metformin groups, respectively.
Nauck et al.[50] (2011) Dapagliflozin 10 mg QD vs glipizide 10 mg BID Studied agent added on to OL dosed metformin.	AC, DB, MC, PG, RCT Patients with T2DM, ≥18 years of age, who were previously treated with oral anti-diabetic agents, inadequately controlled blood sugar, BMI ≤45 kg/m^2 and fasting C-peptide ≥0.34 ng/mL	N=801 52 weeks	Primary: Change from baseline in HbA_{1c} Secondary: Change from baseline in body weight, percentage of patients who lost >5% of body weight, percentage of patients with ≥1 hypoglycemic event and systolic blood pressure changes	Primary: At week 52, both dapagliflozin plus metformin and glipizide plus metformin therapies had identical HbA_{1c} reductions of 0.52% which met the criteria for non-inferiority. Secondary: Treatment with dapagliflozin resulted in weight loss of -3.22 kg vs weight gain of 1.44 kg with glipizide. Other secondary endpoints including percentage of patients who lost >5% of body weight and percentage of patients with ≥1 hypoglycemic event also favored dapagliflozin (P<0.001). Mean systolic blood pressure was reduced with dapagliflozin but not with glipizide at 208 weeks (in an extension cohort): difference, −3.67 mmHg (95% CI, −5.92 to −1.41).
Del Prato et al.[51] (2015) Dapagliflozin vs glipizide Studied agent added on to OL dosed metformin.	DB, MC, RCT Patients with T2DM, ≥18 years of age, who were previously treated with oral anti-diabetic agents, inadequately controlled blood sugar, BMI ≤45 kg/m^2 and fasting C-peptide ≥0.34 ng/mL	N=801 4 year extension study	Primary: Therapeutic glycemic response defined as HbA_{1c} <7.0% Secondary: FPG, blood pressure, body weight, safety	Primary: At 208 weeks, dapagliflozin compared with glipizide produced sustained reductions in HbA_{1c}: −0.30% (95% CI, −0.51 to −0.09), in total body weight: −4.38 kg (95% CI −5.31 to −3.46) and in systolic blood pressure: −3.67 mmHg (95% CI −5.92 to −1.41). Secondary: Dapagliflozin was not associated with glomerular function deterioration, while this occurred more frequently in patients in the glipizide group. Fewer patients reported hypoglycemia in the dapagliflozin compared with the glipizide group (5.4 vs 51.5%). Genital and urinary tract infections were more common with dapagliflozin than with glipizide, but their incidence decreased with time and all events responded well to antimicrobial treatment.
Bailey et al.[52] (2010)	DB, MC, PC, PG, RCT	N=546 24 weeks	Primary:	Primary: Treatment with dapagliflozin 2.5, 5 or 10 mg plus metformin resulted in a significantly greater reduction from baseline to week 24 in HbA_{1c}

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Dapagliflozin 2.5 mg QD vs dapagliflozin 5 mg QD vs dapagliflozin 10 mg QD vs placebo	Patients 18 to 77 years of age with T2DM with a HbA_{1c} of 7.0 to 10.0% who have been on a stable dose of metformin (≥1,500 mg/day) for ≥8 weeks		Change in HbA_{1c} from baseline at week 24 Secondary: Change in fasting blood glucose and weight from baseline at week 24	compared to placebo plus metformin (-0.67, -0.70 and -0.84 for dapagliflozin 2.5, 5 and 10 mg, respectively, compared to -0.30 for placebo; P<0.05 for all). Secondary: Treatment with dapagliflozin 2.5, 5 or 10 mg plus metformin resulted in significantly greater reductions from baseline to week 24 in fasting blood glucose and weight compared to the placebo group (P<0.05 for all).
Bailey et al.[53] (2013) Dapagliflozin 2.5 mg QD vs dapagliflozin 5 mg QD vs dapagliflozin 10 mg QD vs placebo	DB, ES, MC, PC, PG, RCT Patients 18 to 77 years of age with T2DM with a HbA_{1c} of 7.0 to 10.0% who have been on a stable dose of metformin (≥1,500 mg/day) for ≥8 weeks	N=546 102 weeks	Primary: Change in HbA_{1c} from baseline at week 102 Secondary: Change in fasting blood glucose and weight from baseline at week 102	Primary: Treatment with dapagliflozin 2.5, 5 or 10 mg plus metformin resulted in significantly greater reductions from baseline to week 102 in HbA_{1c} compared to placebo (-0.48, -0.58 and -0.78 for dapagliflozin 2.5, 5 and 10 mg, respectively, compared to 0.02 for placebo; P=0.008 for dapagliflozin 2.5 mg vs placebo and P<0.0001 for dapagliflozin 5 and 10 mg vs placebo). Secondary: Patients treated with all doses of dapagliflozin achieved sustained reductions in fasting blood glucose (-1.07 to -1.47) and weight (-1.10 to -1.74) at week 102 compared to increases in fasting blood glucose and weight in the placebo group.
Bolinder et al.[54] (2012)	DB, MC, PC, PG, RCT	N=182	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Dapagliflozin 10 mg QD vs placebo	Diabetic patients	24 weeks	Change in total body weight from baseline at week 24 Secondary: Change in waist circumference and dual-energy x-ray absorptiometry total-body fat mass from baseline at week 24, proportion of patients achieving body weight reduction of ≥5% at week 24	Treatment with dapagliflozin plus metformin resulted in a placebo-corrected reduction in total body weight of -2.08 kg at week 24 (95% CI, -2.84 to -1.31; P<0.0001). Secondary: Treatment with dapagliflozin plus metformin resulted in placebo-corrected reductions in waist circumference and dual-energy x-ray absorptiometry total-body fat mass of -1.52 cm (95% CI, -2.74 to -0.31; P=0.0143) and -1.48 kg (95% CI, -2.22 to -0.74; P=0.0001), respectively, at week 24. The placebo-corrected proportion of patients treated with dapagliflozin plus metformin who achieved ≥5% weight reduction was 26.2% (95% CI, 15.5 to 36.7; P<0.0001).
Strojek et al.[55] (2011) Dapagliflozin 2.5 mg QD vs dapagliflozin 5 mg QD vs dapagliflozin 10 mg QD vs placebo	DB, MC, PC, PG, RCT Patients ≥18 years of age with T2DM with a HbA_{1c} of 7.0 to 10.0% and a fasting blood glucose ≤15 mmol/L who were stabilized on a sulfonylurea monotherapy dose at least half the maximal recommended dose for ≥8 weeks	N=596 24 weeks	Primary: Change in HbA_{1c} from baseline at week 24 Secondary: Change in fasting blood glucose and weight from baseline at week 24	Primary: Compared to placebo plus glimepiride, treatment with dapagliflozin in combination with glimepiride resulted in a significantly greater reduction in HbA_{1c} from baseline to week 24 across all dapagliflozin treatment arms (-0.58, -0.63 and -0.82 for dapagliflozin 2.5, 5 and 10 mg, respectively, compared to -0.13 for placebo; P<0.0001 for all). Secondary: Compared to placebo plus glimepiride, treatment with dapagliflozin 5 and 10 mg in combination with glimepiride resulted in a significantly greater reduction in fasting blood glucose from baseline to week 24 (-1.18 and -1.58 for dapagliflozin 5 and 10 mg, respectively, compared to -0.11 for placebo; P<0.0001 for both). Treatment with dapagliflozin 2.5 mg plus glimepiride did not result in a significantly greater reduction in fasting blood glucose compared to placebo plus glimepiride. Patients treated with dapagliflozin 5 or 10 mg plus glimepiride achieved significantly greater reductions in weight from baseline to week 24 compared to placebo plus glimepiride (-1.56 and -2.26 for dapagliflozin 5

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				and 10 mg, respectively, compared to -0.72 for placebo; P<0.01 and P<0.0001, respectively). Treatment with dapagliflozin 2.5 mg plus glimepiride did not result in a significantly greater reduction in weight compared to placebo plus glimepiride.
Rosenstock et al.[56] (2012) Dapagliflozin 5 mg QD vs dapagliflozin 10 mg QD vs placebo	DB, MC, PC, PG, RCT Patients ≥18 years of age with T2DM with a HbA_{1c} of 7.0 to 10.5% who were treatment naïve or who had previously received metformin, a sulfonylurea or pioglitazone	N=420 24 weeks plus 24-week extension trial	Primary: Change in HbA_{1c} from baseline at week 24 Secondary: Change from baseline at week 24 in FPG, two-hour PPG and weight	Primary: Treatment with dapagliflozin plus pioglitazone resulted in significantly greater reductions in HbA_{1c} from baseline to week 24 compared to placebo plus pioglitazone (-0.82 and -0.97 for dapagliflozin 5 mg and 10 mg, respectively; P=0.0007 and P<0.0001, respectively). Secondary: Treatment with dapagliflozin 5 or 10 mg plus pioglitazone resulted in significantly greater reductions in FPG, two hour PPG and weight from baseline to week 24 (P<0.0001 for all).
Jabbour et al.[57] (2014) Dapagliflozin 10 mg QD ± metformin vs placebo ± metformin Patients taking metformin received doses ≥1,500 mg/day.	DB, MC, PC, PG, RCT Patients aged ≥18 years with T2DM with a HbA_{1c} of 7.0 to 10.5% who were treatment naïve or who had previously received metformin, sitagliptin, vitagliptin or a combination	N=432 24 weeks	Primary: Change in HbA_{1c} from baseline at week 24 Secondary: Change from baseline at week 24 in fasting blood glucose, two-hour PPG and weight	Primary: Treatment with dapagliflozin plus sitagliptin resulted in a significantly greater reduction in HbA_{1c} from baseline to week 24 compared to placebo plus sitagliptin (-0.5 vs 0.1; P<0.0001). Similarly, treatment with dapagliflozin, sitagliptin and metformin combination therapy resulted in a significantly greater reduction in HbA_{1c} compared to the placebo, sitagliptin and metformin group (-0.4 vs -0.0; P<0.0001). Secondary: Treatment with dapagliflozin plus sitagliptin and dapagliflozin, sitagliptin and metformin resulted in significantly greater reductions from baseline to week 24 in fasting blood glucose, two hour PPG and weight compared to their respectively placebo comparator groups (P<0.0001 for all).
Cefalu et al.[58] (2015) Dapagliflozin 10 mg QD	DB, MC, PC, RCT Patients with type 2 diabetes, documented pre-	N=922 24 weeks plus 28-week extension trial	Primary: Change in HbA_{1c} from baseline and the proportion of patients achieving	Primary: At 24 weeks, dapagliflozin significantly reduced HbA_{1c} (−0.38%) from baseline compared with a slight increase with placebo from baseline (0.08%). Significantly more patients met the three-item end point with

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo plus pre-existing stable background treatment, excluding rosiglitazone	existing cardiovascular disease, and a history of hypertension		a combined reduction in HbA_{1c} of ≥0.5%, body weight of ≥3%, and SBP of ≥3 mmHg Secondary: Blood pressure, body weight, FPG, safety	treatment with dapagliflozin than with placebo (11.7 vs 0.9%, respectively). Changes were maintained over 52 weeks. Secondary: Greater reductions in mean seated SBP from baseline were observed at week 24 after treatment with dapagliflozin than with placebo. The mean placebo-subtracted seated reduction in SBP was statistically significant at week 8 (−1.97 mmHg), and was maintained at week 24 (−1.95 mmHg) and week 52 (−3.58 mmHg) (P<0.0001). A greater reduction in mean body weight was observed in patients treated with dapagliflozin versus placebo at week 24 (−2.56 vs −0.30%) and was maintained through week 52 (−2.89 vs −0.29%). The placebo-corrected reduction in body weight was significant at week 24 (−2.10 kg, nominal P<0.05) and persisted through week 52 (−2.51 kg). Patients in the dapagliflozin group, excluding those who received rescue therapy, showed a rapid mean reduction in FPG from baseline at week one that was greater than that with placebo and was maintained through week 24 (−0.57 vs 0.35 mmol/L) and 52 weeks (−0.96 vs –0.01 mmol/L).
Rosenstock et al.[59] (2015) Saxagliptin (SAXA) (5 mg/day) plus dapagliflozin (DAPA) (10 mg/day) vs SAXA (5 mg/day) and placebo vs DAPA (10 mg/day) and placebo	DB, RCT Type 2 diabetics with HbA_{1c} ≥8.0% and ≤12.0% on background metformin extended release ≥1,500 mg/day	N=534 24 weeks	Primary: Change in baseline HbA_{1c} Secondary: Adjusted mean change from baseline in 2-h PPG, FPG, and body weight, adjusted mean proportion of patients achieving a therapeutic glycemic response, defined as HbA_{1c} <7.0%	Primary: At week 24, the adjusted mean change from the baseline HbA_{1c} was –1.5% with SAXA+DAPA+MET vs –0.9% with SAXA+MET (difference −0.59%, P<0.0001) and –1.2% with DAPA+MET (difference −0.27%, P<0.02). Secondary: The adjusted mean reduction in FPG was greater in the SAXA+DAPA+MET group (–38 ± 2.8 mg/dL) than in the SAXA+MET group (–14 ± 2.9 mg/dL) but similar to the DAPA+MET group (–32 ± 2.8 mg/dL). SAXA+DAPA+MET also resulted in a significantly greater adjusted mean reduction from baseline in PPG versus SAXA+MET (difference, –44 mg/dL; 95% CI, –53.7 to –34.3; P<0.0001) but not versus DAPA+MET (difference, –9 mg/dL; 95% CI, –18.8 to 0.5; P=0.06). Reduction in body weight of 2.1 kg (2.4%) was observed in the SAXA+DAPA+MET group and 2.4 kg (2.8%) in the DAPA+MET group compared with no change in the SAXA+MET group. The proportion of patients achieving HbA_{1c} <7% was 41% with SAXA+DAPA+MET versus 18% with SAXA+MET and 22% with DAPA+MET. Urinary and genital

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				infections occurred in ≤1% of patients receiving SAXA+DAPA+MET. Hypoglycemia was infrequent, with no episodes of major hypoglycemia.
Rosenstock et al.[60] (2019) Dapagliflozin 5 mg/day plus saxagliptin 5 mg/day vs dapagliflozin 5 mg/day vs saxagliptin 5 mg/day	DB, MC, RCT Patients ≥18 years of age with type 2 diabetes; stable metformin dose (≥1500 mg/d) for ≥8 weeks before enrolment; BMI ≤45 kg/m^2; fasting plasma glucose ≤15 mmol/L (≤270 mg/dL); and HbA_{1c} 7.5% to 10.0%	N=883 24 weeks	Primary: Mean change in HbA_{1c} from baseline to week 24 Secondary: Proportion of participants achieving HbA_{1c} <7%, change in body weight, safety	Primary: The adjusted mean ± SE change from baseline in HbA_{1c} at 24 weeks was greater with dapagliflozin plus saxagliptin plus metformin than with either dapagliflozin or saxagliptin plus metformin (−1.03 ± 0.06% vs −0.63 ± 0.06% vs −0.69 ± 0.06%; P<0.0001 for both comparisons). Secondary: The proportion of participants who achieved HbA_{1c} levels of <7.0% was greater with dapagliflozin plus saxagliptin plus metformin than with dapagliflozin or saxagliptin plus metformin (adjusted response rate, 41.6%; 95% CI, 36.0 to 47.1 vs 21.8%; 95% CI, 17.2 to 26.4 vs. 29.8%; 95% CI, 24.9 to 34.8; P<0.0001 and P=0.0018 for comparisons vs dapagliflozin plus metformin and saxagliptin plus metformin, respectively). Reductions in total body weight from baseline were greater with dapagliflozin plus saxagliptin plus metformin than with saxagliptin plus metformin (adjusted mean ± SE change, −2.0 ± 0.2 kg vs −0.4 ± 0.2 kg; P<0.0001). The proportions of participants reporting at least one adverse event were 41.3%, 42.0%, and 39.3% for dapagliflozin plus saxagliptin plus metformin, dapagliflozin plus metformin, and saxagliptin plus metformin, respectively. The most commonly reported adverse events with dapagliflozin plus saxagliptin plus metformin were decreased eGFR (4.1%), urinary tract infection (2.4%), and pollakiuria (2.4%). With dapagliflozin plus metformin, the most commonly reported adverse events were decreased eGFR (3.8%), viral upper respiratory tract infection (3.1%), and influenza (3.1%). With saxagliptin plus metformin, viral or non-viral upper respiratory tract infections (2.7% and 2.0%) were the most commonly reported adverse events. In the triple therapy group, 5.8% of participants experienced at least one hypoglycemic event, compared with 2.7% and 3.4% in the dapagliflozin plus metformin and saxagliptin plus metformin groups, respectively.
Vilsbøll et al.[61] (2020)	OL, PG, RCT	N=600 52 weeks	Primary: mean change in HbA_{1c} and body	Primary: At 52 weeks, HbA_{1c} decreased more with DAPA + SAXA (adjusted least squares (LS) mean, −1.5%; 95% CI, −1.6% to −1.4%) than with INS

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Dapagliflozin plus saxagliptin (DAPA + SAXA) vs insulin glargine (INS)	Patients ≥18 years of age with type 2 diabetes and inadequate glycemic control (HbA_{1c} ≥8% to ≤12%) receiving stable metformin therapy (≥1500 mg/day) with or without sulphonylurea (≥50% of maximal dose) for at least 8 weeks before screening		weight from baseline and achieving an optimal glycemic response (HbA_{1c} <7.0%) without hypoglycemia Secondary: Proportion of patients requiring rescue medication or discontinuing due to lack of glycemic control and change from baseline in the average postprandial glucose values; safety	(adjusted LS mean, −1.3%; 95% CI, −1.4% to −1.1%); the LS mean difference (95% CI) was −0.25% (−0.4% to −0.1%; P=0.009). Total body weight reduced with DAPA + SAXA (LS mean, -1.8 kg; 95% CI, -2.4 to -1.3) and increased with INS (LS mean, +2.8 kg; 95% CI, 2.2 to 3.3). More patients on DAPA + SAXA (17.6%) achieved HbA_{1c} <7.0% without hypoglycemia versus those on INS (9.1%). Secondary: Overall, 174 patients required rescue medication or discontinued the study due to lack of glycemic control: 77 (23.8%) in the DAPA + SAXA group and 97 (30.4%) in the INS group at week 52. The adjusted percentage of patients requiring rescue medication or discontinuation at week 52 was 21.0% (95% CI, 16.7% to 26.1%) and 27.7% (95% CI, 22.8% to 33.3%) in the DAPA + SAXA and INS groups, respectively (OR, 0.7; 95% CI, 0.5 to 1.0). At least one adverse event was reported by 209 patients (64.5%) in the DAPA + SAXA group and 217 (68.0%) in the INS group. Adverse events considered by the investigator to be treatment-related were more common in the DAPA + SAXA group (11.1%) versus the INS group (4.7%).
Frias et al.[62] (2020) Dapagliflozin 10 mg (DAPA) + saxagliptin 5 mg (SAXA) vs glimepiride 1 to 6 mg (GLIM)	AC, DB, MC, RCT Patients ≥18 years of age with type 2 diabetes who were inadequately controlled (HbA_{1c} 7.5 to 10.5%) on metformin monotherapy	N=443 52 weeks	Primary: Mean change in HbA_{1c} from baseline Secondary: Change from baseline in total body weight; proportion of patients achieving a therapeutic response, defined as HbA_{1c} <7.0%; change from baseline in systolic	Primary: The adjusted mean change from baseline in HbA_{1c} at 52 weeks was greater with DAPA + SAXA (−1.35%) than with GLIM (−0.98%; P<0.001 vs GLIM). Secondary: The proportion of patients who achieved HbA_{1c} <7.0% at 52 weeks was greater with DAPA + SAXA than with GLIM (P=0.044). Total body weight decreased from baseline to week 52 with DAPA + SAXA, whereas it increased with GLIM (P<0.001). Similarly, SBP decreased from baseline to week 52 with DAPA + SAXA and increased with GLIM (P=0.007). Significantly fewer patients required treatment intensification with DAPA + SAXA than with GLIM (P=0.002); however, these results were not included in sequential testing, because there were <10 patients in each treatment group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			blood pressure (SBP); and time to treatment intensification	
Wilding et al.[63] (2012) Dapagliflozin 2.5 mg QD ± oral antidiabetic agent vs dapagliflozin 5 mg QD ± oral antidiabetic agent vs dapagliflozin 10 mg QD ± oral antidiabetic agent vs placebo	DB, MC, PC, PG, RCT Patients 18 to 80 years of age with T2DM, BMI ≤45 kg/m^2 and a HbA_{1c} of 7.5 to 10.5% who are stabilized on an insulin regimen of >30 IU/day for ≥8 weeks ± other oral antidiabetic agents	N=800 24 weeks plus 24-week extension trial	Primary: Change in HbA_{1c} from baseline at week 24 Secondary: Change from baseline to week 24 in fasting blood glucose, insulin dose and weight	Primary: Treatment with dapagliflozin plus insulin resulted in a significant decrease from baseline to week 24 in HbA_{1c} across all doses compared to placebo plus insulin (-0.79, -0.89 and -0.96 for dapagliflozin 2.5, 5 and 10 mg, respectively, compared to -0.39 for placebo; P<0.001 for all). Secondary: Treatment with dapagliflozin 2.5, 5 or 10 mg plus insulin resulted in significantly greater reductions from baseline to week 24 in fasting blood glucose, insulin dose and weight compared to placebo (P<0.001 for all).
Wiviott et al.[64] (2019) DECLARE-TIMI 58 Dapagliflozin 10 mg QD vs placebo	DB, MC, PC, RCT Patients ≥40 years of age with type 2 diabetes and established atherosclerotic cardiovascular disease or multiple risk factors for atherosclerotic	N=17,160 Median follow-up of 4.2 years	Primary: Major adverse cardiovascular events (MACE), defined as cardiovascular death, myocardial infarction, or ischemic stroke; composite of cardiovascular	Primary: Dapagliflozin met the prespecified criterion for noninferiority with respect to MACE (upper boundary of the 95% CI, <1.3; P<0.001 for noninferiority). Dapagliflozin resulted in a lower rate of cardiovascular death or hospitalization for heart failure than placebo (4.9% vs. 5.8%; HR, 0.83; 95% CI, 0.73 to 0.95; P=0.005). The lower rate of the composite outcome of cardiovascular death or hospitalization for heart failure in the dapagliflozin group than in the placebo group was due to a lower rate of hospitalization for heart failure in the dapagliflozin group (HR, 0.73; 95% CI, 0.61 to 0.88); there was no difference between the groups in the rate of cardiovascular death (HR, 0.98; 95% CI, 0.82 to 1.17).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
The use of other glucose-lowering agents (other than an open-label SGLT2 inhibitor, pioglitazone, or rosiglitazone) was at the discretion of the treating physician	cardiovascular disease		death or hospitalization for heart failure Secondary: Composite renal outcome of a 40% decrease on eGFR to <60 mL/1.73 m^2, new end-stage renal disease, or death from renal or cardiovascular causes; death from any cause	Secondary: Because dapagliflozin resulted in a significantly lower rate of cardiovascular death and hospitalization for heart failure than placebo but did not result in a significantly lower rate of MACE, analyses of additional outcomes are hypothesis-generating. In the overall population, the incidence of the renal composite outcome was 4.3% in the dapagliflozin group and 5.6% in the placebo group (HR, 0.76; 95% CI, 0.67 to 0.87). The rate of death from any cause did not differ significantly between the groups (6.2% in the dapagliflozin group and 6.6% in the placebo group; HR, 0.93; 95% CI, 0.82 to 1.04).
Kato et al.[65] (2019) DECLARE-TIMI 58 Dapagliflozin 10 mg QD vs placebo The use of other glucose-lowering agents (other than an open-label SGLT2 inhibitor, pioglitazone, or rosiglitazone) was at the discretion of the treating physician	DB, MC, PC, RCT Patients ≥40 years of age with type 2 diabetes and established atherosclerotic cardiovascular disease or multiple risk factors for atherosclerotic cardiovascular disease, stratified by HFrEF, HF without reduced EF, and no history of HF at baseline	N=17,160 Median follow-up of 4.2 years	Primary: Dual primary composite end point of the trial of cardiovascular death or hospitalization for HF, its individual components, and all-cause mortality Secondary: Not reported	Primary: Of 17,160 patients, 671 (3.9%) had HFrEF, 1316 (7.7%) had HF without known reduced EF, and 15 173 (88.4%) had no history of HF at baseline. Dapagliflozin reduced cardiovascular death/hospitalization for HF more in patients with HFrEF (HR, 0.62; 95% CI, 0.45 to 0.86) than in those without HFrEF (HR, 0.88; 95% CI, 0.76 to 1.02; P for interaction=0.046), in whom the treatment effect of dapagliflozin was similar in those with HF without known reduced EF (HR, 0.88; 95% CI, 0.66 to 1.17) and those without HF (HR, 0.88; 95% CI, 0.74 to 1.03). Whereas dapagliflozin reduced hospitalization for HF both in those with (HR, 0.64; 95% CI, 0.43 to 0.95) and in those without HFrEF (HR, 0.76; 95% CI, 0.62 to 0.92), it reduced cardiovascular death only in patients with HFrEF (HR, 0.55; 95% CI, 0.34 to 0.90) but not in those without HFrEF (HR, 1.08; 95% CI, 0.89 to 1.31; P for interaction=0.012). Likewise, dapagliflozin reduced all-cause mortality in patients with HFrEF (HR, 0.59; 95% CI, 0.40 to 0.88; P=0.01) but not in those without HFrEF (HR, 0.97; 95% CI, 0.86 to 1.10; P for interaction=0.016). Secondary: Not reported
Häring et al.[66] (2014)	DB, MC, PC, RCT	N=637	Primary: HbA_{1c}	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Empagliflozin 10 mg QD vs empagliflozin 25 mg QD vs placebo Patients continued treatment with metformin.	Patients with type 2 DM and HbA_{1c} of ≥7% to <10%, inadequately controlled on ≥1,500 mg of metformin per day	24 weeks	Secondary: FPG, body weight, SBP and safety evaluations	At week 24, empagliflozin 10 mg or 25 mg QD provided statistically significant reductions in HbA_{1c} compared to placebo (-0.7% and -0.8% vs 0.1%, respectively; P<0.0001 for both comparisons). Secondary: At week 24, empagliflozin 10 mg or 25 mg QD provided statistically significant reductions in FPG (-20 mg/dL and -22 mg/dL vs 6 mg/dL, respectively; P values not reported) and body weight (-2.5 kg and -2.9 kg vs -0.5 kg, respectively; P<0.001 for both comparisons) compared with placebo. SBP was statistically significantly reduced compared to placebo by -4.1 mmHg (placebo-adjusted, P=0.0231) in patients randomized to 10 mg of empagliflozin and by -4.8 mmHg (placebo-corrected, P=0.0028) in patients randomized to 25 mg of empagliflozin. Confirmed hypoglycemic adverse events were reported in 0.5%, 1.8%, and 1.4% of patients receiving placebo, empagliflozin 10 mg, and empagliflozin 25 mg, respectively. Events consistent with urinary tract infections were reported in 4.9%, 5.1%, and 5.6% of patients, and events consistent with genital infections were reported in 0%, 3.7%, and 4.7% of patients, respectively.
Ridderstråle et al.[67] (2014) Empagliflozin 25 mg QD vs glimepiride 1 to 4 mg QD Patients continued treatment with metformin.	AC, DB, MC, RCT Patients with type 2 DM and HbA_{1c} of ≥7% to <10%, inadequately controlled on metformin monotherapy	N=1,545 104 weeks	Primary: HbA_{1c} (tested for non-inferiority at week 52, tested for superiority at week 104) Secondary: FPG, body weight, SBP and safety evaluations	Primary: At week 52, empagliflozin 25 mg meet the non-inferiority criteria for lowering HbA_{1c} compared to glimepiride (-0.7% vs -0.7%). Non-inferiority continued to be demonstrated at week 104. In addition, at week 104, adjusted mean difference in change from baseline in HbA_{1c} with empagliflozin versus glimepiride was -0.11% (95% CI, -0.19 to -0.02; P=0.0153 for superiority). Secondary: At week 52, There was a greater reduction in FPG and body weight with empagliflozin 25 mg compared to glimepiride; however, the significance was not reported (-19 mg/dL vs -9 mg/dL and -3.9 kg vs 2 kg; P values not reported).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				SBP was also statistically significantly reduced compared to glimepiride (-3.6 mmHg vs 2.2 mmHg; P<0.0001). Adverse events were reported in 661 (86%) patients treated with empagliflozin and 673 (86%) patients treated with glimepiride. Severe adverse events were reported in 72 (9%) patients in the empagliflozin group and 68 (9%) in the glimepiride group. Serious adverse events were reported in 119 (16%) patients in the empagliflozin group and 89 (11%) in the glimepiride group. Confirmed hypoglycemic adverse events (plasma glucose ≤3.9 mmol/L or requiring assistance) at week 104 were reported in 19 (2%) patients treated with empagliflozin and 189 (24%) patients treated with glimepiride.
Häring et al.[68] (2013) Empagliflozin 10 mg QD vs empagliflozin 25 mg QD vs placebo Patients continued treatment with metformin and sulfonylurea.	DB, MC, PC, RCT Patients aged ≥18 years with type 2 DM and HbA_{1c} of ≥7% to <10%, inadequately controlled on ≥ 1,500 mg of metformin per day and a sulfonylurea	N=666 24 weeks	Primary: HbA_{1c} Secondary: FPG, body weight, SBP and safety evaluations	Primary: At week 24, empagliflozin 10 mg or 25 mg QD provided statistically significant reductions in HbA_{1c} compared to placebo (-0.8% and -0.8% vs -0.2%, respectively; P<0.0001 for both comparisons). Secondary: At week 24, empagliflozin 10 mg or 25 mg QD provided statistically significant reductions in FPG (-23 mg/dL and -23 mg/dL vs. 6 mg/dL, respectively; P values not reported) and body weight (-2.9 kg and -3.2 kg vs. -0.5 kg, respectively; P<0.001 for both comparisons) compared with placebo. Decreases in SBP were also significantly greater with both empagliflozin doses than placebo. Adverse events were reported in 62.7, 67.9, and 64.1% of patients on placebo and empagliflozin 10 and 25 mg, respectively. Events consistent with urinary tract infection were reported in 8.0, 10.3, and 8.3% of patients on placebo and empagliflozin 10 and 25 mg, respectively (females: 13.3, 18.0, and 17.5%, respectively; males: 2.7, 2.7, and 0%, respectively). Events consistent with genital infection were reported in 0.9, 2.7, and 2.3% of patients on placebo and empagliflozin 10 and 25 mg, respectively (females: 0.9, 4.5, and 3.9%, respectively; males: 0.9% in each group).
Kovacs et al.[69] (2014)	DB, MC, PC, RCT	N=498	Primary: HbA_{1c}	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Empagliflozin 10 mg QD vs empagliflozin 25 mg QD vs placebo Patients continued treatment with pioglitazone with or without metformin.	Patients with type 2 DM and HbA_{1c} of ≥7% to <10%, inadequately controlled on pioglitazone 30 mg per day, with or without metformin ≥1,500 mg per day	24 weeks	Secondary: FPG, body weight, SBP and safety evaluations	At week 24, empagliflozin 10 mg or 25 mg QD provided statistically significant reductions in HbA_{1c} compared to placebo (-0.6% and -0.7% vs -0.1%, respectively; P<0.0001 for both comparisons). Secondary: At week 24, empagliflozin 10 mg or 25 mg QD provided statistically significant reductions in FPG (-17 mg/dL and -22 mg/dL vs 7 mg/dL, respectively; P<0.001) and body weight (-2.0 kg and -1.8 kg vs -0.6 kg, respectively; P<0.001) compared with placebo. Adverse events were reported in 661 (86%) patients treated with empagliflozin and 673 (86%) patients treated with glimepiride. Severe adverse events were reported in 72 (9%) patients in the empagliflozin group and 68 (9%) in the glimepiride group. Serious adverse events were reported in 119 (16%) patients in the empagliflozin group and 89 (11%) in the glimepiride group. Confirmed hypoglycemic adverse events (plasma glucose ≤3·9 mmol/L or requiring assistance) at week 104 were reported in 19 (2%) patients treated with empagliflozin and 189 (24%) patients treated with glimepiride. Similar proportions of patients reported adverse events with empagliflozin (67.3 to 71.4%) and placebo (72.7%). Confirmed hypoglycemia was reported by 1.2 to 2.4% of patients on empagliflozin and 1.8% on placebo.
Rosenstock et al.[70] (2015) Empagliflozin 10 mg QD vs empagliflozin 25 mg QD vs placebo	DB, MC, PC, RCT Patients with type 2 diabetes and HbA_{1c} of ≥7% to <10%, inadequately controlled on basal insulin	N=494 78 weeks	Primary: Change in HbA_{1c} at week 18 Secondary: Change in HbA_{1c} and insulin dose at week 78	Primary: At week 18, adjusted mean ± standard error changes from baseline in HbA_{1c} were 0 ± 0.1% with placebo compared with −0.6 ± 0.1% with empagliflozin 10 mg and −0.7 ± 0.1% with empagliflozin 25 mg (both P<0.001). Secondary: At week 78, adjusted mean HbA_{1c} changes from baseline were 0 ± 0.1% with placebo compared with −0.5 ± 0.1%) with empagliflozin 10 mg and −0.6 ± 0.1% with empagliflozin 25 mg (both p < 0.001). Adjusted mean changes from baseline in insulin doses were 5.5 ± 1.6 IU with placebo compared with −1.2 ± 1.5 IU with empagliflozin 10 mg (P=0.002) and −0.5 ± 1.6 IU with empagliflozin 25 mg (P=0.009).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
as add-on to basal insulin, with or without metformin and/or sulphonylureas				
Zinman et al.[71] (2015) EMPA-REG OUTCOME Empagliflozin 10 mg QD vs empagliflozin 25 mg QD vs placebo	DB, PC, RCT Patients with type 2 diabetes at high risk for cardiovascular events who were receiving standard care	N=7,020 Median observation time of 3.1 years	Primary: Composite of death from cardiovascular causes, nonfatal myocardial infarction (excluding silent myocardial infarction), or nonfatal stroke Secondary: Composite of the primary outcome plus hospitalization for unstable angina	Primary: The primary outcome occurred in a significantly lower percentage of patients in the empagliflozin group (490 of 4687 [10.5%]) than in the placebo group (282 of 2333 [12.1%]) (HR in the empagliflozin group, 0.86; 95.02% CI, 0.74 to 0.99; P<0.001 for noninferiority and P=0.04 for superiority). Secondary: The secondary outcome occurred in 599 of 4687 patients (12.8%) in the empagliflozin group and 333 of 2333 patients (14.3%) in the placebo group (HR, 0.89; 95% CI, 0.78 to 1.01; P<0.001 for noninferiority and P=0.08 for superiority).
Zinman et al.[72] (2017) EMPA-REG OUTCOME Empagliflozin 10 mg QD vs empagliflozin 25 mg QD vs	DB, PC, RCT Patients with type 2 diabetes at high risk for cardiovascular events who were receiving standard care	N=7,020 Median observation time of 3.1 years	Primary: Time to first stroke event Secondary: Not reported	Primary: During the trial, 3.0% of patients in the placebo group and 3.5% of patients in the empagliflozin group had ≥1 adjudicated fatal or nonfatal stroke. In the prespecified modified intent-to-treat analysis of time to first stroke, there was no significant difference between empagliflozin and placebo in the occurrence of stroke (HR, 1.18; 95% CI, 0.89 to 1.56; P=0.26). There was no significant difference in the risk of TIA (HR, 0.85; 95% CI, 0.51 to 1.42; P=0.54) or the composite of stroke or TIA (HR, 1.05; 95% CI, 0.82 to 1.35; P=0.87) with empagliflozin versus placebo. In a sensitivity analysis based on events during treatment or ≤90 days after last dose of drug, the hazard ratio for stroke with empagliflozin versus placebo was 1.08 (95% CI, 0.81 to 1.45; P=0.60). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo				Not reported
Rodbard et al.[73] (2019) PIONEER 2 Empagliflozin 25 mg QD vs semaglutide 14 mg orally QD All patients randomized to oral semaglutide initiated treatment with 3 mg QD with dose escalations every four weeks until the randomized maintenance dose was achieved.	AC, DB, MC, PG, RCT Adults with type 2 DM insufficiently controlled with diet and exercise and HbA_{1c} 7.0 to 10.5% and on a stable dose of metformin ≥90 days before screening	N=822 52 weeks	Primary: Change in HbA_{1c} from baseline Secondary: Changes in measures of glucose control, achievement of an HbA_{1c} target of ,7% or ≤6.5% and achievement of weight loss of at least 5% or 10%, as well as C-reactive protein, fasting lipid levels from baseline and safety	Primary: Treatment with semaglutide resulted in a statistically significant reduction in HbA_{1c} compared to empagliflozin 25 mg once daily (-1.3% vs -0.9%, respectively; P<0.001). Secondary: The mean changes from baseline to week 26 were -3.8 kg and -3.7 kg in the semaglutide 14 mg and empagliflozin 25 mg arms, respectively (95% CI -0.1, -0.7 to 0.5). Select secondary endpoints involving measures of glycemic control, weight loss and lipid levels favored semaglutide over empagliflozin, however select comparisons demonstrated no difference.
Rosenstock et al.[74] (2018) VERTIS MET Ertugliflozin 15 mg QD vs ertugliflozin 5 mg QD vs	DB, MC, PC, PG, RCT Patients ≥18 years of age with type 2 DM and HbA_{1c} ≥7.0% to ≤10.5% on ≥1,500 mg/day of metformin monotherapy for at least eight weeks and with a BMI 18.0 to 40.0 kg/m^2	N=621 104 weeks (26 week phase and 78 week phase)	Primary: Change from baseline at week 26 in HbA_{1c} Secondary: Changes from baseline at week 26 in FPG, body weight and SBP and diastolic blood pressure	Primary: The placebo-adjusted least-squares mean change from baseline HbA_{1c} (8.1%) at week 26 was -0.7% and -0.9% for ertugliflozin 5 and 15 mg, respectively (both P< 0.001). Secondary: Ertugliflozin significantly reduced FPG, body weight, and SBP and diastolic blood pressure compared to placebo. The least-squares mean change from baseline at week 26 in FPG was -0.1, -1.5 and -2.2 and in body weight was -1.3, -3.0 and -2.9 in the placebo, ertugliflozin 5 mg and ertugliflozin 15 mg, respectively (P<0.001 compared to placebo for all). The least-squares mean change from baseline in SBP was -0.7 mmHg in the placebo group, -4.4 mmHg in the ertugliflozin 5 mg group (P=0.002 compared to placebo) and -5.2 mmHg in the ertugliflozin 15 mg (P<0.001

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo Subjects received glycemic rescue therapy with open-label glimepiride if they exceeded certain hyperglycemia thresholds.				compared to placebo). The least-squares mean change from baseline in diastolic blood pressure was 0.2 mmHg in the placebo group, -1.6 mmHg in the ertugliflozin 5 mg group (P=0.013 compared to placebo) and -2.2 mmHg in the ertugliflozin 15 mg (P=0.001 compared to placebo).
Hollander et al.[75] (2018) VERTIS SU Ertugliflozin 15 mg QD vs ertugliflozin 5 mg QD vs glimepiride titrated from 1 mg up to 6 or 8 mg QD Glycemic rescue therapy with open-label sitagliptin was prescribed for subjects meeting progressively more stringent glycemic rescue criteria.	AC, DB, MC, PG, RCT Patients ≥18 years of age with type 2 DM and HbA_{1c} ≥7.0% to ≤9.0% on ≥1,500 mg/day of metformin monotherapy for at least eight weeks at screening	N=1,326 104 weeks (two 52 week phases)	Primary: Change from baseline in HbA_{1c} at week 52 Secondary: Changes from baseline in body weight and SBP at week 52	Primary: The least-squares mean change from baseline at week 52 in HbA_{1c} was -0.6% (95% CI, -0.7 to -0.5), -0.6% (95% CI, -0.6 to -0.5), and - 0.7% (95% CI, -0.8 to -0.7) in the ertugliflozin 15mg, ertugliflozin 5 mg, and glimepiride groups respectively. The between-group difference for ertugliflozin 15 mg and glimepiride of 0.1% (95% CI, -0.0 to 0.2) met the pre-specified non-inferiority criterion. However, the between-group difference for ertugliflozin 5 mg and glimepiride at week 52 was 0.2% (95% CI, 0.1 to 0.3) and did not satisfy the criterion for non-inferiority to glimepiride. Secondary: Greater body weight and SBP reductions from baseline at week 52 were observed with ertugliflozin compared to glimepiride. The least-squares mean changes in body weight from baseline at week 52 were -3.4 kg (95% CI, -3.7 to -3.0), -3.0 kg (95% CI, -3.3 to -2.6) and 0.9 kg (95% CI, 0.6 to 1.3) in the ertugliflozin 15 mg, ertugliflozin 5 mg and glimepiride groups, respectively. The least-squares mean differences versus glimepiride at week 52 were -4.3 kg (95% CI, -4.8 to -3.8) and -3.9 kg (95% CI, -4.4 to -3.4) for ertugliflozin 15 mg and 5 mg respectively (P<0.001). Least square mean changes in SBP from baseline at week 52 were -3.8 mmHg (95% CI, -4.9 to -2.7), -2.2 mmHg (95% CI, -3.4 to -1.1) and 1.0 mmHg (95% CI, -0.1 to 2.1) in the ertugliflozin 15 mg, ertugliflozin 5 mg and glimepiride groups, respectively. The least-squares mean differences versus glimepiride at week 52 were -4.8 mmHg (95% CI, -6.3 to -3.2) and -3.2 mmHg (95% CI, -4.7 to -1.7) for ertugliflozin 15 mg and 5 mg, respectively (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Pratley et al.[76] (2017) VERTIS FACTORIAL Ertugliflozin 15 mg QD vs ertugliflozin 5 mg QD vs sitagliptin 100 mg QD vs ertugliflozin 15 mg/sitagliptin 100 mg QD vs ertugliflozin 5 mg/sitagliptin 100 mg QD Subjects received glycemic rescue therapy with open-label glimepiride (or insulin glargine) if they met certain rescue criteria	DB, MC, RCT Patients ≥18 years of age with type 2 DM and HbA_{1c} ≥7.5% to ≤11.0% on ≥1,500 mg/day of metformin monotherapy for at least eight weeks	N=1,233 52 weeks (two 26 phases)	Primary: Change from baseline at week 26 in HbA_{1c} Secondary: Change from baseline in FPG, body weight and SBP at week 26	Primary: The least-squares mean HbA_{1c} reductions from baseline at week 26 were greater with ertugliflozin 5 mg/sitagliptin 100 mg (-1.5%) and ertugliflozin 15 mg/sitagliptin 100 mg (-1.5%) than with individual agents (-1.0%, -1.1% and -1.1% for ertugliflozin 5 mg, ertugliflozin 15 mg and sitagliptin 100 mg, respectively; P<0.001 for all comparisons). Secondary: FPG reductions were significantly greater with ertugliflozin 5 mg/sitagliptin 100 mg and ertugliflozin 15 mg/sitagliptin 100 mg compared with individual agents. Body weight and SBP significantly decreased with ertugliflozin 5 mg/sitagliptin 100 mg and ertugliflozin 15 mg/sitagliptin 100 mg compared to sitagliptin 100 mg alone. Glycemic control, body weight and SBP effects of ertugliflozin were maintained to week 52.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Dagogo-Jack et al.[77] (2018) VERTIS SITA2 Ertugliflozin 5 mg QD vs ertugliflozin 15 mg QD vs placebo Glycemic rescue therapy with open-label glimepiride (or insulin glargine) was prescribed for patients meeting glycemic rescue criteria.	DB, MC, PC, PG, RCT Patients ≥18 years of age with type 2 DM and HbA_{1c} ≥7.0% to ≤10.5% receiving stable treatment with ≥1,500 mg/day of metformin and 100 mg/day of sitagliptin for at least eight weeks at screening	N=464 52 weeks (two 26 week phases)	Primary: Change from baseline in HbA_{1c} at week 26 Secondary: Change from baseline at week 26 in FPG, body weight and SBP and the proportion of subjects with HbA_{1c} <7.0% at week 26	Primary: The placebo-adjusted least-squares mean changes in HbA_{1c} from baseline at week 26 were -0.7% and -0.8% for ertugliflozin 5 and 15 mg, respectively (both P <0.001). Secondary: Significantly greater reductions from baseline were observed at week 26 for both ertugliflozin groups compared to placebo in FPG, body weight and SBP. A higher proportion of ertugliflozin-treated subjects had HbA_{1c} <7.0% at week 26 compared to placebo with 17.0% of subjects in the placebo group, 32.1% of subjects in the ertugliflozin 5 mg group and 39.9% of subjects in the ertugliflozin 15 mg group of subjects having HbA_{1c} <7.0%.
Miller et al.[78] (2018) VERTIS SITA ertugliflozin 5 mg/sitagliptin 100 mg QD vs ertugliflozin 15 mg/sitagliptin 100 mg QD	DB, MC, PC, PG, RCT Patients ≥18 years of age with type 2 DM and HbA_{1c} ≥8.0% to ≤10.5% on diet and exercise alone for >8 weeks prior to screening	N=291 26 weeks	Primary: Change from baseline at week 26 in HbA_{1c} Secondary: Change from baseline in FPG and 2-hour PPG, proportion of patients with HbA_{1c} <7.0%, change from	Primary: At week 26, both ertugliflozin/sitagliptin treatments provided significant reductions from baseline in HbA_{1c} compared with placebo. The least-squares mean HbA_{1c} change from baseline was −0.4% (95% CI, −0.7 to −0.2) for placebo, −1.6% (95% CI, −1.8 to −1.4) for ertugliflozin 5 mg/sitagliptin 100 mg and −1.7% for ertugliflozin 15 mg/sitagliptin 100 mg (95% CI, −1.9 to −1.5). The placebo-adjusted least-squares mean changes for ertugliflozin 5 mg/sitagliptin 100 mg and ertugliflozin 15 mg/sitagliptin 100 mg were −1.2% (95% CI, −1.5 to −0.8) and −1.2% (95% CI, −1.6 to −0.9), respectively (P <0.001 for both). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo Glycemic rescue therapy with open-label glimepiride was prescribed for patients who met progressively more stringent glycemic rescue criteria.			baseline in body weight, SBP and diastolic blood pressure at week 26	At week 26, 8.3%, 35.7%, and 31.3% of patients receiving placebo, ertugliflozin 5 mg/sitagliptin 100 mg and ertugliflozin 15 mg/sitagliptin 100 mg, respectively, had HbA_{1c} <7.0%. Significant reductions in FPG, 2-hour PPG, body weight, and SBP were observed with both ertugliflozin/sitagliptin groups compared with placebo. Placebo-adjusted reductions in diastolic blood pressure were observed for ertugliflozin 5 mg/sitagliptin 100 mg and ertugliflozin 15 mg/sitagliptin 100 mg, but were not statistically significant.
Grunberger et al.[79] (2018) VERTIS RENAL Ertugliflozin 5 mg QD vs ertugliflozin 15 mg QD vs placebo Subjects who met progressively stricter protocol-defined glycemic rescue criteria were permitted to have an adjustment in the dose(s) of	DB, MC, PC, PG, RCT Patients ≥25 years of age with type 2 DM, stage 3 CKD (eGFR ≥30 and <60 mL/min/1.73m^2) with stable renal function and HbA_{1c} ≥7.0% to ≤10.5% on diet/exercise with or without antihyperglycemic agent monotherapy or combination therapy using other antihyperglycemic agents including insulin and sulfonylureas receiving stable treatment with ≥1,500 mg/day of	N=468 52 weeks (two 26 week phases)	Primary: Change from baseline in HbA_{1c} at week 26 in the overall cohort Secondary: Changes from baseline in HbA_{1c}, body weight, SBP, FPG and proportion of subjects with A_{1C} <7.0% in the stage 3A CKD cohort	Primary: Reductions from baseline in HbA_{1c} were observed across groups in the overall cohort at week 26. The least-squares mean changes was -0.3% (95% CI, -0.4 to -0.1), -0.3% (95% CI, -0.4 to -0.1), and -0.4% (95% CI, -0.6 to -0.3) for placebo, ertugliflozin 5 mg and 15 mg. There was not a statistically significant difference in the HbA_{1c} change from baseline between the placebo and ertugliflozin groups at week 26. Secondary: In the stage 3A CKD cohort, the placebo-adjusted least-squares mean changes from baseline in HbA_{1c} at week 26 were -0.2% (95% CI, -0.5 to 0.1) and -0.4% (95% CI, -0.6 to -0.1) in the ertugliflozin 5 mg and 15 mg groups, respectively. Relative to placebo, ertugliflozin led to greater reductions from baseline in FPG at week 26. The least-squares mean reductions from baseline in body weight and SBP at week 26 were greater in the ertugliflozin groups than in the placebo group. In the stage 3A CKD cohort, the odds of having an HbA_{1c} <7.0% at week 26 were similar in the ertugliflozin and placebo groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
background antihyperglycemic agent or the addition of new antihyperglycemic agent therapy.	metformin and 100 mg/day of sitagliptin for at least eight weeks at screening			
Cannon et al.[80] (2020) VERTIS CV Ertugliflozin 5 or 15 mg once daily vs placebo added to background standard-of-care treatment	DB, MC, NI, RCT Patients ≥40 years of age with type 2 diabetes (HbA_{1c} 7.0 to 10.5%) and atherosclerotic cardiovascular disease	N=8,246 Mean of 3.5 years	Primary: Composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke Secondary: Composite of death from cardiovascular causes or hospitalization for HF; death from cardiovascular causes; and a composite of death from renal causes, renal replacement therapy, or doubling of the serum creatinine level	Primary: The primary outcome occurred in 653 of 5493 patients (11.9%) in the ertugliflozin group and in 327 of 2745 patients (11.9%) in the placebo group (HR, 0.97; 95.6% CI, 0.85 to 1.11; P<0.001 for noninferiority). Secondary: Death from cardiovascular causes or hospitalization for heart failure (the first key secondary outcome) occurred in 444 of 5499 patients (8.1%) in the ertugliflozin group and in 250 of 2747 patients (9.1%) in the placebo group (HR, 0.88; 95.8% CI, 0.75 to 1.03; P=0.11 for superiority). With respect to the other key secondary outcomes, the hazard ratio (ertugliflozin vs placebo) for death from cardiovascular causes was 0.92 (95.8% CI, 0.77 to 1.11), and the hazard ratio for death from renal causes, renal replacement therapy, or doubling of the serum creatinine level was 0.81 (95.8% CI, 0.63 to 1.04).
Kosiborod et al.[81] (2017) CVD-REAL	Cohort, MC Patients with type 2 diabetes who were newly started on either SGLT-2i or	N=309,056 Variable	Primary: Hospitalization for heart failure Secondary:	Primary: Mean duration of follow-up for hospitalization for heart failure was 239 days in the SGLT-2i group and 211 days in the oGLD group. Initiation of SGLT-2i versus oGLD was associated with a lower risk of hospitalization for heart failure (pooled HR, 0.61; 95% CI, 0.51 to 0.73; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
sodium-glucose cotransporter-2 inhibitor (SGLT-2i) vs other glucose-lowering drugs (oGLDs)	oGLDs (as initial or add-on therapy); data obtained from deidentified health records across six countries		All-cause death, and a composite of hospitalization for heart failure or all-cause death (time-to-first-event), evaluated in all countries, except Germany	Secondary: Use of SGLT-2i, versus other glucose-lowering drugs, was associated with lower rates of death (HR, 0.49; 95% CI, 0.41 to 0.57; P<0.001); and hospitalization for heart failure or death (HR, 0.54; 95% CI, 0.48 to 0.60; P<0.001) with no significant heterogeneity by country.
Mearns et al.[82] (2015) Hypoglycemic medications (Alpha-glucosidase inhibitors, DPP-4 inhibitors, colesevelam, meglitinides, GLP-1 analogs, long-acting, once-daily basal insulin, SGLT2 inhibitors, sulfonylureas, TZDs, and combinations of the above agents)	Network MA (62 RCTs) Patients with inadequately controlled type 2 diabetes on metformin alone	N=32,185 3 to 12 months	Primary: Changes in HbA_{1c}, body weight, and SBP; risk of developing hypoglycemia and urinary and genital tract infection Secondary: Not reported	Primary: All agents significantly reduced HbA_{1c} vs placebo; although not to the same extent (range, 0.43% for miglitol to 1.29% for glibenclamide). Glargine, sulfonylureas, and nateglinide were associated with increased hypoglycemia risk vs placebo. SGLT2 inhibitors, GLP-1 analogs, miglitol, and empagliflozin/linagliptin significantly reduced body weight (range, 1.15 to 2.26 kg) whereas sulfonylureas, TZDs, glargine, and alogliptin/pioglitazone caused weight gain (range, 1.19 to 2.44 kg). SGLT2 inhibitors, empagliflozin/linagliptin, liraglutide, and sitagliptin decreased SBP (range, 1.88 to 5.43 mmHg). No therapy increased UTI risk vs placebo; however, SGLT2 inhibitors were associated with an increased risk of genital tract infection (RR range, 2.16 to 8.03). Secondary: Not reported

Drug regimen abbreviations: BID=two times a day, QAM=once every morning, QD=once-daily, QPM=once every evening
Study abbreviations: AC=active-controlled, CI=confidence interval, DB=double-blind, ES=extension study, OL=open label, MC=multicenter, PC=placebo-controlled, PG=parallel group, RCT=randomized controlled trial
Miscellaneous: BMI=body mass index, EF=ejection fraction, FPG=fasting plasma glucose, HbA_{1c}=glycosylated hemoglobin, HDL-C= high density lipoprotein cholesterol, HF=heart failure, NYHA=New York Heart Association, PPG=postprandial glucose, T2DM=type 2 diabetes mellitus

Additional Evidence

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

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

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

IX. Cost

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

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

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

Rx=prescription

Table 11. Relative Cost of the Sodium-glucose Cotransport 2 Inhibitors

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Single Entity Agents				
Canagliflozin	tablet	Invokana®	$$$$$	N/A
Dapagliflozin	tablet	Farxiga®	$$$$$	N/A
Empagliflozin	tablet	Jardiance®	$$$$$	N/A
Ertugliflozin	tablet	Steglatro®	$$$$$	N/A
Combination Products				
Canagliflozin and Metformin	extended-release tablet, tablet	Invokamet®, Invokamet XR®	$$$$$	N/A
Dapagliflozin and Metformin	extended-release tablet	Xigduo XR®	$$$$$	N/A
Dapagliflozin and Saxagliptin	tablet	Qtern®	$$$$$	N/A
Empagliflozin and Linagliptin	tablet	Glyxambi®	$$$$$	N/A
Empagliflozin and Metformin	tablet	Synjardy®	$$$$$	N/A
Empagliflozin, Linagliptin, and Metformin	extended-release tablet	Trijardy XR®	$$$$$	N/A
Ertugliflozin and Metformin	tablet	Segluromet®	$$$$$	N/A

Ertugliflozin and Sitagliptin	tablet	Steglujan®	$$$$$	N/A

N/A=Not available

X. Conclusions

The sodium-glucose cotransport 2 (SGLT2) inhibitors are approved for use as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.[3-16] Canagliflozin, dapagliflozin, and empagliflozin also have cardiovascular indications, and canagliflozin and dapagliflozin also have renal indications.[3-16] There are currently no generic products available.

The goal of treatment for type 2 diabetes is to control hyperglycemia and reduce the risk of long-term complications. A notable new theme in diabetes treatment guidelines is an emphasis on a complication-centric approach, beyond glucose levels, to frame decisions regarding first-line pharmacologic choices for the treatment of persons with diabetes. Pharmacologic therapy should be guided by person-centered treatment factors, including comorbidities and treatment goals. In adults with type 2 diabetes and established/high risk of atherosclerotic cardiovascular disease, heart failure, and/or chronic kidney disease, the treatment regimen should include agents that reduce cardiorenal risk. Pharmacologic approaches that provide adequate efficacy to achieve and maintain treatment goals should be considered, such as metformin or other agents, including combination therapy.[17-20] Guidelines recommend that for patients with type 2 diabetes and atherosclerotic cardiovascular disease (e.g., those with prior myocardial infarction, stroke, or any revascularization procedure) or indicators of high risk, a GLP-1 receptor agonist or SGLT2 inhibitor with proven cardiovascular benefit should be the initial treatment option.[17,20]

The SGLT2 inhibitors have demonstrated to be more effective than placebo in reducing HbA_{1c} and fasting plasma glucose.[28-31,36] Combination and add-on therapy with SGLT2 inhibitors and metformin, a sulfonylurea, a thiazolidinedione, and insulin consistently demonstrates improved benefits in glycemic control over placebo. Limited trials have compared the SGLT2 inhibitors to other classes or oral antidiabetic agents: Studies thus far have demonstrated noninferiority to glimepiride, glipizide, and sitagliptin.[43,44,47,49,50,67,75]

In patients with cardiovascular or kidney comorbidities, many SGLT2 inhibitors have demonstrated benefit for cardiovascular and kidney outcomes, and therefore they are appropriate to use in combination with metformin (and/or another oral agent) in this setting. Canagliflozin, dapagliflozin, and empagliflozin have approval for cardiovascular indications. Canagliflozin and dapagliflozin have approval for renal indications. Empagliflozin has gained approval for the treatment of type 2 diabetes in patients 10 years of age and older.[3-16]

A variety of warnings and precautions are listed in the package inserts for the SGLT2 inhibitors, including risks for hypotension, ketoacidosis, acute kidney injury, urosepsis and pyelonephritis, hypoglycemia, necrotizing fasciitis of the perineum (Fournier's Gangrene), genital mycotic infections, hypersensitivity reactions, bone fracture, and increased LDL-C.[3-16] During clinical trials, common adverse side effects associated with the SGLT2 inhibitors included increased incidence of female genital mycotic infections, urinary tract infection, and increased urination.[3-16]

There is insufficient evidence to support that one brand SGLT2 inhibitor is safer or more efficacious than another within its given indication. The SGLT2 inhibitors that have demonstrated cardiovascular disease benefit (currently canagliflozin, dapagliflozin, and empagliflozin) should be available for treatment of patients with type 2 diabetes and atherosclerotic cardiovascular disease (or for heart failure for dapagliflozin and empagliflozin), and agents that have demonstrated kidney disease benefit (currently canagliflozin and dapagliflozin) should be available for treatment of patients with (canagliflozin) or without (dapagliflozin) type 2 diabetes and end-stage kidney disease.

Therefore, all brand products 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 within its given indication.

XI. Recommendations

No brand sodium-glucose cotransport 2 inhibitor is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

XII. References

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Sulfonylureas
AHFS Class 682020
November 8, 2023

I. Overview

Diabetes mellitus is a chronic condition which results in hyperglycemia. It is differentiated into four main classes: 1) type 1 diabetes; 2) type 2 diabetes; 3) gestational diabetes; and 4) other types (drug- or chemical-induced, genetic defects in β-cell function or insulin action, and diseases of the exocrine pancreas). Type 2 diabetes is the most prevalent form of the disease in the United States. Inadequate glycemic control may lead to both acute and long-term complications, including microvascular and macrovascular events. There are a variety of oral and injectable antidiabetic agents currently available to treat diabetes. The antidiabetic agents are categorized into 12 different American Hospital Formulary Service (AHFS) classes, which differ with regards to their mechanism of action, efficacy, safety profiles, tolerability, and ease of use.

The sulfonylureas are approved for use as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.[1-7] They stimulate the release of insulin from functioning pancreatic beta cells.[1-7] There may also be additional extrapancreatic effects; however, the mechanism by which these agents lower blood glucose during long-term administration has not been clearly established. The sulfonylureas block ATP-dependent potassium channels in pancreatic beta cells. This leads to depolarization of the beta cell, followed by an influx of calcium and stimulation of insulin secretion.[8]

The sulfonylureas may be further classified as first generation or second generation agents. The first generation sulfonylureas include chlorpropamide, tolazamide, and tolbutamide. The second generation sulfonylureas include glimepiride, glipizide, and glyburide. The second generation agents have structural characteristics that allow them to be given in much lower doses than the first generation agents. The sulfonylureas primarily differ in their pharmacokinetic parameters; however, they appear to have similar glucose-lowering effects when administered in equipotent doses.[6] Glipizide and glyburide are also available in combination with metformin. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose and improves insulin sensitivity by increasing peripheral glucose uptake and utilization.[5]

The sulfonylureas that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. All of the sulfonylureas are available in a generic formulation, including the fixed-dose combination products. This class was last reviewed in November 2021.

Table 1. Sulfonylureas Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Single Entity Agents			
Glimepiride	tablet	N/A	glimepiride
Glipizide	extended-release tablet, tablet	Glucotrol®*, Glucotrol XL®*	glipizide, glipizide extended-release
Glyburide	tablet	N/A	glyburide
Glyburide, micronized	tablet	Glynase®*	glyburide, micronized
Combination Products			
Glipizide and metformin	tablet	N/A	glipizide and metformin
Glyburide, micronized and metformin	tablet	N/A	glyburide, micronized and metformin

*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 clinical guidelines are summarized in Table 2. Please note that guidelines addressing the treatment of type 2 diabetes are presented globally, addressing the role of various medication classes.

Table 2. Treatment Guidelines Using the Sulfonylureas

Clinical Guideline	Recommendation(s)
American Diabetes Association: **Standards of Care in Diabetes (2023)**[9]	Current criteria for the diagnosis of diabetes • The following are the criteria for a diagnosis of diabetes: glycosylated hemoglobin (HbA_{1c}) ≥6.5%, or a fasting plasma glucose (FPG) ≥126 mg/dL, or a two-hour plasma glucose ≥200 mg/dL during an oral glucose tolerance test or patients with classic symptoms of hyperglycemia, or classic symptoms of hyperglycemia or hyperglycemic crisis (random plasma glucose ≥200 mg/dL). Prevention or delay of type 2 diabetes • Refer adults with overweight/obesity at high risk of type 2 diabetes, as typified by the Diabetes Prevention Program (DPP), to an intensive lifestyle behavior change program to achieve and maintain a weight reduction of at least 7% of initial body weight through healthy reduced-calorie diet and ≥150 minutes/week of moderate-intensity physical activity. • A variety of eating patterns can be considered to prevent diabetes in individuals with prediabetes. • Metformin therapy for prevention of type 2 diabetes should be considered in adults at high risk of type 2 diabetes, as typified by the DPP, especially those aged 25 to 59 years with BMI ≥35 kg/m^2, higher FPG) (e.g., ≥110 mg/dL), and higher A1C (e.g., ≥6.0%), and in individuals with prior gestational diabetes mellitus (GDM). • Long-term use of metformin may be associated with biochemical vitamin B12 deficiency; consider periodic measurement of vitamin B12 levels in metformin-treated individuals, especially in those with anemia or peripheral neuropathy. Glycemic goals in adults • An A1C goal for many nonpregnant adults of <7% (53 mmol/mol) without significant hypoglycemia is appropriate. • If using ambulatory glucose profile (AGP)/glucose management indicator (GMI) to assess glycemia, a parallel goal for many nonpregnant adults is time in range (TIR) of >70% with time below range (TBR) <4% and time <54 mg/dL <1%. For those with frailty or at high risk of hypoglycemia, a target of >50% TIR with <1% TBR is recommended. • On the basis of health care provider judgment and patient preference, achievement of lower A1C levels than the goal of 7% may be acceptable and even beneficial if it can be achieved safely without significant hypoglycemia or other adverse effects of treatment. • Less stringent A1C goals (such as <8% [64 mmol/mol]) may be appropriate for patients with limited life expectancy or where the harms of treatment are greater than the benefits. HCPs should consider deintensification of therapy if appropriate to reduce the risk of hypoglycemia in patients with inappropriate stringent A1C targets. Pharmacologic therapy for type 1 diabetes • Most individuals with type 1 diabetes should be treated with multiple dose insulin injections (three to four injections per day of basal and pre-prandial insulin) or continuous subcutaneous (SC) insulin infusion therapy. • Most patients should use rapid-acting insulin analogs to reduce hypoglycemia risk.

Clinical Guideline	Recommendation(s)
	• Patients with type 1 diabetes should receive education on how to match prandial insulin doses to carbohydrate intake, premeal blood glucose, and anticipated physical activity. Pharmacologic therapy for type 2 diabetes • Healthy lifestyle behaviors, diabetes self-management education and support, avoidance of clinical inertia, and social determinants of health should be considered in the glucose-lowering management of type 2 diabetes. Pharmacologic therapy should be guided by person-centered treatment factors, including comorbidities and treatment goals. • In adults with type 2 diabetes and established/high risk of atherosclerotic cardiovascular disease, heart failure, and/or chronic kidney disease, the treatment regimen should include agents that reduce cardiorenal risk. • Pharmacologic approaches that provide adequate efficacy to achieve and maintain treatment goals should be considered, such as metformin or other agents, including combination therapy. • Weight management is an impactful component of glucose-lowering management in type 2 diabetes. The glucose-lowering treatment regimen should consider approaches that support weight management goals. • Metformin should be continued upon initiation of insulin therapy (unless contraindicated or not tolerated) for ongoing glycemic and metabolic benefits. • Early combination therapy can be considered in some individuals at treatment initiation to extend the time to treatment failure. • The early introduction of insulin should be considered if there is evidence of ongoing catabolism (weight loss), if symptoms of hyperglycemia are present, or when A1C levels (>10% [86 mmol/mol]) or blood glucose levels (≥300 mg/dL [16.7 mmol/L]) are very high. • A person-centered approach should guide the choice of pharmacologic agents. Consider the effects on cardiovascular and renal comorbidities, efficacy, hypoglycemia risk, impact on weight, cost and access, risk for side effects, and individual preferences. • Among individuals with type 2 diabetes who have established atherosclerotic cardiovascular disease or indicators of high cardiovascular risk, established kidney disease, or heart failure, a sodium–glucose cotransporter 2 inhibitor and/or glucagon-like peptide 1 receptor agonist with demonstrated cardiovascular disease benefit is recommended as part of the glucose-lowering regimen and comprehensive cardiovascular risk reduction, independent of A1C and in consideration of person-specific factors. • In adults with type 2 diabetes, a glucagon-like peptide 1 receptor agonist is preferred to insulin when possible. • If insulin is used, combination therapy with a glucagon-like peptide 1 receptor agonist is recommended for greater efficacy, durability of treatment effect, and weight and hypoglycemia benefit. • Recommendation for treatment intensification for individuals not meeting treatment goals should not be delayed. • Medication regimen and medication-taking behavior should be reevaluated at regular intervals (every three to six months) and adjusted as needed to incorporate specific factors that impact choice of treatment. • Clinicians should be aware of the potential for over-basalization with insulin therapy. Clinical signals that may prompt evaluation of over-basalization include basal dose more than ~0.5 units/kg/day, high bedtime–morning or post-preprandial glucose differential, hypoglycemia (aware or unaware), and high glycemic variability. Indication of over-basalization should prompt reevaluation to further individualize therapy.

Clinical Guideline	Recommendation(s)
American Diabetes Association/ European Association for the Study of Diabetes: **Management of Hyperglycemia in Type 2 Diabetes. A consensus report by the American Diabetes Association and the European Association for the Study of Diabetes (2022)[10]**	Consensus recommendations • All people with type 2 diabetes should be offered access to ongoing diabetes self-management education and support programs. • Providers and health care systems should prioritize the delivery of person-centered care. • Optimizing medication adherence should be specifically considered when selecting glucose-lowering medications. • Medical nutrition therapy focused on identifying healthy dietary habits that are feasible and sustainable is recommended in support of reaching metabolic and weight goals. • Physical activity improves glycemic control and should be an essential component of type 2 diabetes management. • Adults with type 2 diabetes should engage in physical activity regularly (>150 min/week of moderate- to vigorous-intensity aerobic activity) and be encouraged to reduce sedentary time and break up sitting time with frequent activity breaks. • Aerobic activity should be supplemented with two to three resistance, flexibility, and/or balance training sessions/week. Balance training sessions are particularly encouraged for older individuals or those with limited mobility/poor physical function. • Metabolic surgery should be considered as a treatment option in adults with type 2 diabetes who are appropriate surgical candidates with a BMI ≥40.0 kg/m^2 (BMI ≥37.5 kg/m^2 in people of Asian ancestry) or a BMI of 35.0 to 39.9 kg/m^2 (32.5 to 37.4 kg/m^2 in people of Asian ancestry) who do not achieve durable weight loss and improvement in comorbidities (including hyperglycemia) with nonsurgical methods. • In people with established CVD, a GLP-1 RA with proven benefit should be used to reduce MACE, or an SGLT2i with proven benefit should be used to reduce MACE and HF and improve kidney outcomes. • In people with CKD and an eGFR ≥20 ml/min per 1.73 m^2 and a urinary albumin/creatinine ratio >3.0 mg/mmol (>30 mg/g), an SGLT2i with proven benefit should be initiated to reduce MACE and HF and improve kidney outcomes. Indications and eGFR thresholds may vary by region. If such treatment is not tolerated or is contraindicated, a GLP-1 RA with proven cardiovascular outcome benefit could be considered to reduce MACE and should be continued until kidney replacement therapy is indicated. • In people with HF, SGLT2i should be used because they improve HF and kidney outcomes. • In individuals without established CVD but with multiple cardiovascular risk factors (such as age ≥55 years, obesity, hypertension, smoking, dyslipidemia, or albuminuria), a GLP-1 RA with proven benefit could be used to reduce MACE, or an SGLT2i with proven benefit could be used to reduce MACE and HF and improve kidney outcomes. • In people with HF, CKD, established CVD, or multiple risk factors for CVD, the decision to use a GLP-1 RA or SGLT2i with proven benefit should be independent of background use of metformin. • SGLT2i and GLP-1 RA reduce MACE, which is likely to be independent of baseline HbA1c. In people with HF, CKD, established CVD, or multiple risk factors for CVD, the decision to use a GLP-1 RA or an SGLT2i with proven benefit should be independent of baseline HbA1c. • In general, selection of medications to improve cardiovascular and kidney outcomes should not differ for older people. • In younger people with diabetes (<40 years), consider early combination therapy.

Clinical Guideline	Recommendation(s)
	• In women with reproductive potential, counseling regarding contraception and taking care to avoid exposure to medications that may adversely affect a fetus are important.
American Association of Clinical Endocrinologists/ American College of Endocrinology: **Clinical Practice Guidelines for Developing a Diabetes Mellitus Comprehensive Care Plan (2022)**[11]	Antihyperglycemic Pharmacotherapy for Persons with Type 2 Diabetes • Individualized pharmacotherapy for persons with T2D should be prescribed based on evidence for benefit that includes glucose lowering, avoidance of hypoglycemia and weight gain, and reduction of cardio-renal risk. • Persons with T2D and their health care professionals should use patient-centered shared decision-making to agree on therapy targets and treatments as well as a regimen for glucose monitoring (i.e., BGM, structured BGM, or CGM). • Glycemic targets include A1C, BGM, and, for those using CGM, achievement of CGM targets such as time in range (TIR), percentage in low and very low range, time above range, and glycemic variability. Nonglycemic targets include avoidance of hypoglycemia, control of BP, lipids, other CVD risk factors, and achieving and maintaining a healthy body weight. • Independent of glycemic control, targets, or treatment, if there is established or high risk for ASCVD, HF, and/or CKD, clinicians should prescribe a GLP-1 RA or an SGLT2i with proven efficacy for the specific condition(s) of the person with T2D being treated. • DM therapy should be individualized based on level of glycemia and the presence of comorbidities, complications, and access. Metformin is often the preferred initial therapy. Other agents may be appropriate as first line or in addition to metformin to reduce BG and/or to address specific comorbidities (such as ASCVD, HF, CKD, obesity, NAFLD), independent of glucose-lowering effects. • For some recently diagnosed individuals with T2D and more severe hyperglycemia (A1C ≥7.5%), unlikely to attain the A1C target with a single agent, early combination pharmacotherapy should be considered, usually to include metformin plus another agent that does not cause hypoglycemia, especially a GLP-1 RA, SGLT2i, or dipeptidyl peptidase 4 (DPP-4) inhibitor. • For newly diagnosed persons with T2D and an entry A1C >9.0% and/or ≥1.5% above target, one should initiate, along with lifestyle modifications, dual- or possibly triple-combination pharmacotherapy usually including metformin. Basal insulin along with noninsulin therapy is recommended if there are significant signs or symptoms of hyperglycemia, especially including catabolism (e.g., weight loss) or a very high A1C >10% (86 mmol/mol) or BG levels (≥300 mg/dL [16.7 mmol/L]). • Clinicians should discuss with persons with T2D the likelihood that most persons with T2D ultimately require a combination of multiple complementary antihyperglycemic agents, in addition to lifestyle interventions, to attain and maintain optimal glycemic control. • The DM care team should assess medication adherence and safety and glycemic control in persons with T2D quarterly or more frequently as needed. Subsequent visits will depend upon the metabolic targets achieved and the stability of metabolic control. • Persons with T2D who start on metformin should continue it unless intolerance or contraindications occur. When intensification of antihyperglycemic treatment is needed, other agents should be added to metformin. • Most persons with T2D who require intensification of antihyperglycemic therapy with a GLP-1 RA or insulin should initially be prescribed a GLP-1 RA. If further intensification is required, one should prescribe a basal insulin or a switch to a fixed-ratio combination of a basal insulin and a GLP-1 RA (insulin

Clinical Guideline	Recommendation(s)
	glargine U100 + lixisenatide [GlarLixi] or insulin degludec + liraglutide [IdegLira]). • Insulin should be prescribed for persons with T2D when noninsulin antihyperglycemic therapy fails to achieve target glycemic control or when a person has symptomatic hyperglycemia. • Long-acting basal insulin analogs are the recommended initial choice of insulin therapy for persons with T2D. The insulin analogs glargine (U100 or U300), degludec (U100 or U200), or detemir are preferred over intermediate-acting Neutral Protamine Hagedorn (NPH) insulin because analog insulins have demonstrated less hypoglycemia in some studies. Glargine U300 and degludec can be associated with less hypoglycemia than glargine U100 or detemir. • Many persons with T2D receiving basal insulin and not at goal A1C can have significantly improved glycemia by the addition of a GLP-1 RA or being switched to a fixed-ratio combination basal insulin–GLP-1 RA (GlarLixi or IdegLira). One of these changes should be considered before adding a meal-time insulin for postprandial glycemic control. • When control of postprandial hyperglycemia is needed and a basal insulin and a GLP-1 RA are already being used, preference should be given to rapid-acting insulins (the analogs lispro, aspart, and glulisine or the rapid-acting inhaled human insulin powder) over regular human insulin. The former have a more consistent and a more rapid onset and offset of action with less risk of hypoglycemia. • Ultra-rapid-acting insulins (faster-acting insulin aspart, lispro aabc, and [human insulin] inhalation powder) may allow a decrease in the time between insulin administration and food intake and reduce the postprandial peak of PG as compared with rapid-acting insulins. The significance of this on long-term complications is unknown. • Basal-bolus insulin regimens or continuous subcutaneous insulin infusion (CSII) (i.e., insulin pump) allow for adjustment of insulin doses according to carbohydrate intake and activity levels and are recommended for intensive insulin therapy in persons with T2D. • Premixed insulin formulations (fixed combinations of shorter- and longer-acting components) of human or analog insulin may be considered for persons with T2D who have consistent dietary and exercise patterns and in whom adherence to more intensive insulin regimens is problematic. However, these preparations have reduced dosage flexibility and may increase the risk of hypoglycemia compared with basal insulin or basal-bolus regimens. • In persons with T2D who are treated with basal-bolus insulin therapy, adding a GLP-1 RA, or switching to a fixed-ratio combination of a GLP-1 RA and a basal insulin, or adding an SGLT2i or pramlintide (less commonly used) may be able to reduce postprandial hyperglycemia, A1C, and weight. GLP-1 RAs may also allow reduction or discontinuation of bolus insulin in some individuals. <u>How should insulin therapy be used for management of persons with type 1 diabetes?</u> • Insulin must be used to treat all persons with T1D. • Physiologic insulin replacement regimens, which provide both basal and prandial (meal-related or bolus) insulin, are recommended for most persons with T1D. • Achievement of glucose targets using either MDI of insulin or CSII, is needed to prevent development of life-threatening crises, such as acute hyperglycemic crises (DKA and hyperglycemic hyperosmolar state) and catabolic state. • A multi-component self-management DM education program is recommended for persons with T1D. Ideally, this is provided by a professional with expertise

Clinical Guideline	Recommendation(s)
	(i.e., certified diabetes care and education specialist) in the topics of healthy lifestyle, insulin technique including prandial insulin dosing guided by carbohydrate counting and diet adjustments for special situations, such as physical activity and prolonged fasting. Instruction is also needed in how to deal with sick days and prevention of DKA and hypoglycemia, and other relevant issues. Due to changes in DM self-management practices and each individual's medical history, personal and cultural background, and educational needs, specific education topics may need to be repeated at regular intervals. • The ideal insulin regimen should be personalized to an individual's needs and glycemic targets, attempting to better emulate physiological insulin replacement to maintain near normoglycemia, to prevent the development and progression of DM complications, while minimizing hypoglycemia and providing flexibility for specific daily life situations/scenarios such as: exercise, sleep, acute illness, psychological stress, etc. • Insulin regimens usually should involve the use of insulin analogs for most persons with T1D and include the following approaches: o MDI, which usually involve 1 to 2 subcutaneous injections daily of basal insulin to suppress ketogenesis and gluconeogenesis and to control glycemia between meals and overnight, and subcutaneous injections of prandial insulin or use of inhaled insulin before each meal to control meal-related glycemic excursions. CGM is the preferred method of glucose monitoring for all individuals with T1D. o Insulin pump therapy (CSII) provides constant/continuous infusion of fast-acting insulin driven by mechanical force and delivered via a cannula inserted under the skin. CSII can improve (or enhance) glycemic control and should be an option for insulin delivery for appropriate persons with DM. Ideally, these individuals should also use CGM as stated in R13.6.a. o Automated insulin delivery systems (AIDs), which include an insulin pump, an integrated CGM, and computer software algorithm, aim to better emulate physiological insulin replacement and achieve glycemic targets. This technology is recommended for many persons with T1D since its use has been shown to increase TIR while often reducing hypoglycemia or at least without causing increased hypoglycemia. o Open-loop (use of a pump and sensor which do not communicate) and sensor-augmented pump (SAP) systems: (CGM communicates with pump facilitating needed adjustments to basal rate; temporary interruption of insulin delivery when glucose levels are low or forecast to be low within 30 min). Insulin pump with a CGM or an SAP is recommended to manage persons with DM treated with intensive insulin management who prefer not to use AIDs or have no access to them. <u>How should diabetes mellitus in pregnancy be managed?</u> • For women with GDM, the following treatment goals are recommended: preprandial glucose concentration ≤95 mg/dL and either a 1-h post-meal glucose ≤140 mg/dL or a 2-h post-meal glucose ≤120 mg/dL to decrease adverse fetal outcomes. • All women with preexisting DM (T1D, T2D, or previous GDM) need access to preconception care and counseling to ensure adequate nutrition, healthy weight, and glucose control before conception, during pregnancy, and in the postpartum period. • Rapid-acting insulin analogs (insulin-lispro, insulin-aspart) should be used to treat postprandial hyperglycemia in pregnant women. • Options for basal insulin include long-acting insulin (e.g., NPH, detemir, or glargine) or rapid-acting insulin via a CSII. Regular insulin, although not

Clinical Guideline	Recommendation(s)
	recommended as first-line therapy, is acceptable to use in managing pregnant women with DM when rapid-acting insulin analogs are not available. • Insulin is the preferred therapeutic choice for pregnant women with GDM or T2D, but metformin has been given a category B for pregnancy with accumulating clinical evidence of metformin's safety during the first trimester and beyond. Metformin has been shown to improve pregnancy and fetal outcomes except for increased rates of infants with SGA and later onset of obesity. The prescriber should discuss the potential risks and benefits of oral agent therapy during pregnancy as well as the need for longer-term outcome studies.
American Association of Clinical Endocrinologists/ American College of Endocrinology: **Consensus Statement on the Comprehensive Type 2 Diabetes Management Algorithm (2023)**[12]	Principles underlying the algorithm • Lifestyle modification underlies all therapy. • Maintain or achieve optimal weight. • Choice of antihyperglycemic therapy reflects glycemic targets, atherosclerotic cardiovascular disease (ASCVD), congestive heart failure (CHF), chronic kidney disease (CKD), overweight/obesity, and nonalcoholic fatty liver disease (NAFLD). • Choice of therapy includes ease of use and access. • Optimal hemoglobin A1c (A1C) is ≤6.5% or as close to normal as is safe and achievable for most patients. • Individualize all glycemic targets (A1C, glucose management indicator [GMI], time in range [TIR], fasting blood glucose [FBG], and PPG). • Get to goal as soon as possible (adjust ≤3 months). • Avoid hypoglycemia. Hypoglycemia, defined as blood glucose (BG) <70 mg/dL, is associated with an increased risk for adverse outcomes including mortality. • CGM is highly recommended to assist persons with diabetes in reaching goals safely. • Comorbidities must be managed for comprehensive care. Algorithm summative information • The algorithm is intended as a more concise document than the guideline, providing easily accessible, visual guidance for decision-making in the clinic setting. • In this 2023 algorithm, there continues to be an emphasis on lifestyle modification and treatment of overweight/obesity as key pillars of the management of prediabetes and DM. • The importance of appropriate management of the atherosclerotic risk factors of dyslipidemia and hypertension is highlighted. • One notable new theme is an obvious emphasis on a complication-centric approach, beyond glucose levels, to frame decisions regarding first-line pharmacologic choices for the treatment of persons with diabetes. • The algorithm is divided into discrete graphic sections that outline the principles for management of T2D and guide management of adiposity-based chronic disease (ABCD), prediabetes, and atherosclerotic risk factors of dyslipidemia and hypertension. In addition, the algorithms for antihyperglycemic agents include both complication-centric and glucose-centric approaches, and there is direction for insulin initiation and titration. Tables summarizing the benefits and risks of antihyperglycemic medications (updated) and weight-loss pharmacotherapy (new) are provided.
American Academy of Pediatrics:	• Clinicians must ensure that insulin therapy is initiated for children and adolescents with T2DM who are ketotic or in diabetic ketoacidosis and in whom

Clinical Guideline	Recommendation(s)
Management of Newly Diagnosed Type 2 Diabetes Mellitus (T2DM) in Children and Adolescents (2013)[13]	the distinction between types 1 and 2 diabetes mellitus is unclear and, in usual cases, should initiate insulin therapy for patients. o Who have random venous or plasma blood glucose (BG) concentrations ≥250 mg/dL. o Whose HbA_{1c} is >9%. • In all other instances, clinicians should initiate a lifestyle modification program, including nutrition and physical activity, and start metformin as first-line therapy for children and adolescents at the time of diagnosis of T2DM. • Monitoring of HbA_{1c} concentrations is recommended every three months and intensifying treatment is recommended if treatment goals for finger-stick BG and HbA_{1c} concentrations are not being met. • Advise patients to monitor finger-stick BG concentrations in patients who: o Are taking insulin or other medications with a risk of hypoglycemia; or o Are initiating or changing their diabetes treatment regimen; or o Have not met treatment goals; or o Have intercurrent illnesses. • Incorporate the Academy of Nutrition and Dietetics' *Pediatric Weight Management Evidence-Based Nutrition Practice Guidelines* in dietary or nutrition counseling of patients with T2DM at the time of diagnosis and as part of ongoing management. • Encourage children and adolescents with T2DM to engage in moderate-to-vigorous exercise for at least 60 minutes daily and to limit nonacademic "screen time" to less than two hours a day.
American Diabetes Association: **Type 1 Diabetes in Children and Adolescents: A Position Statement by the American Diabetes Association (2018)[14]**	<u>Blood Glucose Management: Monitoring and Treatment</u> • Most children with type 1 diabetes should be treated with intensive insulin regimens via either multiple daily injections of prandial insulin and basal insulin or continuous subcutaneous insulin infusion. • An HbA_{1c} target of <7.5% should be considered in most children and adolescents but should be individualized based on the needs and situation of the patient and family. • Children and adolescents with type 1 diabetes should have blood glucose levels monitored up to six to ten times/day including premeal, pre-bedtime, and as needed for safety (e.g. exercise, driving, illness, or the presence of symptoms of hypoglycemia). • Continuous blood glucose monitoring should be considered in all children and adolescents whether using insulin injections or an insulin pump. • In pediatric patients with type 1 diabetes automated insulin delivery systems can improve glycemic control and reduce hypoglycemia. <u>Lifestyle Management</u> • Individualized medical nutrition therapy is recommended for children and adolescents with type 1 diabetes. • Monitoring carbohydrate intake, whether by carbohydrate counting or experience-based estimation, is key to achieving optimal glycemic control. • Exercise if recommended for all children and adolescents with type 1 diabetes. The suggested goal is 60 minutes of moderate to vigorous aerobic activity daily with muscle-strengthening and bone-strengthening activities three times a week. • Children and adolescents with type 1 diabetes should be educated about prevention and management of potential hypoglycemia during and after exercise. • Strategies to prevent hypoglycemia during exercise, after exercise, and overnight following exercise include reducing prandial insulin dosing for the meal/snack preceding exercise, increasing carbohydrate intake, eating bedtime snacks, using continuous blood glucose monitoring, and/or reducing basal insulin doses.

Clinical Guideline	Recommendation(s)
	Behavioral Aspects of Self-Management • Children and adolescents with diabetes should be assessed for psychosocial issues and family stresses that could impact diabetes management at diagnosis and routine follow-up. • Consider including children in consent processes as early as cognitive development indicates understanding of health consequences of behavior. • Offer adolescents time by themselves with their care provider(s) starting at age 12 years, or when developmentally appropriate. Complications and Comorbidities • Diabetic Ketoacidosis o All individuals with type 1 diabetes should have access to an uninterrupted supply of insulin. Lack of access and insulin omissions are major causes of diabetic ketoacidosis. o Patients with type 1 diabetes should have continuous access to medical support for sick-day management. • Hypoglycemia o The recommended treatment of hypoglycemia (blood glucose <70 mg/dL) in conscious patients is 15 g of glucose, although any form of carbohydrate can be used. If hypoglycemia continues after 15 minutes, treatment should be repeated. Once blood glucose has returned to normal patients should consider consuming a meal/snack and/or reduce insulin. o All individuals with type 1 diabetes should be prescribed glucagon and families/caregivers should be educated on administration. o Treatment regimens should be reevaluated in those with hypoglycemia unawareness or one or more episodes of severe hypoglycemia. • Diabetic Kidney Disease o Annual screening for albuminuria with a random spot urine sample for albumin-to-creatinine ratio should be considered at puberty or at age >10 years, whichever is earlier, once the child has had diabetes for 5 years. o An angiotensin-converting-enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB), titrated to normalization of albumin excretion, may be considered when elevated urinary albumin-to-creatinine ratio is documented. • Retinopathy o An initial dilated and comprehensive eye examination is recommended at age 10 years or after puberty has started, whichever is earlier, once the patient has had diabetes for three to five years. o Annual routine follow-up is recommended but may be given every two years based on the advice of an eye care professional. • Neuropathy o Consider an annual comprehensive foot exam for adolescents at the start of puberty or at age 10 years, whichever is earlier, once the patient has had type 1 diabetes for 5 years. • Hypertension o Children and adolescents with type 1 diabetes should have blood pressure monitored at each visit. Elevated blood pressure should be confirmed on three separate days. o Initial treatment of high-normal blood pressure should include dietary modification and increased exercise. Pharmacologic treatment should be considered if blood pressure is not controlled after three to six months. o In patients with conformed hypertension pharmacologic treatment should be added to lifestyle modification at diagnosis. o ACE inhibitors and ARBs should be considered for initial treatment. • Dyslipidemia

Clinical Guideline	Recommendation(s)
	○ A fasting lipid profile should be taken in children ≥10 years of age or older after the diagnosis of diabetes. Obtain a fasting lipid profile in children 10 years of age or older as soon as convenient after the diagnosis of diabetes ○ If lipids are abnormal, initial therapy should consist of optimizing glucose control and medical nutrition therapy using a Step 2 American Heart Association diet that restricts saturated fat to 7% of total calories and dietary cholesterol to 200 mg/day. ○ If lipids remain abnormal after six months of lifestyle intervention, consider adding a statin in children at least 10 years of age.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the sulfonylureas are noted in Table 3.

Table 3. FDA-Approved Indications for the Sulfonylureas[1-7]

Generic Name	Adjunct to Diet and Exercise to Improve Glycemic Control in Adults with Type 2 Diabetes Mellitus
Single Entity Agents	
Glimepiride	✔
Glipizide	✔
Glyburide	✔
Glyburide, micronized	✔
Combination Products	
Glipizide and metformin	✔
Glyburide, micronized and metformin	✔

IV. Pharmacokinetics

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

Table 4. Pharmacokinetic Parameters of the Sulfonylureas[6]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Single Entity Agents					
Glimepiride	100	>99	Liver (% not reported)	Renal (60), Feces (40)	9
Glipizide	100	97 to 99	Liver (% not reported)	Renal (63 to 89), Feces (11)	2 to 5
Glyburide	Not reported	99	Liver (% not reported)	Renal (50), Bile (50)	5 to 10
Glyburide, micronized	Not reported	99	Liver (% not reported)	Renal (80 to 90)	5 to 10
Combination Products					
Glipizide and metformin	100/50 to 60	98/Negligible	Liver	Renal (10), Bile (11)/Renal (90)	2 to 4/6
Glyburide, micronized and metformin	Not reported/50 to 60	99/Negligible	Liver	Renal (80 to 90)/Renal (90)	5 to 10/6

V. Drug Interactions

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

Table 5. Major Drug Interactions with the Sulfonylureas[6]

Generic Name(s)	Interaction	Mechanism
Metformin	Iodinated contrast materials, parenteral	Iodinated contrast materials-induced renal failure can interfere with the renal elimination of metformin; therefore, there is an increased risk of metformin-induced lactic acidosis. Glipizide/metformin or glyburide/metformin should not be restarted until renal function returns to normal.
Sulfonylureas	Quinolones	The hypoglycemic effect of glimepiride and glyburide may be increased by quinolones, especially in elderly patients with renal compromise. The mechanism of this interaction is unknown.
Sulfonylureas	Salicylates	Increased hypoglycemia may occur. Salicylates reduce basal plasma glucose levels and enhance insulin secretion. Inhibition of prostaglandin synthesis may inhibit acute insulin responses to glucose. Displaced sulfonylurea protein binding has been suggested.
Sulfonylureas (glimepiride)	Azole antifungals	Azole antifungals may inhibit the cytochrome P450 2C9 isoenzyme-mediated metabolism of certain sulfonylureas, increasing the hypoglycemic effects.
Sulfonylureas (glyburide)	Bosentan	Bosentan may increase the metabolism (cytochrome P450 2C9 and 3A4 isoenzyme-mediated) of glyburide. Other mechanisms may also be involved. Plasma levels of bosentan and glyburide may be decreased. Increased risk of elevated liver enzymes, resulting in serious liver injury may occur.
Sulfonylureas (glimepiride, glipizide, glyburide)	Entacapone	Concurrent use of entacapone and sulfonylureas may result in increased glimepiride exposure.
Sulfonylureas	Acarbose	Concurrent use of acarbose and sulfonylureas may result in an increased risk of hypoglycemia.
Sulfonylureas	Aspirin	Concurrent use of aspirin and oral hypoglycemics may result in increased risk of hypoglycemia.
Sulfonylureas	Desmopressin	Concurrent use of desmopressin and sulfonylureas may result in increased risk of hyponatremia.
Sulfonylureas	Disopyramide	Concurrent use of disopyramide and sulfonylureas may result in increased risk of hypoglycemia.
Sulfonylureas	Dulaglutide	Concurrent use of dulaglutide and selected sulfonylureas may result in increased risk of hypoglycemia.
Sulfonylureas	Lixisenatide	Concurrent use of lixisenatide and sulfonylureas may result in increased risk of hypoglycemia.
Insulin secretagogues	Metreleptin	Concurrent use of metreleptin and insulin secretagogues may result in increased risk of hypoglycemia.

VI. Adverse Drug Events

The most common adverse drug events reported with the sulfonylureas are listed in Table 6. The boxed warning for glipizide/metformin and glyburide/metformin is listed in Table 7. The administration of oral hypoglycemic drugs has been reported to be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin. This association has led to a warning and is based on the study conducted by the University Group Diabetes Program (UGDP), a long-term, prospective clinical trial designed to evaluate the effectiveness of glucose-lowering drugs in preventing or delaying vascular complications in patients with non-insulin-dependent diabetes. However it is important to note that only tolbutamide was included in this study.[1-7]

Table 6. Adverse Drug Events (%) Reported with the Sulfonylureas[1-7]

Adverse Events	Single Entity Agents				Combination Products	
	Glimepiride	Glipizide	Glyburide	Glyburide, micronized	Glipizide and Metformin	Glyburide, Micronized and Metformin
Cardiovascular						
Chest discomfort	-	-	-	-	✔	✔
Flushing	-	-	-	-	✔	✔
Hypertension	-	-	-	-	3 to 4	-
Palpitations	-	-	-	-	✔	✔
Syncope	-	✔	-	-	✔	-
Central Nervous System						
Anxiety	-	✔	-	-	✔	-
Depression	-	✔	-	-	✔	-
Dizziness	2	✔	✔	✔	2 to 5	✔
Drowsiness	-	✔	-	-	✔	-
Headache	2	✔	✔	✔	6 to 13	6
Insomnia	-	✔	-	-	✔	-
Nervousness	-	✔	-	-	✔	-
Paresthesia	-	✔	✔	✔	✔	✔
Tremor	-	✔	-	-	✔	-
Weakness	2	-	-	-	9	9
Dermatological						
Allergic skin reactions	✔	✔	✔	✔	✔	✔
Angioedema	-	-	✔	✔	-	✔
Eczema	-	✔	-	-	✔	-
Erythema	✔	✔	✔	✔	✔	✔
Morbilliform or maculopapular eruptions	✔	✔	✔	✔	✔	✔
Photosensitivity	✔	✔	✔	✔	✔	✔
Porphyria cutanea tarda	✔	✔	✔	✔	✔	✔

Adverse Events	Single Entity Agents				Combination Products	
	Glimepiride	Glipizide	Glyburide	Glyburide, micronized	Glipizide and Metformin	Glyburide, Micronized and Metformin
Pruritus	✔	✔	✔	✔	✔	✔
Purpura	-	-	✔	✔	-	✔
Rash	✔	✔	✔	✔	✔	✔
Sweating	-	✔	-	-	✔	✔
Urticaria	✔	✔	✔	✔	✔	✔
Vasculitis	✔	-	✔	✔	✔	✔
Endocrine and Metabolic						
Edema	✔	✔	-	-	✔	-
Hypoglycemia	✔	✔	✔	✔	✔	✔
Hyponatremia	✔	✔	✔	✔	✔	✔
Lactic acidosis	-	-	-	-	✔	✔
Syndrome of inappropriate antidiuretic hormone	✔	✔	✔	✔	✔	✔
Gastrointestinal						
Abdominal/gastrointestinal pain	✔	-	-	-	6	6
Anorexia	✔	✔	✔	✔	✔	-
Constipation	✔	✔	✔	✔	✔	✔
Diarrhea	✔	✔	✔	✔	2 to 53	10 to 53
Dyspepsia	-	-	-	-	✔	✔
Epigastric fullness	✔	✔	✔	✔	✔	✔
Flatulence	-	✔	-	-	12	12
Gastralgia	-	✔	-	-	✔	-
Heartburn	✔	✔	✔	✔	✔	✔
Indigestion	-	-	-	-	7	7
Nausea	5	✔	✔	✔	1 to 26	7 to 26
Taste alteration	-	-	-	-	✔	✔
Vomiting	✔	✔	-	-	1 to 26	7 to 26
Genitourinary						
Diuresis	✔	✔	✔	✔	✔	-
Dysuria	-	-	-	-	✔	-
Urinary tract infection	-	-	-	-	1	-
Hematologic						
Agranulocytosis	✔	✔	✔	✔	✔	-
Aplastic anemia	✔	✔	✔	✔	✔	-
Blood dyscrasias	-	✔	-	-	✔	-

Adverse Events	Single Entity Agents				Combination Products	
	Glimepiride	Glipizide	Glyburide	Glyburide, micronized	Glipizide and Metformin	Glyburide, Micronized and Metformin
Hemolytic anemia	✔	✔	✔	✔	✔	✔
Leukopenia	✔	✔	✔	✔	✔	-
Megaloblastic anemia	-	-	-	-	✔	✔
Pancytopenia	✔	✔	✔	✔	✔	-
Thrombocytopenia	✔	✔	✔	✔	✔	-
Hepatic						
Cholestatic jaundice	✔	✔	✔	✔	✔	✔
Elevated liver enzyme levels	✔	-	-	-	-	-
Hepatic porphyria	✔	✔	-	-	✔	-
Hepatitis	✔	-	✔	✔	-	✔
Liver function abnormalities	✔	-	✔	✔	-	✔
Transaminases increased	-	-	✔	✔	-	✔
Musculoskeletal						
Arthralgia	-	✔	✔	✔	✔	-
Leg cramps	-	✔	-	-	✔	-
Musculoskeletal pain	-	-	-	-	8	-
Myalgia	-	✔	✔	✔	✔	✔
Respiratory						
Pneumonitis	-	-	-	-	✔	✔
Rhinitis	-	✔	-	-	✔	-
Upper respiratory tract infection	-	-	-	-	✔	✔
Other						
Blurred vision	✔	✔	✔	✔	✔	✔
Changes in accommodation	✔	-	✔	✔	✔	✔
Chills	-	-	-	-	✔	✔
Decreased Vitamin B_{12} levels	-	-	-	-	✔	✔
Disulfiram-like reaction	✔	✔	✔	✔	✔	✔
Flu-like symptoms	5	-	-	-	✔	✔
Hypersensitivity reaction	-	-	✔	✔	✔	✔
Nail disorder	-	-	-	-	✔	✔
Pain	-	✔	-	-	✔	-

✔ Percent not specified.
-Event not reported.

Table 7. Boxed Warning for glipizide and metformin and glyburide, micronized and metformin[7]

WARNING
Lactic acidosis: Lactic acidosis is a rare, but serious, metabolic complication that can occur because of metformin accumulation during treatment with glipizide/metformin; when it occurs, it is fatal in approximately 50% of cases. Lactic acidosis may also occur in association with a number of pathophysiologic conditions, including diabetes mellitus, and whenever there is significant tissue hypoperfusion and hypoxemia. Lactic acidosis is characterized by elevated blood lactate levels (more than 5 mmol/L), decreased blood pH, electrolyte disturbances with an increased anion gap, and an increased lactate/pyruvate ratio. When metformin is implicated as the cause of lactic acidosis, metformin plasma levels of more than 5 µg/mL are generally found. The reported incidence of lactic acidosis in patients receiving metformin is very low (approximately 0.03 cases per 1,000 patient-years, with approximately 0.015 fatal cases per 1,000 patient-years). In more than 20,000 patient-years of exposure to metformin in clinical trials, there were no reports of lactic acidosis. Reported cases have occurred primarily in diabetic patients with significant renal function impairment, including both intrinsic renal disease and renal hypoperfusion, often in the setting of multiple concomitant medical/surgical problems and multiple concomitant medications. Patients with congestive heart failure (CHF) requiring pharmacologic management, in particular those with unstable or acute CHF who are at risk of hypoperfusion and hypoxemia, are at increased risk of lactic acidosis. The risk of lactic acidosis increases with the degree of renal function impairment and the patient's age. The risk of lactic acidosis may, therefore, be significantly decreased by regular monitoring of renal function in patients taking metformin and the use of the minimum effective dose of metformin. In particular, accompany the treatment of elderly patients with careful monitoring of renal function. Do not initiate glipizide/metformin treatment in patients 80 years of age and older unless measurement of creatinine clearance demonstrates that renal function is not reduced, because these patients are more susceptible to developing lactic acidosis. In addition, promptly withhold glipizide/metformin in the presence of any condition associated with dehydration, hypoxemia, or sepsis. Because hepatic function impairment may significantly limit the ability to clear lactate, generally avoid glipizide/metformin in patients with clinical or laboratory evidence of hepatic disease. Caution patients against excessive alcohol intake, acute or chronic, when taking glipizide/metformin, because alcohol potentiates the effects of metformin on lactate metabolism. In addition, temporarily discontinue glipizide/metformin prior to any intravascular radiocontrast study and for any surgical procedure. The onset of lactic acidosis is often subtle and accompanied only by nonspecific symptoms, such as increasing somnolence, malaise, myalgia, nonspecific abdominal distress, and respiratory distress. There may be associated hypotension, hypothermia, and resistant bradyarrhythmias with more marked acidosis. The patient and the patient's health care provider must be aware of the possible importance of such symptoms. Instruct the patient to notify their health care provider immediately if symptoms occur. Withdraw glipizide/metformin until the situation is clarified. Serum electrolytes, ketones, blood glucose, and, if indicated, blood pH, lactate levels, and even blood metformin levels may be useful. Once a patient is stabilized on any dose level of glipizide/metformin, gastrointestinal symptoms, which are common during initiation of therapy with metformin, are unlikely to be drug-related. Later occurrence of gastrointestinal symptoms could be caused by lactic acidosis or other serious disease. Levels of fasting venous plasma lactate above the upper limit of normal but less than 5 mmol/L in patients taking glipizide/metformin do not necessarily indicate impending lactic acidosis and may be explainable by other mechanisms, such as poorly controlled diabetes or obesity, vigorous physical activity, or technical problems in sample handling. Suspect lactic acidosis in any diabetic patient with metabolic acidosis lacking evidence of ketoacidosis (e.g., ketonemia, ketonuria). Lactic acidosis is a medical emergency that must be treated in a hospital setting. In a patient with lactic acidosis who is taking glipizide/metformin, discontinue the drug immediately and institute general supportive measures promptly. Because metformin is dialyzable (with a clearance of up to 170 mL/min under good hemodynamic conditions), prompt hemodialysis is recommended to correct the acidosis and remove the accumulated metformin. Such management often results in prompt reversal of symptoms and recovery.

VII. Dosing and Administration

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

Table 8. Usual Dosing Regimens for the Sulfonylureas[1-7]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Single Entity Agents			
Glimepiride	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus: Tablet: initial, 1 or 2 mg QD; maximum, 8 mg/day	Not recommended in pediatric patients.	Tablet: 1 mg 2 mg 4 mg
Glipizide	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus: Extended-release tablet: initial, 5 mg QD; maintenance, 5 to 10 mg QD; maximum, 20 mg/day Tablet: initial, 2.5 or 5 mg QD; maximum, 40 mg/day	Safety and efficacy in children have not been established.	Extended-release tablet: 2.5 mg 5 mg 10 mg Tablet: 5 mg 10 mg
Glyburide	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus: Tablet: initial, 1.25 to 5 mg QD; maintenance, 1.25 to 20 mg/day; maximum, 20 mg/day	Safety and efficacy in children have not been established.	Tablet: 1.25 mg 2.5 mg 5 mg
Glyburide, micronized	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus: Tablet: initial, 0.75 to 3 mg QD; maintenance, 0.75 to 12 mg QD; maximum, 12 mg/day	Safety and efficacy in children have not been established.	Tablet: 1.5 mg 3 mg 6 mg
Combination Products			
Glipizide and metformin	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus: Tablet: dosage must be individualized on the basis of both effectiveness and tolerance while not exceeding the maximum recommended daily dose of 20-2,000 mg	Safety and efficacy in children have not been established.	Tablet: 2.5-250 mg 2.5-500 mg 5-500 mg
Glyburide, micronized and metformin	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus: Tablet: dosage must be individualized on the basis of both effectiveness and tolerance while not exceeding the maximum recommended daily dose of 20-2,000 mg	Safety and efficacy in children have not been established.	Tablet: 1.25-250 mg 2.5-500 mg 5-500 mg

QD=once daily

VIII. Effectiveness

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

Table 9. Comparative Clinical Trials with the Sulfonylureas

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Type 2 Diabetes – Monotherapy				
United Kingdom Prospective Diabetes Study Group[15] (1998) Chlorpropamide 100 to 500 mg daily vs glibenclamide* 2.5 to 20 mg daily vs glipizide 2.5 to 40 mg daily vs insulin vs conventional therapy with diet	RCT Patients newly diagnosed with type 2 diabetes, baseline HbA_{1c} 7.05% in the dietary treatment group and 7.09% in the intensive therapy group	N=3,867 10 years	Primary: Time to the first occurrence of any diabetes-related endpoint, time to diabetes-related death, all-cause mortality Secondary: MI, sudden death, stroke, amputation or death due to peripheral vascular disease, microvascular complications, retinopathy, vitreous hemorrhage, and/or fatal or nonfatal renal failure	Primary: There was a 12% risk reduction (95% CI, 1 to 21; P=0.029) for any diabetes-related end point, 10% risk reduction (95% CI, -11 to 27; P=0.34) for any diabetes-related death, and a 6% risk reduction (95% CI, -10 to 20; P=0.44) for all-cause mortality when intensive therapy (sulfonylurea or insulin) was compared to conventional therapy with diet. Patients receiving an intensive treatment (sulfonylurea or insulin) had a 25% risk reduction (95% CI, 7 to 40; P=0.0099) in microvascular end points compared to conventional therapy with diet. Most of this reduction was due to fewer cases of retinal photocoagulation. There were no differences between the intensive and conventional treatment groups or between the three intensive treatment groups in the number of patients who had a silent MI, cardiomegaly, evidence of peripheral vascular disease, or absent peripheral pulses. Secondary: There was no significant difference between chlorpropamide, insulin, and glibenclamide in macrovascular events. There was no significant difference between the three intensive treatments in microvascular end points or in the risk reduction for retinal photocoagulation.
Feinbock et al.[16] (2003)	MC, OL, PG, RCT Patients from 36 to 80 years of age with	N=219 20 weeks	Primary: Number of responders in each group (defined as a	Primary: Glimepiride treatment was associated with a significant responder rate compared to acarbose, 61 vs 34% respectively (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Glimepiride 1 to 6 mg QD vs acarbose 50 to 200 mg TID	type 2 diabetes uncontrolled on diet alone, with an HbA_{1c} ≥7.8%, and a BMI 24 to 35 kg/m^2		FPG ≤7.8 mmol/L at the final visit) Secondary: Changes in HbA_{1c}, weight, PPG, and C-peptide levels from baseline	Glimepiride resulted in significant decreases in HbA_{1c} (2.5±2.2%) as compared to acarbose (1.8±2.2%; P=0.014). Secondary: FPG levels were significantly decreased with glimepiride as compared to acarbose (2.6±2.6 mmol/L vs 1.4±2.8 mmol/L; P=0.004). There was a greater reduction in HbA_{1c} in the glimepiride group (2.5±2.2%) compared to the acarbose group (1.8±2.2%; P=0.014). Decreased glucose response to breakfast was significant for glimepiride compared to acarbose (P=0.0001). Weight loss was observed in the acarbose group (P=0.001) and glimepiride group (P=0.8) from baseline. C-peptide levels were higher in the glimepiride group compared to the acarbose group at study end point (5.44±2.26 ng/mL vs 4.57±1.93 ng/mL; P=0.0004; intra-individual difference: 0.53±1.7 ng/mL vs –0.31±1.72 ng/mL; P=0.002).
Martin et al.[17] (2003) Glimepiride vs glibenclamide*	MC, OS Drug treatment-naïve patients ≥35 years of age with a confirmed type 2 diabetes diagnosis who with or without dieting received initial dose adjustment with glimepiride or glibenclamide during the study period from April 1998 to March 1999, disease	N=520 1 year ±3 months	Primary: Mean change in body weight and BMI Secondary: Changes in HbA_{1c}, FPG, cholesterol	Primary: Both treatments led to significant reductions in body weight and BMI over the observed treatment period as compared to baseline (P<0.01). Mean weight loss from baseline to end point was greater with glimepiride compared to glibenclamide (-2.04±3.99 vs -0.58±3.65 kg, respectively; P<0.001). The variability of the changes between centers was significant (P<0.001), the differences between the treatment arms in change in body weight from baseline was still significant (P=0.027) if the centers were taken into account as an additional factor. Glimepiride achieved a greater reduction in BMI compared to glibenclamide over the observed period (-0.72±1.38 vs -0.20±1.28 kg/m^2, respectively; P<0.001). Secondary: There were significant decreases from baseline in FPG and HbA_{1c} from baseline for both groups (P<0.001). The mean change from baseline for

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	duration <5 years, BMI ≥27 kg/m^2, patients before or during the study were not taking any antidiabetic medications other than glimepiride or glibenclamide or any other medication known to influence body weight			HbA_{1c} was -1.23±0.09% for glimepiride and -1.26±0.09% for glibenclamide. The mean change from baseline for FPG was -2.43±0.24 mmol/L for glimepiride and -3.03±0.24 mmol/L for glibenclamide. Changes from baseline for TC were significant for both groups (P<0.001). The change was -0.31±0.06 mmol/L for glimepiride and -0.29±0.06 mmol/L for glibenclamide. Change from baseline for HDL-C were 0.07±0.02 mmol/L for glimepiride (P=0.004) and -0.02±0.04 mmol/L for glibenclamide (P=0.924). Change from baseline for LDL-C was -0.21±0.06 mmol/L for glimepiride (P=0.001) and -0.33±0.07 mmol/L for glibenclamide (P<0.001). Change from baseline for TG was -0.03±0.12 mmol/L for glimepiride (P=0.111) and -0.29±0.09 mmol/L for glibenclamide (P<0.001).
Garber et al.[18] (2009) LEAD-3 Liraglutide 1.2 and 1.8 mg SC QD vs glimepiride 8 mg/day	AC, DB, DD, MC, PG, RCT Type 2 diabetic patients 18 to 80 years of age treated previously with diet and exercise or up to half the highest dose of an oral glucose lowering agent monotherapy including sulfonylureas, meglitinides, amino acid derivatives, biguanides, α-glucosidase inhibitors, and TZDs for ≥2 months; and HbA_{1c}	N=746 52 weeks	Primary: Change in baseline HbA_{1c} Secondary: Change in baseline body weight, FPG, eight-point self-measured glucose concentrations, BP, β cell function, fasting glucagon, and patient-reported QOL	Primary: Decreases in HbA_{1c} were -0.84±1.23% with liraglutide 1.2 mg, -1.14±1.24% with liraglutide 1.8 mg, and -0.51±1.20% with glimepiride. Decreases with liraglutide were significantly greater compared to glimepiride. Differences between glimepiride and liraglutide 1.2 mg were -0.62% (95% CI, -0.83 to -0.42; P<0.0001) and liraglutide 1.8 mg were -0.33% (95% CI, -0.53 to -0.13; P=0.0014). Additionally, decreases with liraglutide 1.8 mg were significantly greater compared to liraglutide 1.2 mg (-0.29%; 95% CI, -0.50 to -0.09; P=0.0046). Secondary: Liraglutide-treated patients lost body weight and those receiving glimepiride gained weight (P values not reported). The weight loss with liraglutide after 16 weeks was sustained throughout the 52 weeks. Decreases in FPG with liraglutide (1.2 mg, -0.84 mmol/L; P=0.027 and 1.8 mg, -1.42 mmol/L; P=0.0001) were significantly greater compared to glimepiride (-0.29 mmol/L).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	7.0 to 11.0% (previous diet and exercise) or 7.0 to 10.0% (previous oral glucose lowering agent monotherapy)			Decreases in PPG occurred with all three treatments (liraglutide 1.2 mg vs glimepiride; P=0.1616, liraglutide 1.8 mg vs glimepiride; P=0.0038, and liraglutide 1.8 mg vs liraglutide 1.2 mg; P=0.1319). Decreases in SBP were -0.7 mm Hg with glimepiride compared to -0.1 mm Hg with liraglutide 1.2 mg (P=0.2912) and -3.6 mm Hg with liraglutide 1.8 mg (P<0.0118). Mean DBP decreased but not significantly with any treatment. HOMA-IR and fasting glucagon significantly decreased with liraglutide, but increased with glimepiride. HOMA-IR was decreased by -0.65% with liraglutide 1.2 mg and by -1.35% with liraglutide 1.8 mg, and increased by 0.85% with glimepiride (P=0.0249 and P=0.0011 for liraglutide 1.2 and 1.8 mg vs glimepiride). Patients receiving liraglutide 1.8 mg reported improved QOL scoring for physical and emotional domains compared to glimepiride (P=0.02). Improvements were largely as a result of improvements in weight image and weight concern (P<0.01).
Garber et al.[19] (2011) LEAD-3 Liraglutide 1.2 mg and 1.8 mg SC QD vs glimepiride 8 mg/day	ES (LEAD-3) Type 2 diabetic patients 18 to 80 years of age treated previously with diet and exercise or up to half the highest dose of an oral glucose lowering agent monotherapy including sulfonylureas, meglitinides, amino acid derivatives, biguanides, α-glucosidase inhibitors, and	N=440 52 weeks	Primary: Change in baseline HbA_{1c} Secondary: Change in baseline body weight, FPG, β cell function, fasting glucagon, and BP	Primary: The decrease in HbA_{1c} was significantly greater with liraglutide 1.2 mg (-0.9 vs -0.6%; P=0.0376) and 1.8 mg (-1.1 vs -0.6%; P=0.0016) compared to glimepiride over two years of treatment. Secondary: Over two years, patients receiving liraglutide 1.2 or 1.8 mg experienced weight loss compared to weight gain with patients receiving glimepiride (-2.3 and -2.8 vs 1.0 kg, respectively; P<0.001 for both comparisons). Compared to glimepiride (-1.8 mmol/L), both liraglutide 1.2 (-1.9 mmol/L) and 1.8 mg (-2.6 mmol/L) were significantly more effective at decreasing FPG over the course of the extension period (P=0.0015 and P=0.0001, respectively). In patients who completed two years of treatment, baseline HOMA-IR decreased by -1.1% with liraglutide 1.2 mg and -0.8% with liraglutide 1.8

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	TZDs for ≥2 months; and HbA_{1c} 7.0 to 11.0% (previous diet and exercise) or 7.0 to 10.0% (previous oral glucose lowering agent monotherapy)			mg, and increased by 0.8% with glimepiride (P=0.0451 for liraglutide 1.2 mg vs glimepiride). The proinsulin:insulin ratio increased slightly with all treatments, by 0.108 with liraglutide 1.2 mg, 0.018 with liraglutide 1.8 mg, and 0.141 with glimepiride (P values not reported). After two years, all three treatments had increases in HOMA-B, fasting insulin, and fasting C-peptide; and had decreases in fasting glucagon, but there were no differences between treatments (P values not reported). No differences between treatments in change in pulse, DBP, and SBP were observed in any patient completing two years of treatment.
Bode et al.[20] (2010) LEAD-3 Liraglutide 1.2 and 1.8 mg SC QD vs glimepiride 8 mg/day	Post-hoc analysis (LEAD-3) Type 2 diabetic patients 18 to 80 years of age treated previously with diet and exercise or up to half the highest dose of oral glucose lowering agent monotherapy including sulfonylureas, meglitinides, amino acid derivatives, biguanides, α-glucosidase inhibitors, and TZDs for ≥2 months and HbA_{1c} 7.0 to 11.0% (previous diet and exercise) or 7.0 to 10.0%	N=746 52 weeks	Primary: Impact of treatment on patient-reported perceptions of body image, weight, and weight concern; psychological well-being and distress, cognitive functioning and health Secondary: Not reported	Primary: Both measures of weight perception (weight assessment and weight concern) were more favorable with liraglutide compared to glimepiride. Baseline-adjusted mean weight assessment compared to the reference point "my weight is just right" was significantly more favorable (i.e., shifted from more overweight to less overweight) with liraglutide 1.8 mg (P=0.002). Furthermore, weight concern decreased markedly with liraglutide, with mean scores significantly less compared to glimepiride (liraglutide 1.2 mg; P<0.0001 and liraglutide 1.8 mg; P<0.001). Logistic regression estimates indicated that patients receiving liraglutide 1.8 mg were 52% less likely to report feeling either "somewhat" or "very overweight" vs "just right", "somewhat underweight," or "very overweight" during treatment compared to patients receiving glimepiride (OR, 0.480; 95% CI, 0.331 to 0.696; P value not reported). Also, liraglutide 1.8 mg-treated patients were 39% less likely to report being "somewhat worried", "very worried," or "extremely worried" vs "a little concerned" or "not concerned at all" about their weight during treatment compared to glimepiride treated patients (OR, 0.608; 95% CI, 0.440 to 0.850; P value not reported). There were no differences between liraglutide and glimepiride for the body image scales (body size evaluation and body appearance distress) or for any

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	(previous oral glucose lowering agent monotherapy)			of the cognitive functioning and performance scales during treatment (P values not reported). The health-related QOL composite score significantly improved more favorably with liraglutide 1.8 mg compared to glimepiride (P=0.004). Favorable improvements were seen in the composite scales of mental and emotional healthy, psychological well-being, psychological distress, and general perceived health (P<0.05 for all). The higher scores with liraglutide 1.8 mg for mental and emotional health reflected greater improvement in both domains of psychological well-being and psychological distress compared to glimepiride. There were no differences for these scales between liraglutide 1.2 mg and glimepiride (P values not reported). However, there was a significant difference between liraglutide 1.2 mg and glimepiride in general health status favoring liraglutide (P=0.006). Correlation analyses using data pooled from all treatments confirmed that decreases in BMI were correlated with improvements in both weight assessment and weight concern (P<0.0001 for both), indicating that patients' reports were valid representations of actual weight losses. Decreases in HbA_{1c} corresponded to improvements in general perceived health (P<0.0001), cognitive functioning composite score (P=0.006), and cognitive performance (P=0.004). Correlations of change in HbA_{1c} within treatment groups with change in patient-reported measures were strongest with liraglutide 1.8 mg. Secondary: Not reported
Gottschalk et al.[21] (2007) Glimepiride 1 to 8 mg QD vs	AC, MC, PG, RCT, SB Pediatric subjects 8 to 17 years of age with type 2 diabetes (HbA_{1c} >7.1 and <12.0%) with inadequate control	N=285 24 weeks	Primary: Mean change in HbA_{1c} from baseline to week 24 Secondary: Mean change in HbA_{1c} from	Primary: Significant reductions from baseline HbA_{1c} were seen in both the glimepiride (−0.54%, P=0.001) and metformin (−0.71%, P=0.0002) groups. No significant differences were observed between groups in reductions in HbA_{1c}. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
metformin 500 to 1,000 mg BID	despite treatment with either diet and exercise alone for at least 2 weeks prior to randomization or diet and exercise combined with 3 months of ongoing or previous oral antidiabetic monotherapy		baseline to week 12, proportion of patients achieving an HbA_{1c} <7.0% at week 24, mean change in fasting self monitoring blood glucose from baseline to weeks four, eight, 12, 18, and 24, mean changes in serum lipid concentrations from baseline to week 24 and changes in BMI, safety, adverse events, hypoglycemic episodes and vital signs	Significant reductions in the adjusted mean change from baseline HbA_{1c} to week 12 were –0.69 and –0.76% in patients receiving glimepiride and metformin, respectively (P<0.05). A total of 42.4 and 48.1% of patients in the glimepiride and metformin groups, respectively, achieved HbA_{1c} <7.0% at week 24 (P=0.347). Significant reductions were seen in fasting self monitoring blood glucose levels from baseline to weeks 18 and 24 in patients receiving metformin (P<0.05) but no similar reductions were reported in the glimepiride group. There were no significant differences between the glimepiride and metformin groups in the mean change from baseline in any of the serum lipid concentrations. Significant between-group differences were observed in the mean change from baseline BMI to week 24. Values were 0.26 kg/m^2 and 0.33 kg/m^2 in patients receiving glimepiride and metformin, respectively (P=0.003). No deaths occurred during the study. The proportions of patients experiencing ≥1 adverse event were comparable between both treatment groups, with the most common adverse events being hyperglycemia, upper abdominal pain, diarrhea, nausea and headache. Two patients experienced serious adverse events that were considered possibly related to treatment: one patient in the glimepiride group had hyperglycemia, diabetic ketoacidosis and increased serum osmolarity and one patient in the metformin group had a non-hypoglycemic convulsion. The incidence of clinically relevant hypoglycemia was similar in both groups (P=0.554). No clinically significant differences in vital signs were seen between treatment groups.
Hartley et al.[22] (2015) Glimepiride	DB, MC, NI, RCT Patients ≥65 and ≤85 years of age	N=480 30 weeks	Primary: Change in baseline HbA_{1c}, FPG, and body weight;	Primary: After 30 weeks, the least squares (LS) mean change in HbA_{1c} baseline was −0.32% with sitagliptin and −0.51% with glimepiride, for a between-group difference of 0.19% (95% CI, 0.03 to 0.34). This result met the pre-specified

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs sitagliptin	with type 2 diabetes that was inadequately controlled with diet and exercise alone		incidence of symptomatic hypoglycemia Secondary: Not reported	criterion for declaring non-inferiority. The LS mean change in FPG from baseline was −14.5 mg/dL with sitagliptin and −21.2 mg/dL with glimepiride, for a between-group difference of 6.7 mg/dL (95% CI, 0.7 to 12.7). The percentages of patients with adverse events of symptomatic hypoglycemia were 0.8% in the sitagliptin group and 4.7% in the glimepiride group (between-treatment difference, −3.9 %; P=0.009). The LS mean change in body weight from baseline was 0.4 kg with sitagliptin and 1.1 kg with glimepiride, for a between-group difference of −0.7 kg (P=0.011). Secondary: Not reported
Go et al.[23] (2004) Glipizide XL 5 to 20 mg QD in the morning vs glipizide XL 5 to 20 mg QD in the evening vs glibenclamide* 5 to 20 mg QD in the morning vs placebo	DB, PC, RCT Patients 30 to 80 years of age with a documented diagnosis of type 2 diabetes for ≥6 months prior to the study and who had been treated with diet alone and/or sulfonylureas for at least 2 months	N=42 8 weeks	Primary: Change from baseline in hepatic glucose production Secondary: Changes in fasting and 24 hour glucose and insulin, fructosamine, HbA_{1c}	Primary: Hepatic glucose production in the patients receiving glipizide XL in the morning (P<0.05) or glibenclamide (P<0.01) was significantly reduced at the end of the study compared to baseline. There were no significant differences in hepatic glucose production found when comparing glipizide XL in the morning, glipizide XL in the evening, and glibenclamide. Secondary: Fasting and 24 hour glucose were significantly reduced from baseline to a similar degree by glipizide XL in the morning (33%; P<0.001, 39%; P<0.0001, respectively), glipizide XL in the evening (33%; P<0.0001, 32%; P<0.0001), and glibenclamide (37%; P<0.05, 37%; P<0.0001). Fructosamine and HbA_{1c} were significantly reduced from baseline by glipizide XL in the morning (28%; P<0.001, 22%; P<0.0001, respectively), glipizide XL in the evening (25%; P<0.005, 24%; P<0.005), and glibenclamide (17%; P<0.001, 14%; P<0.05). Each active treatment group improved glycemic control and resulted in beneficial effects on fructosamine and HbA_{1c}.
Birkeland et al.[24] (1994)	DB, PC, PRO, RCT	N=46 15 months	Primary: Changes in HbA_{1c}, PPG, fasting and	Primary: There was a comparable reduction in HbA_{1c} by both active treatments compared to placebo throughout the study. There was a marked initial

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Glipizide vs glyburide vs placebo	Patients with non-insulin-dependent diabetes (type 2) mellitus		postprandial insulin levels Secondary: Not reported	decrease in the glipizide and glyburide groups, but all three groups showed gradually increasing HbA_{1c} levels. Glipizide and glyburide achieved and maintained lower PPG levels and increased fasting and postprandial insulin levels compared to placebo. Secondary: Not reported
Burge et al.[25] (1998) <u>Week 1</u> Placebo <u>Week 2</u> glipizide XL 10 mg every morning vs glyburide 10 mg every morning <u>Week 3</u> glipizide XL 20 mg every morning vs glyburide 20 mg every morning	DB, PC, PRO, RCT Patients 55 to77 years of age with type 2 diabetes treated with oral sulfonylureas alone for ≥2 months	N=58 3 weeks	Primary: Development of hypoglycemia during the final nine hours of the 23-hour fast Secondary: Changes in plasma glucose, C-peptide, glucagon, catecholamine concentrations	Primary: No hypoglycemia occurred during any of the fasting studies. Secondary: Plasma glucose was significantly decreased from baseline when comparing all active treatments to placebo (P<0.001). When the dose of each agent was doubled, an additional decrease of plasma glucose was observed. Plasma glucose parameters did not differ between the two sulfonylureas. Mean and peak C-peptide levels were significantly increased compared to placebo for both treatment groups at the 10 and 20 mg doses. Mean C-peptide concentration were increased in the glyburide group compared to the glipizide XL group during the 20 mg study (P=0.05). Concentrations of glucagon and norepinephrine did not differ according to treatment group or dosage. There were no differences in plasma epinephrine concentrations according to treatment group. Baseline and nadir levels of epinephrine did not differ from placebo with active treatment. Mean and peak levels of epinephrine were significantly increased compared to placebo during both the 10 and 20 mg studies when the treatment groups were combined (P<0.001). There was no difference in epinephrine response between the 10 mg and 20 mg studies.
Chung et al.[26] (2002) Glipizide 10 mg BID	OL, RCT, XO Patients 42 to 71 years of age with type 2 diabetes with	N=25 1 month	Primary: Changes in pharmacokinetic parameters, serum glucose, insulin,	Primary: For each tablet formulation, plasma glipizide concentrations at the start (C_0) and end (C_{24}) of the dosage interval on the fifth day were not significant (P>0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs glipizide XL 20 mg QD	no significant history of hepatic, renal, gastrointestinal, or cardiovascular disease, who were not receiving β-blockers at the time of the study and who had not received insulin for a period of more than 1 week in the 3 months before the study		and C-peptide levels Secondary: Not reported	At two hours after the morning and evening doses of glipizide, plasma glipizide concentrations were two to four times higher with the glipizide XL at the same times. Mean glipizide maximum concentrations after glipizide were significantly higher after glipizide XL (P≤0.05). Relative bioavailability was 100% for glipizide doses and 81±22% for glipizide XL. Glipizide and glipizide XL had similar effects on serum glucose levels, serum insulin levels, and C-peptide levels. Secondary: Not reported
Hseih et al.[27] (2006) Glipizide XR 10 mg daily vs glipizide 5 mg BID	DB, DD, PC, PG, RCT Chinese patients 30 to 70 years of age with type 2 diabetes for ≥6 months and maintenance of stable diet and treatment with a sulfonylurea drug regimen for the previous 3 months	N=57 12 weeks	Primary: Change in fasting plasma glucose Secondary: Change in HbA_{1c}	Primary: In the intent-to-treat analysis, the mean changes in FPG between groups were not significantly different (P value not reported). Secondary: In the intent-to-treat analysis, the mean changes in HbA_{1c} between groups were not significantly different (P value not reported).
Kitabchi et al.[28] (2000) Glipizide daily vs glyburide daily	PRO, RCT Patients with type 2 diabetes who were unresponsive to diet therapy	N=18 15 months	Primary: Changes in FPG, two-hour PPG after a standard breakfast, insulin and glucose response to test meal challenge,	Primary: Similar doses of glipizide (11 mg/day) or glyburide (10 mg/day) resulted in comparable reduction of FPG and HbA_{1c}. Additionally, there was an increase in first phase insulin response to intravenous glucose tolerance testing. The reduction in FPG and two-hour PPG was greater with glipizide compared to glyburide in six months. Results demonstrated that glipizide

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			HbA_{1c}, glucose tolerance Secondary: Not reported	and glyburide are equipotent at similar doses in controlling hyperglycemia in type 2 diabetes. Secondary: Not reported
Hong et al.[29] (SPREAD-DIMCAD) (2013) Metformin 0.75 to 1.5 grams daily vs glipizide 15 to 30 mg daily	DB, MC, PC, RCT Patients 80 years of age or below with coronary artery disease (CAD) and type 2 diabetes	N=304 3 years	Primary: Composite of recurrent cardiovascular events (myocardial infarction [MI], nonfatal stroke, arterial revascularization, death) Secondary: New or worsening angina, new or worsening heart failure, new critical cardiac arrhythmia, and new peripheral vascular events.	Primary: A total of 103 composite primary end points occurred in 91 during the whole study period: 60 events in the glipizide group (14 deaths from any causes [including 11 deaths from cardiovascular events and 3 from sudden death; autopsies were not performed to confirm the 3 patients' precise causes of death], 6 nonfatal myocardial infarctions, 15 nonfatal strokes, and 25 arterial revascularizations), as compared with 43 events in the metformin group (7 deaths from any causes [all were deaths from cardiovascular events], 5 nonfatal myocardial infarctions, 10 nonfatal strokes, and 21 arterial revascularizations). As compared with the patients treated with glipizide, the HR for the composite cardiovascular events for metformin treatment was 0.54 (95% CI 0.30 to 0.90; P=0.026) after adjustment for the duration of diabetes, duration of CAD, age, sex, and smoking history at baseline. No significant difference in the mortality rate between the two groups was found (P=0.55). Secondary: During the study drug administration, the following secondary end points occurred: • new or worsening heart failure: 10 (6.8%) patients in the glipizide group and 9 (5.8%) patients in the metformin group (adjusted HR, 0.82; 95% CI, 0.31 to 2.13; P=0.677) • new critical cardiac arrhythmia: 27 (18.2%) patients in the glipizide group and 30 (19.2%) patients in the metformin group (HR, 1.01; CI, 0.60 to 1.72; P=0.958) • new or worsening angina: 71 (48%) patients in the glipizide group and 77 (49.4%) patients in the metformin group (HR, 1.07; CI, 0.77 to 1.48; P=0.696) • new peripheral vascular events: 6 (4.1%) patients in the glipizide group and 1 (0.6%) patient in the metformin group (HR, 0.13; CI, 0.02 to 1.08; P=0.059) Furthermore, the two groups did not differ significantly with respect to the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				number of patients who reported one or more hypoglycemic attacks during study drug administration.
Scott et al.[30] (2007) Sitagliptin 5 mg BID vs sitagliptin 12.5 mg BID vs sitagliptin 25 mg BID vs sitagliptin 50 mg BID vs glipizide 5 to 20 mg daily vs placebo	AC, DB, PC, RCT Type 2 diabetics 21 to 75 years of age, inadequately controlled (HbA_{1c} 7.9%) with diet and exercise	N=743 12 weeks	Primary: Change in baseline HbA_{1c}, FPG, mean daily glucose, and body weight; adverse effects Secondary: Not reported	Primary: Sitagliptin (-0.38 to -0.77%) significantly decreased HbA_{1c} compared to placebo (P<0.001). Sitagliptin 50 mg achieved the greatest decrease. The placebo subtracted difference in HbA_{1c} of glipizide was -1.00%. Sitagliptin significantly decreased FPG and mean daily glucose compared to placebo (P values not reported). There was no difference between sitagliptin and placebo with changes in body weight. Glipizide resulted in a modest weight gain compared to placebo (no P value reported). The incidence of hypoglycemia was highest with glipizide (17%) compared to placebo (2%) and sitagliptin (0 to 4%, not dose-dependent). Secondary: Not reported
Chan et al.[31] (2008) <u>Phase I</u> Sitagliptin 25 to 50 mg once daily	DB, PC, PG, RCT Patients ≥18 years of age with type 2 diabetes, baseline HbA_{1c} 6.5 to 10.0%,	N=91 54 weeks (Phase I was 12 weeks;	Primary: Safety and tolerability Secondary: Efficacy	Primary: Adverse events were similar among patients receiving sitagliptin and placebo/glipizide, including serious adverse events (30.8 and 38.5%, respectively), drug-related serious adverse events (1.5 and 0.0%, respectively), and adverse events leading to discontinuation.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo <u>Phase II</u> Glipizide 2.5 to 20 mg daily and placebo vs sitagliptin 25 to 50 mg daily and placebo	and renal insufficiency	Phase II was 42 weeks)		Incidences of adverse events by body systems and specific clinical adverse events were also similar between the sitagliptin and placebo/glipizide groups, with the exception of hypoglycemia and anemia. Hypoglycemia occurred in 4.6% of patients receiving sitagliptin and 23.1% of patients receiving placebo/glipizide. Anemia occurred in 3.1% of patients receiving sitagliptin and 15.4% of patients receiving placebo/glipizide. There was a higher incidence of MI (4.6 and 0.0%) and heart failure (7.7 and 3.8%) in the sitagliptin group compared to the placebo/glipizide group, respectively. The number of patients experiencing cardiovascular events per 100 patient-years was similar between groups. There were six deaths (7.7%) in the sitagliptin group and one death (3.8%) in the placebo/glipizide group. This represents an overall mortality rate of 7.3 deaths per 100 patient-years, with 8.8 and 4.0 deaths per 100 patient-years in the sitagliptin and placebo/glipizide groups, respectively. No clinically meaningful differences were observed for laboratory safety measures, including alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, creatine phosphokinase, uric acid, electrolytes, white blood cell count or absolute neutrophil count between groups. At week 54, the mean change from baseline in serum creatinine for patients with moderate renal insufficiency was -0.02 and 0.69 mg/dL in the sitagliptin and placebo/glipizide groups, respectively. At week 54, small (2 mm Hg) mean decreases in systolic, diastolic and mean arterial BPs were observed for patients on sitagliptin compared to those on placebo/glipizide. At week 54, there was a small mean decrease in body weight from baseline in the sitagliptin group (-0.9 kg) compared with no mean change in the placebo/glipizide group (0.0 kg). Secondary: At week 12, the mean change from baseline in HbA_{1c} was -0.6% (95% CI,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				-0.8 to -0.4) in the sitagliptin group compared with -0.2% (95% CI, -0.4 to 0.1) in the placebo group At week 12, the mean change from baseline in FPG was -25.5 mg/dL (95% CI, -38.2 to -12.8) with sitagliptin and -3.0 mg/dL (95% CI, -15.7 to 9.6) with placebo. At week 54, the mean and least squares mean change from baseline in HbA_{1c} with sitagliptin was -0.7% in the prespecified analysis and in the ANCOVA analysis. The mean and least squares mean changes from baseline were -1.0 and -0.8%, respectively in the placebo/glipizide group. Between-group testing for efficacy was not performed at the week 54 time point. At week 54, the mean percent changes in lipids were as follows for sitagliptin: TC (+4.3%; 95% CI, -1.5 to 10.1), LDL-C (+11.9%; 95% CI, 1.6 to 22.2), and non-HDL-C (+7.1%; -1.2 to 15.3), TG (-0.7%; 95% CI, -13 to 11.5), and HDL-C (+0.9%; 95% CI, -5.9 to 7.7). The mean percent changes in lipids in the placebo/glipizide group were as follows: TC (-0.2%; 95% CI, -10.5 to 10), LDL-C (3.3%; 95% CI, -8.6 to 15.2), non-HDL-C (-1.6%; 95% CI, -13.7 to 10.5), TG (+0.9%; 95% CI, -27.5 to 29.3), and HDL-C (+6.6%; 95% CI, -5 to 18.2).
Sami et al.[32] (1996) Glyburide 20 mg daily in two divided doses vs glipizide 40 mg daily in two divided doses	RCT Patients 43 to 73 years of age with non-insulin-dependent (type 2) diabetes mellitus for 5 to 15 years who manifested secondary failure to a first generation sulfonylurea (19 patients on chlorpropamide and 36 patients on	N=55 6 months	Primary: Changes in body weight, FPG, HbA_{1c}, serum lipid profiles Secondary: Not reported	Primary: Body weight, FPG, HbA_{1c} levels, and lipid profiles were not significantly changed following the change over from the first generation agents (chlorpropamide and tolazamide) to second generation agents (glyburide and glipizide) in all patients, irrespective of the specific first and second generation agents given. Additionally, these values were not significantly changed when the patients were divided into two groups according to the second generation agent used. There were no significant changes ($P<0.5$) in the levels of FBG and HbA_{1c} in the patients following the change over to glipizide. FPG was 211±34 mg/L and HbA_{1c} was 11.7±1.8% compared to 209±31 mg/L and 12.3±2.1% respectively, obtained following treatment with the first generation agents (chlorpropamide and tolazamide).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	tolazamide) while attending a diabetes clinic were randomly changed, at the discretion of the caring physician at the clinic			There were no significant changes (P>0.5) observed in the patients changed over to glyburide. FPG was 184±20 mg/dL and HbA_{1c} was 11.0±1.4% following the change over from the first generation agents (chlorpropamide and tolazamide). Prior to the change over, FPG was 180±16 mg/dL and HbA_{1c} was 11.2±1.6%. Lipid concentrations were not significantly changed in either groups following the change over to glyburide or glipizide when compared to prior treatment with the first generation agents. There were no significant changes in the metabolic values when the glyburide and glipizide groups were further subdivided according to the specific first generation agent used. Secondary: Not reported
Hollander et al.[33] (2003) Nateglinide 120 mg TID before each meal vs glyburide 5 to 10 mg QD vs placebo	DB, MC, PC, RCT Patients 32 to 75 years of age with type 2 diabetes ≥3 months prior to entry into the trial on diet modification alone for ≥4 weeks before initial visit, mean HbA_{1c} 6.8 to 11.0%, and a BMI 20 to 35 kg/m^2	N=152 8 weeks	Primary: Change from week 0 to week eight during liquid meal challenges in FPG, fasting insulin, fasting C-peptide, and fasting proinsulin Secondary: Not reported	Primary: At week eight, FPG was reduced more with glyburide compared to nateglinide (-1.9 mmol/L; P<0.001). Nateglinide treatment did not have significant changes from baseline with fasting levels of C-peptide, insulin, or proinsulin. Glyburide treatment increased fasting C-peptide vs placebo and nateglinide (P<0.001), fasting insulin vs placebo (P<0.001) and nateglinide (P<0.05), and proinsulin vs placebo (P<0.001) and nateglinide (P<0.025). Reduction of mealtime glucose excursions from nateglinide was approximately twice that from glyburide (-4.94±0.74 vs -2.71±0.71 mmol/hr/L; P<0.03). The insulin secretion reflected by the C-peptide AUCs was approximately twice that in the glyburide group than in the nateglinide group (1.83±0.24 vs 0.95±0.23 nmol/hr/L, respectively; P=0.063 vs nateglinide). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Not reported
Kahn et al.[34] (2006) Glyburide 2.5 to 7.5 mg BID vs metformin 500 to 1,000 mg BID vs rosiglitazone 4 mg QD to 4 mg BID	DB, MC, RCT Recently diagnosed (within 3 years) type 2 diabetic patients between the ages of 30 to 75 years who had not received previous pharmacologic treatment, with FPG levels ranging from 126 to 180 mg/dL while their only treatment was lifestyle management	N=4,360 4 to 6 years (median treatment durations 3.3 years for glyburide and 4 years for rosiglitazone and metformin)	Primary: Time from randomization to treatment failure (defined as FPG >180 mg/dL on consecutive testing after at least six weeks of treatment at the maximum tolerated dose) Secondary: Time from randomization to a confirmed FPG >140 mg/dL after at least six weeks of treatment at the maximum tolerated dose (for patients who entered the study with FPG ≤140 mg/dL); also FPG, HbA_{1c}, weight, measures of insulin sensitivity, β-cell function, and adverse events	Primary: At five years, 15% of patients receiving rosiglitazone, 21% of those on metformin, and 34% of those on glyburide had failed monotherapy. This represents a risk reduction of 32% for rosiglitazone as compared with metformin and 63% for rosiglitazone as compared with glyburide (P<0.001 for both comparisons). Secondary: Progression to a confirmed FPG ≥140 mg/dL was seen in 79 of 511 patients in the rosiglitazone group as compared with 127 of 520 patients in the metformin group (P=0.002) and 160 of 480 patients in the glyburide group (P<0.001). At the 4-year evaluation, 40% of the patients in the rosiglitazone group achieved an HbA_{1c} <7.0% compared with 36% of the patients in the metformin group (P=0.03) and 26% of the patients in the glyburide group (P<0.001). The annual rate of β-cell function decline after 6 months was greatest in the glyburide group (6.1% decreased), followed by the metformin group (3.1% decreased) and rosiglitazone group (2.0% decreased) (P<0.001 for rosiglitazone vs glyburide and P=0.02 for rosiglitazone vs metformin). Over a period of five years, the mean weight increased in the rosiglitazone group but decreased in the metformin group. In the glyburide group, weight gain occurred in the first year then remained stable. Treatment with glyburide group was associated with lower risk of cardiovascular events (including congestive heart failure) than was seen in the rosiglitazone and metformin groups (P<0.05). Rosiglitazone was associated with more weight gain and edema than either metformin or glyburide, but fewer gastrointestinal events were reported with rosiglitazone compared to metformin and fewer hypoglycemic events were seen with rosiglitazone compared to with glyburide (P<0.001 for all comparisons).
Giles et al.[35] (2008)	DB, MC, RCT	N=518	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Glyburide 10 to 15 mg daily vs pioglitazone 30 to 45 mg QD Insulin was the only rescue medication allowed.	Patients ≥18 years of age with type 2 diabetes, HbA_{1c} ≥7.0%, BMI ≤48 kg/m^2, NYHA functional Class II/III heart failure, left ventricular systolic dysfunction (≤40%), and receiving sulfonylurea therapy (+/- insulin) for ≥30 days before screening or discontinued metformin therapy within 30 days of screening	6 months	Heart failure progression (defined as the composite of cardiovascular mortality and hospitalization or emergency room visit for heart failure) and metabolic parameters. Secondary: Not reported	Pioglitazone was associated with a higher incidence rate of the composite end point compared with glyburide (13.4 vs 8.2%, respectively; P=0.024). Death from cardiovascular cause was similar between the treatment groups (1.9 and 2.3% for pioglitazone and glyburide, respectively). Overnight hospitalization for heart failure was higher in the pioglitazone group (9.9%) compared to glyburide group (4.7%). Emergency room visits for heart failure occurred in 1.5% of pioglitazone patients compared to 1.2% of glyburide patients. Echocardiographic data demonstrated preserved cardiac function with similar changes in the left ventricular mass index (P=0.959) and left ventricular ejection fraction (P=0.413) among the treatment groups. Cardiac index was significantly increased with pioglitazone compared with glyburide (P=0.012). FPG was significantly decreased with glyburide relative to pioglitazone during the first 4 weeks of treatment. By week 16, a significant difference in mean FPG was observed favoring pioglitazone. At week 24, pioglitazone decreased the HbA_{1c} by -0.98% compared to -0.73% with glyburide (P=0.007). At week 24, significant differences were seen between pioglitazone and glyburide in TGs (-36.8 vs +7.6 mg/dL, respectively; P<0.001), HDL-C (+4.8 vs -0.8 mg/dL, respectively; P<.001), and LDL-C (+6.9 vs -2.4 mg/dL, respectively; P<0.016). Rates of adverse events and serious adverse events were similar between treatment groups. Hypoglycemia was more common with glyburide and edema was more common with pioglitazone. Weight gain was reported as an adverse event more frequently with pioglitazone than glyburide. (6.1 vs 2.7%, respectively). Mean weight gain was greater (2.10 vs 1.23 kg, respectively; P=0.012) with pioglitazone than with glyburide. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Not reported
Johnston el al.[36] (1998) Glyburide 1.25 to 20 mg QD vs miglitol 25 to 50 mg TID vs placebo	DB, MC, PC, PG, RCT Patients ≥60 years of age with type 2 diabetes treated with diet alone for ≥12 weeks, HbA_{1c} 6.5 to 10.0%, and FPG >140 mg/dL	N=411 1 year	Primary: Change in baseline HbA_{1c} Secondary: Change in baseline plasma glucose, serum insulin, and TG	Primary: Mean placebo-subtracted HbA_{1c} reduction from baseline was -0.50% with miglitol 25 mg TID (P<0.05 vs glyburide), -0.41% with miglitol 50 mg TID (P<0.05 vs glyburide), -0.93% for glyburide QD, and -0.01% for placebo (P<0.05 vs all active treatments). Secondary: Changes in mean plasma glucose (AUC) were +716 mg·min/dL with placebo (P<0.05 vs all active treatments), -3,361 mg·min/dL with miglitol 25 mg TID, -5,462 mg·min/dL with miglitol 50 mg TID, and -3,615 mg·min/dL with glyburide (P=0.0001 for miglitol 50 mg TID vs placebo). Postprandial insulin levels were significantly greater with glyburide compared to placebo and miglitol (P<0.01). Mean changes from baseline to end point for fasting TG were 1.01 with placebo and miglitol 25 mg TID, 0.98 with miglitol 50 mg TID, and one with glyburide (P=0.573 for miglitol 50 mg vs placebo). Mean changes from baseline to end point for TG (AUC) were 1.01 with placebo, 1.03 with miglitol 25 mg TID, 1.00 with miglitol 50 mg TID, and 1.06 with glyburide (P=0.8559 miglitol 50 mg TID vs placebo). Hypoglycemia, weight gain, and routine and serious cardiovascular events were more frequent in the glyburide group (P<0.05 vs placebo and miglitol).
van de Laar et al.[37] (2004) Tolbutamide titrated 2,000 mg daily in 3 divided doses vs acarbose titrated to 100 mg TID	DB, RCT Newly diagnosed patients with type 2 diabetes 40 to 70 years of age and a FPG level 6.7 to 20 mmol/L after an 8-week dietary treatment period	N=96 30 weeks	Primary: Change in HbA_{1c} from baseline Secondary: Change in fasting and post-load blood glucose and insulin levels, plasma lipids, and tolerability	Primary: Both treatment groups showed a decrease in HbA_{1c}. The HbA_{1c} change from baseline for the acarbose group was –1.1 vs -1.8% for the tolbutamide group. The difference between the groups was 0.6% in favor of tolbutamide (90% CI, 0.3 to 0.9 and 95% CI, 0.2 to 1.0). Secondary: Difference in mean decrease of FPG was 1.0 mmol/L in favor of tolbutamide (95% CI, 0.3 to 1.7).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				No significant differences were seen in post-load blood glucose, fasting and post-load insulin levels, or lipids. Significantly more patients in the acarbose group (15 vs 3) discontinued therapy because of adverse effects, mostly gastrointestinal.
Sullivan et al.[38] (2011) FIELD Metformin vs sulfonylurea vs diet alone	PRO Patients with type 2 diabetes	N=6,005 5 years	Primary: Cardiovascular disease outcomes Secondary: Hypoglycemic therapy	Primary: Patients receiving monotherapy with either metformin or a sulfonylurea appeared to be at greater risk of cardiovascular disease compared to those on diet alone, but results were only significant for the sulfonylurea group, ranging from 42% higher risk of coronary revascularization to a doubled risk of coronary heart disease death. However, adjustment for the duration and intensity of diabetes and the severity of other cardiovascular risk factors abolished the significance of this effect. Total revascularization and total mortality were significantly higher in the sulfonylurea group compared to the metformin group, but all differences became non-significant on adjustment. Secondary: Use of oral hypoglycemic agents increased progressively as the trial proceeded. Over five years, treatment with diet alone decreased from 31 to 15%, and dual therapy with metformin plus a sulfonylurea increased from 29 to 36%. Insulin therapy was introduced at a rate of 4% per year. Metformin monotherapy declined from 21 to 18% but the sulfonylurea monotherapy rate declined from 20 to 12%. Patients on sulfonylurea monotherapy were more likely to progress to dual therapy.
Simpson et al.[39] (2006) First-generation sulfonylurea vs glyburide vs	RETRO New users of one oral diabetic agent	N=5,95 ~4.6 years	Primary: Mortality Secondary: Not reported	Primary: An increased risk of death was associated with higher daily doses of first-generation sulfonylureas (adjusted HR, 2.1; 95% CI, 1.0 to 4.7) and glyburide (HR, 1.3; 95% CI, 1.2 to 1.4) compared to metformin (HR, 0.8; 95% CI, 0.7 to 1.1). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
metformin				
Nichols et al.[40] (2007) Metformin vs sulfonylurea vs insulin vs TZDs	MC, OS, RETRO Patients who initiated metformin, sulfonylurea, insulin or TZDs between 1996 and 2002 and continued use of that drug for at least 12 months without adding other therapies	N=9,546 ≥12 months	Primary: Weight changes Secondary: Not reported	Primary: Patients treated with metformin lost an average of 2.4 kg, sulfonylurea-treated patients gained 1.8 kg, insulin-treated patients gained 3.3 kg, and thiazolidinedione-treated patients gained 5.0 kg. All comparisons with metformin were statistically significant. Secondary: Not reported
Gangji et al.[41] (2001) Glyburide vs sulfonylureas, meglitinides, insulin	MA (21 trials) Patients with type 2 diabetes	N=not reported Duration varied	Primary: Hypoglycemia, glycemic control, cardiovascular events, body weight, death Secondary: Not reported	Primary: Glyburide was associated with a 52% higher risk of experiencing at least one episode of hypoglycemia compared to other secretagogues (RR, 1.52; 95% CI, 1.21 to 1.92) and with an 83% higher risk compared to other sulfonylureas (RR, 1.83; 95% CI, 1.35 to 2.49). Glyburide was not associated with a higher risk of cardiovascular events (RR, 0.84; 95% CI, 0.56 to 1.26), death (RR, 0.87; 95% CI, 0.70 to 1.07), or end-of-trial weight (95% CI, -0.4 to 3.80) compared to other secretagogues. Secondary: Not reported
Bolen et al.[42] (2007) Biguanides vs meglitinides	MA (Analysis of 216 controlled trials and cohort studies, and 2 SRs) Patients with type 2 diabetes	N=136 (articles on intermediate outcomes) N=167 (articles on	Primary: Intermediate outcomes: HbA_{1c}, body weight, BP, lipid panels, all-cause mortality, cardiovascular morbidity and	Primary: Results from clinical trials showed that most oral agents including TZDs, metformin, and repaglinide improved glycemic control to the same degree as sulfonylureas (absolute decrease in HbA_{1c} level of about 1%). Nateglinide and α-glucosidase inhibitors have slightly weaker effects, on the basis of indirect comparisons of placebo-controlled trials.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs TZDs vs α-glucosidase inhibitors vs second-generation sulfonylureas		adverse events) N=68 (articles on micro-vascular outcomes and mortality) Duration varied	mortality, microvascular outcomes Secondary: Adverse events: hypoglycemia, gastrointestinal problems, congestive heart failure, edema or hypervolemia, lactic acidosis, elevated liver enzymes, allergic reactions requiring hospitalization, other serious adverse events	TZDs were the only class with beneficial effect on HDL-C (mean relative increase, 3 to 5 mg/dL) but a harmful effect on LDL-C (mean relative increase, 10 mg/dL) compared to other oral agents. Metformin decreased LDL-C levels by about 10 mg/dL, whereas other oral agents had no effects on LDL-C. TZDs, second-generation sulfonylureas, and metformin had similarly minimal effects on SBP. Most agents except metformin increased body weight by 1 to 5 kg. In the ADOPT (A Diabetes Outcome Progression Trial), the incidence of cardiovascular events was lower with glyburide compared to rosiglitazone or metformin (1.8, 3.4, and 3.2%, respectively; P<0.05). In the RECORD study (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of glycemia in Diabetes), rosiglitazone plus metformin or a sulfonylurea compared to metformin plus a sulfonylurea had a HR of 1.08 (95% CI, 0.89 to 1.31) for the primary end point of hospitalization or death from cardiovascular disease. The HR was driven by more congestive heart failure in the rosiglitazone plus metformin group compared to the control group of metformin plus sulfonylurea (absolute risk, 1.7 vs 0.8%, respectively). Too few comparisons were made to draw firm comparative conclusions on microvascular outcomes. Secondary: According to several RCTs and some OS trials, sulfonylureas and repaglinide were associated with greater risk for hypoglycemia. In many RCTs, TZDs were associated with a higher risk for edema than sulfonylureas or metformin (absolute risk difference, 2 to 21%). In cohort studies, TZDs were associated with higher risk for congestive heart failure although absolute risks were small (1 to 3%) and higher risk for mild anemia yet produced similarly low rates of elevated aminotransferase levels (<1%) compared to sulfonylureas and metformin.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				In many trials and a few OS trials, metformin was associated with greater risk for gastrointestinal problems compared to other oral diabetes agents. According to a SR of 176 comparative trials, lactic acidosis events were similar between metformin and other oral diabetes agents.
Monami et al.[43] (2008) Metformin vs sulfonylureas, α-glucosidase inhibitors, TZDs, glinides, GLP-1 agonists	MA Patients with type 2 diabetes mellitus	N=7,890 (27 RCT) Variable duration	Primary: Reduction in HbA_{1c} at 16 to 36 months Secondary: Not reported	Primary: Combining the results of different placebo-controlled trials, sulfonylurea, α-glucosidase inhibitors, and TZDs led to a reduction in HbA_{1c} by -0.85% (95% CI, 0.78 to 0.94], -0.61% (95% CI, 0.55 to 0.67), and -0.42% (95% CI, 0.40 to 0.44), respectively when combined with metformin. In direct comparisons, sulfonylureas led to a greater reduction in HbA_{1c} (0.17%; 95% CI, 0.16 to 0.18; P<0.05) than TZDs. Differences between sulfonylureas and α-glucosidase inhibitors, and between α-glucosidase inhibitors and TZDs, were not statistically significant. Secondary: Not reported
Saenz et al.[44] (2005) Metformin monotherapy vs placebo, sulfonylureas, TZDs, meglitinides, α-glucosidase inhibitors, diet, any other oral antidiabetic intervention, insulin	MA (29 RCTs) Adult patients with type 2 diabetes	N=5,259 ≥3 months	Primary: Incidence of any diabetes-related outcomes (sudden death, death from hyperglycemia or hypoglycemia, fatal or nonfatal MI, angina, heart failure, stroke, renal failure, amputation [of at least one digit], vitreous hemorrhage, retinopathy requiring photo-coagulation,	Primary: Obese patients receiving metformin showed a greater benefit than chlorpropamide, glibenclamide*, or insulin for any diabetes-related outcomes (P=0.009) and for all-cause mortality (P=0.03). Obese patients receiving metformin showed a greater benefit than overweight patients on conventional treatment (diet) for any diabetes-related outcomes (P=0.004), diabetes-related death (P=0.03), all cause mortality (P=0.01), and MI (P=0.02). Secondary: Patients receiving metformin monotherapy showed a significant benefit for glycemic control, weight, dyslipidemia, and DBP. Metformin presents a strong benefit for HbA_{1c} when compared to diet and placebo. Additionally, metformin showed a moderate benefit for glycemic control, LDL-C, and BMI or weight when compared to sulfonylureas.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			blindness in one eye, or cataract extraction); diabetes-related death (death from MI, stroke, peripheral vascular disease, renal disease, hypo-glycemia or hyperglycemia, and sudden death); all-cause mortality Secondary: Changes in HbA_{1c}, FPG, QOL, weight, BMI, lipids, insulin, C-peptide, BP, micro-albuminuria, glomerular filtration rate, renal plasma flow	
Shyangdan et al.[45] (2011) GLP-1 receptor agonist based therapies (albiglutide*, exenatide ER, liraglutide, lixisenatide*, semaglutide*, and taspoglutide*)	MA (RCTs) Type 2 diabetics ≥18 years of age	N=not reported 8 to 26 weeks	Primary: Change in baseline HbA_{1c}, incidence of hypoglycemia, weight change Secondary: Health-related QOL, safety, mortality, morbidity, BP, FPG, PPG, lipid	Primary: Change in baseline HbA_{1c} Exenatide ER significantly decreased HbA_{1c} compared to TZDs (-1.5 vs -1.2%; P=0.02), DPP-4 inhibitors (-1.5 vs -0.9%; P<0.0001), and insulin glargine (-1.5 vs -1.3%; treatment difference, -0.2%; 95% CI, -0.35 to -0.05; P=0.03). There was no difference in the proportion of patients achieving an HbA_{1c} <7.0% between exenatide ER and TZDs (60 vs 52%; P=0.15). A significantly greater proportion of patients receiving exenatide ER achieved an HbA_{1c} <7.0% compared to patients receiving DPP-4 inhibitors (60 vs 35%; P<0.0001) and patients receiving insulin glargine (60 vs 48%; P=0.03).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs non-GLP-1 receptor based therapies (placebo, TZDs, DPP-4 inhibitors, insulin glargine, and sulfonylureas)			profile, β cell function	Compared to placebo, treatment with liraglutide 1.2 mg significantly decreased HbA_{1c} (-1.15%; 95% CI, -1.33 to -0.96; P<0.00001). Patients receiving liraglutide 1.2 mg were more likely to achieve an HbA_{1c} <7.0% compared to patients receiving placebo (OR, 2.91; 95% CI, 1.74 to 4.87; P<0.05). Liraglutide 1.2 mg decreased HbA_{1c} to a greater extent compared to TZDs (-0.64%; 95% CI -0.83 to -0.45; P value not reported). The likelihood of achieving an HbA_{1c} <7.0% was greater with liraglutide 1.2 mg compared to TZDs (OR, 1.60; 95% CI, 1.18 to 2.15; P value not reported). Liraglutide 1.2 mg decreased HbA_{1c} to a greater extent compared to DPP-4 inhibitors (-0.34%; 95% CI, -0.53 to -0.15; P value not reported). The likelihood of achieving an HbA_{1c} <7.0% was greater with liraglutide 1.2 mg compared to DPP-4 inhibitors (OR, 2.56; 95% CI, 1.94 to 3.37; P value not reported). Liraglutide 1.2 mg was not associated with a decrease in HbA_{1c} compared to sulfonylureas (-0.01%; 95% CI -0.27 to 0.29; P value not reported). The likelihood of achieving an HbA_{1c} <7.0% was not greater with liraglutide 1.2 mg compared to sulfonylureas (OR, 0.98; 95% CI, 0.84 to 1.14; P=0.78). Compared to placebo, liraglutide 1.8 mg significantly decreased an HbA_{1c} (-1.15%; 95% CI, -1.31 to -0.99; P<0.05). Patients receiving liraglutide 1.8 mg were more likely to achieve HbA_{1c} <7.0% compared to patients receiving placebo (OR, 3.25; 95% CI, 1.97 to 5.36; P<0.05). Liraglutide 1.8 mg decreased HbA_{1c} to a greater extent compared to TZDs (-0.69%; 95% CI -0.88 to -0.50%; P value not reported). The likelihood of achieving an HbA_{1c} <7.0% was greater with liraglutide 1.8 mg compared to TZDs (OR, 1.91; 95% CI, 1.43 to 2.53; P value not reported). Liraglutide 1.8 mg decreased HbA_{1c} to a greater extent compared to DPP-4 inhibitors (-0.60%; 95% CI -0.78 to -0.42; P value not reported). The likelihood of achieving HbA_{1c} <7.0% was greater with liraglutide 1.8 compared to DPP-4 inhibitors (OR, 1.99; 95% CI, 1.48 to 2.66; P value not reported). Liraglutide 1.8 mg was not associated with a reduction in HbA_{1c} compared to sulfonylureas (-0.02%; 95% CI -0.30 to 0.26; P value not reported). The likelihood of achieving an HbA_{1c} <7.0% was not greater with liraglutide 1.8 mg compared to sulfonylureas (OR, 1.09; 95% CI, 0.94 to 1.26; P=0.27). Liraglutide decreased HbA_{1c} to a greater extent compared to insulin glargine (-0.24%; 95% CI, -0.49 to 0.01; P value not reported). The likelihood of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				achieving an HbA_{1c} <7.0% was not different between insulin glargine and liraglutide (OR, 1.16; 95% CI, 0.96 to 1.40; P value not reported). Liraglutide 1.2 mg was associated with a non-significant increase in HbA_{1c} compared to 1.8 mg (0.10%; 95% CI, -0.03 to 0.23; P=0.13). Patients receiving liraglutide 1.2 mg were not more likely to achieve an HbA_{1c} <7.0% compared to the 1.8 mg dose (P=0.92). Incidence of hypoglycemia The incidence of minor hypoglycemia was similar between exenatide ER and TZDs. The incidence of minor hypoglycemia was higher with DPP-4 inhibitors (five vs two patients) and insulin glargine (26 vs 8%) compared to exenatide ER. The incidence of major hypoglycemia was higher with insulin glargine compared to exenatide ER (two vs one patients). Overall, there was no difference in the incidence of minor hypoglycemia between liraglutide 1.2 mg and placebo (P=0.42), and there was significantly more hypoglycemia with liraglutide 1.8 mg (OR, 1.66; 95% CI, 1.15 to 2.40; P=0.007). The incidence of minor hypoglycemia was higher with insulin glargine compared to liraglutide (29 vs 27%). Liraglutide was associated with a significantly higher rate of minor hypoglycemia compared to TZDs (P=0.048), and similar rates compared to DPP-4 inhibitors (P values not reported). Liraglutide was associated with a significantly lower incidence of hypoglycemia compared to sulfonylureas (P<0.00001). Weight loss Exenatide ER significantly decreased weight compared to TZDs (-2.3 vs 2.8 kg; P<0.00001), DPP-4 inhibitors (-2.3 vs -0.8 kg; P=0.0009), and insulin glargine (-2.6 vs 1.4 kg; P<0.00001). Patients receiving liraglutide 1.2 mg experienced an average weight loss of -0.75 kg (95% CI, -1.95 to 0.45; P=0.22). Liraglutide 1.2 mg was associated with a greater decrease in weight compared to insulin glargine (-3.40 kg; 95% CI, -4.31 to -2.49; P value not reported), TZDs (-3.40 kg; 95% CI, -4.31 to -2.49; P value not reported), DPP-4 inhibitors (-1.90 kg; 95% CI, -2.65 to -1.15; P value not reported), and sulfonylureas (-3.60 kg; 95% CI, -4.15 to -3.05; P value not reported).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Patients receiving liraglutide 1.8 mg experienced a significant weight loss compared to placebo (-1.33 kg; 95% CI, -2.38 to 0.27; P=0.0014). Liraglutide 1.8 mg was associated with a greater decrease in weight compared to TZDs (-2.30 kg; 95% CI, -2.85 to -1.75; P value not reported), DPP-4 inhibitors (-2.42 kg; 95% CI, -3.17 to -1.67; P value not reported), and sulfonylureas (-3.80 kg; 95% CI, -4.35 to -3.25; P value not reported). Patients were more likely to experience weight gain with liraglutide 1.2 compared to 1.8 mg (0.48 kg; 95% CI, 0.16 to 0.80; P value not reported). Secondary: Data on mortality and morbidity were not reported for any treatment. QOL Exenatide ER significantly improved weight-related QOL and IWQOL total scores compared to TZDs (IWQOL treatment difference, 3.94; 95% CI, 1.28 to 6.61; P=0.0038). Both exenatide ER (IWQOL total score, 5.15; 95% CI, 3.11 to 7.19) and DPP-4 inhibitors (4.56; 95% CI, 2.56 to 6.57) resulted in significant improvements in weight-related QOL and IWQOL total scores. Treatment satisfaction was significantly greater with exenatide ER compared to DPP-4 inhibitors (treatment difference, 1.61; 95% CI, 0.07 to 3.16; P=0.0406). Exenatide ER significantly improved the self-esteem IWQOL domain and one EQ-5D dimensions compared to insulin glargine. Data for liraglutide were not reported. Safety Withdrawals due to adverse events were greater with exenatide ER compared to TZDs (6.9 vs 3.6%), DPP-4 inhibitors (6.9 vs 3.0%), and insulin glargine (4.7 vs 0.9%). More serious adverse events occurred with TZDs (6 vs 3%) compared to exenatide ER. The incidence of serious adverse events was similar between exenatide ER and DPP-4 inhibitors (3 vs 3%) and insulin glargine (5 vs 4%). Compared to placebo, withdrawals due to adverse events were between 5 and 10% with liraglutide 1.2 mg and between 4 and 15% with liraglutide 1.8

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				mg. Withdrawals were also higher with liraglutide compared to sulfonylureas (9.4 to 12.9 vs 1.3 to 3.0%). Liraglutide was associated with more gastrointestinal adverse events (nausea, vomiting, and diarrhea) compared to insulin glargine, TZDs, DPP-4 inhibitors, and sulfonylureas. BP There was no difference in the decreases in SBP and DBP between exenatide ER and TZDs. Exenatide ER significantly decreased SBP compared to DPP-4 inhibitors (treatment difference, -4 mm Hg; 95% CI, -6 to -1; P=0.0055). There was no difference in the decrease in DBP between treatments. Data comparing exenatide ER and insulin glargine were not reported. Liraglutide 1.2 mg did not significantly decrease SBP (P=0.15) compared to placebo (P=0.15) and DPP-4 inhibitors (P=0.76). Liraglutide 1.8 mg significantly decreased SBP (P=0.05) compared to placebo, but not DPP-4 inhibitors (P=0.86). Liraglutide also significantly decreased SBP compared to insulin glargine (P=0.0001) and sulfonylureas (P value not reported). No difference in SBP was observed between liraglutide and DPP-4 inhibitors. There was no difference between liraglutide in the decrease in DBP compared to placebo, insulin glargine, or sulfonylureas. DPP-4 inhibitors significantly decreased DBP compared to liraglutide 1.8 mg (P value not reported). Data comparing liraglutide and TZDs were not reported. FPG There was no difference in the decrease in FPG between exenatide ER and TZDs (-1.8 vs -1.5 mmol/L; P=0.33). Exenatide ER significantly decreased FPG compared to DPP-4 inhibitors (-0.90 mmol/L; 95% CI, -1.50 to -0.30; P=0.0038), and insulin glargine significantly decreased FPG compared to exenatide ER (-0.70 mmol/L; 95% CI, 0.14 to 1.26; P=0.01). Liraglutide significantly decreased FPG compared to placebo (1.2 mg; P<0.0001 and 1.8 mg; P<0.00001), TZDs (P≤0.006), and DPP-4 inhibitors (P<0.00001). There was no difference between liraglutide and insulin glargine or sulfonylureas in decreases in FPG (P value not reported). PPG

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				There was no difference in the decrease in PPG between exenatide ER and TZDs. Exenatide ER significantly decreased PPG at all measurements on a six-point self-monitored glucose concentrations profile compared to DPP-4 inhibitors (P<0.05). Both exenatide ER and insulin glargine decreased PPG at all eight time points, with significant difference in favor of exenatide ER after dinner (P=0.004) and insulin glargine at 03000 hour (P=0.022) and before breakfast (P<0.0001). Liraglutide significantly decreased PPG compared to placebo (P value not reported), TZDs (P<0.05), and sulfonylureas (liraglutide 1.8 mg; P<0.0001). There was no difference between liraglutide and insulin glargine in decreases in PPG (P value not reported). It was reported that PPG recorded in trials comparing liraglutide and DPP-4 inhibitors was highly variable. Lipid profile TZDs significantly decreased TG compared to exenatide ER. Exenatide ER decreased TC and LDL-C, while TZDs and DPP-4 inhibitors increased these measures. All treatments increased HDL-C. Data comparing exenatide ER and insulin glargine were not reported. Compared to placebo, liraglutide 1.2 decreased TG (P<0.05) and LDL-C (P<0.05), and no difference was observed with liraglutide 1.8 mg. Data comparing liraglutide to insulin glargine, TZDs, DPP-4 inhibitors, and sulfonylureas were not reported. β cell function Data for exenatide ER are not reported. Liraglutide significantly improved HOMA-B compared to placebo (P value not reported), TZDs (P<0.05), and DPP-4 inhibitors (P value not reported); and proinsulin:insulin ratio compared to placebo (P value not reported), insulin glargine (P=0.0019), and TZDs (P≤0.02). There was no difference between liraglutide and sulfonylureas in the improvements in HOMA-B and proinsulin:insulin ratio.
Frederich et al.[46] (2010) Saxagliptin 2.5 to 10 mg QD	SR (RCTs) Inadequately controlled type 2 diabetics	N=4,607 16 to 116 weeks	Primary: Composite of cardiovascular events, cardiovascular	Primary: There were 38 (1.1%) cardiovascular events with saxagliptin compared to 23 (1.8%) with the comparator drugs (RR, 0.59; 95% CI, 0.35 to 1.00). There were 23 (0.7%) cardiovascular deaths, MIs, and stroke events with saxagliptin compared to 18 (1.4%) with the comparator drugs (RR, 0.44;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs glyburide, metformin, or placebo			death, MI, and stroke Secondary: Not reported	95% CI, 0.24 to 0.82). There were seven (0.2%) cardiovascular deaths with saxagliptin compared to 10 (0.8%) with comparator drugs (RR, 0.24; 95% CI, 0.09 to 0.63). Secondary: Not reported
Singh et al.[47] (2011) TZDs (pioglitazone, rosiglitazone) vs placebo, sulfonylurea, or metformin	MA, SR (13 RCTs) Type 2 diabetics	N=17,627 1 to 5.5 years (follow-up)	Primary: Any pneumonia or lower respiratory tract infection reported as an adverse event, pneumonia or lower respiratory tract infection reported as a serious adverse event Secondary: Not reported	Primary: TZDs are associated with a significantly increased risk for any pneumonia or lower respiratory tract infection compared to control (130/8,163 vs 100/9,464; RR, 1.40; 95% CI, 1.08 to 1.82; P=0.01). In addition TZDs were associated with a significantly increased risk of serious pneumonia or lower respiratory tract infection compared to control (111/7,391 vs 87/8,692; RR, 1.39; 95% CI, 1.05 to 1.83; P=0.02). Secondary: Not reported
Louisa et al.[48] (2011) TZDs (pioglitazone, rosiglitazone) vs placebo or other hypoglycemic agents	MA (37 RCTs) Type 2 diabetics	N=3,000 >3 months	Primary: Glycemic outcomes Secondary: Change in baseline BMI, lipid profile, BP, high-sensitivity CRP, and insulin sensitizing effect; cardiovascular and clinical endpoints	Primary: Both pioglitazone (WMD, -0.12%; 95% CI, -0.38 to -0.16) and rosiglitazone (WMD, -0.47%; 95% CI, -0.62 to -0.33) significantly decreased HbA_{1c}. Pioglitazone only demonstrated a significant decrease compared to placebo, while rosiglitazone significantly decreased HbA_{1c} compared to placebo and a sulfonylurea. Both pioglitazone (WMD, -9.16 mg/dL; 95% CI, -15.60 to -2.72) and rosiglitazone (WMD, -16.10 mg/dL; 95% CI, -22.20 to -10.01) significantly decreased FPG compared to control. Pioglitazone demonstrated a significant decrease compared to placebo, metformin, and voglibose†, while rosiglitazone significantly decreased FPG compared to placebo, metformin, and a sulfonylurea. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Pioglitazone and rosiglitazone had similar effects on BMI (pioglitazone: WMD, 0.57; 95% CI, 0.34 to 0.80 and rosiglitazone: WMD, 0.72; 95% CI, 0.29 to 1.14). Pioglitazone demonstrated a neutral effect of LDL-C (WMD, 3.89 mg/dL; 95% CI, -0.04 to 7.83) and TC (WMD, 2.30 mg/dL; 95% CI, -3.81 to 8.41). Rosiglitazone significantly increased LDL-C (WMD, 11.30 mg/dL; 95% CI, 7.80 to 14.79) and TC (WMD, 7.34 mg/dL; 95% CI, 2.34 to 12.31). Both agents had favorable effects on HDL-C and TGs. Pioglitazone produced a small decrease in DBP and SBP, while rosiglitazone demonstrated a neutral effect. In 13 trials, pioglitazone demonstrated a neutral effect on high sensitivity CRP, while rosiglitazone demonstrated a small improvement in hsCRP. Consistent increase in adiponectin and improvement in HOMA-IR were observed with both pioglitazone and rosiglitazone. Four trials evaluated cardiovascular events as secondary endpoints. There were significant decreases in major cardiac events with both pioglitazone vs control (RR, 0.24; 95% CI, 0.09 to 0.63) and rosiglitazone vs control (RR, 0.41; 95% CI, 0.19 to 0.87).
Mannucci et al.[49] (2008) Pioglitazone vs active comparators, placebo, no treatment	MA (94 trials) Patients treated with pioglitazone (with or without type 2 diabetes)	N=21,180 Variable duration	Primary: All-cause mortality, non-fatal coronary event (defined as MI, unstable angina or coronary re-vascularization), non-fatal chronic heart failure requiring hospitalization	Primary: In PROactive, pioglitazone treatment was not associated with a significant reduction in all-cause mortality (P value not reported). In non-diabetic patients, only one death was observed occurring among pioglitazone-treated patients. In type 2 diabetic patients (excluding PROactive), the total number of deaths reported was 17 and 39 in the pioglitazone and comparator groups, respectively (RR, 0.41; 95% CI, 0.23 to 0.72). When analyzing all trials, no significant reduction of mortality was observed with pioglitazone.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Secondary: Not reported	Comparing different agents, pioglitazone was associated with a lower mortality rate compared to sulfonylureas. There was no significant difference in all-cause mortality with metformin, rosiglitazone, glitazars, or placebo. When trials with zero events were included in the analysis, no significant difference was observed with sulfonylureas (RR, 0.22; 95% CI, 0.05 to 1.03), metformin (RR, 0.66; 95% CI 0.19 to 2.34), rosiglitazone (RR, 0.49; 95% CI, 0.04 to 5.36), glitazars (RR, 0.42; 95% CI, 0.11 to 1.61), or placebo (RR, 0.16; 95% CI, 0.02 to 1.45). In PROactive, pioglitazone significantly reduced the incidence of non-fatal coronary events (P value not reported). In non-diabetic subjects, only two non-fatal coronary events occurred and one case of heart failure in pioglitazone group were reported. In type 2 diabetes, 44 and 50 non-fatal coronary events were observed in pioglitazone and comparator groups, respectively (RR, 0.82; 95% CI, 0.55 to 1.23). Combining trials with at least one event, the difference between pioglitazone and comparators was not statistically significant. In PROactive, pioglitazone was associated with an increased risk for chronic heart failure. In the other 40 trials reporting data on non-fatal heart failure requiring hospitalization, 58 cases were reported in pioglitazone-treated subjects and 39 in controls (RR ,1.32; 95% CI, 0.88 to 1.98). Combining the results of all trials with at least one event except PROactive, the overall difference between pioglitazone and comparators was not significant (P value not reported). When adding PROactive or excluding trials vs dual PPARα/γ agonists pioglitazone was associated with a significant increase of risk for chronic heart failure. In comparison with different agents, pioglitazone was associated with an increased risk of chronic heart failure in PC trials, while differences with sulfonylureas or glitazars did not reach significance.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Richter et al.[50] (2006) Pioglitazone monotherapy (16 trials) vs acarbose (1 trial), metformin (4 trials), placebo (4 trials), repaglinide (1 trial), rosiglitazone (1 trial), or a sulfonylurea (8 trials) or pioglitazone combination therapy vs a similar combination with another compound (9 trials including 2 trials vs rosiglitazone) Some studies had more than one treatment arm.	MA of DB (15) or OL (4) RCTs (last search conducted in August 2006, included PROactive Study), PG Adults with type 2 diabetes, trial duration of at least 24 weeks	22 trials N=6,200 randomized to pioglitazone treatment (total N not reported) 24 weeks to 34.5 months	Primary: Patient-oriented outcomes including mortality, morbidity and adverse effects Secondary: Health-related QOL and HbA_{1c}	Primary: Only one trial (PROactive Study) evaluated mortality and morbidity as an end point. The primary composite end point (time from randomization to all-cause mortality, nonfatal MI, stroke, acute coronary syndrome, endovascular or surgical intervention on the coronary or leg arteries, or amputation above the ankle) did not show statistically significant differences between the pioglitazone and placebo group (HR, 0.90; 95% CI, 0.80 to 1.02; P=0.095). Time to the first event of the composite end point of death from any cause, MI and stroke indicated a statistically significant difference between pioglitazone and placebo (HR, 0.84; 95% CI, 0.72 to 0.98; P=0.027). The individual components of the primary composite end point did not disclose statistically significant differences between the intervention and control groups. Significantly more patients developed heart failure requiring hospitalization following administration of pioglitazone (6 vs 4% on placebo; P=0.007). The percentage of overall and serious adverse events was comparable between the intervention and control groups. Six trials reported a more pronounced (sometimes dose-related) decrease of hemoglobin after pioglitazone intake in comparison to other active compounds or placebo; hemoglobin reductions ranged between -0.50 and- 0.75 g/dL. Fifteen trials evaluated body weight and observed an increase up to 3.9 kg after pioglitazone treatment; seven trials described a rise in BMI up to 1.5 kg/m^2. Eleven of the 22 included trials showed data on hypoglycemic episodes: compared to the active monotherapy control, pioglitazone treatment resulted in somewhat lower rates of hypoglycemia (P value not reported). The RR for development of edema with pioglitazone compared to the control was 2.86 (95% CI, 2.14 to 3.18; P<0.00001) when results from 18 trials were pooled. Secondary: No study investigated health-related QOL.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Active glucose-lowering compounds like metformin, glibenclamide*, gliclazide† or glimepiride resulted in similar reductions of HbA_{1c} compared to pioglitazone treatment (P values not reported).
Lago et al.[51] (2007) Pioglitazone 15 to 45 mg/day (2 trials) or rosiglitazone 4 to 8 mg/day (5 trials) vs placebo (4 trials), glibenclamide‡ (1 trial), glimepiride (1 trial), metformin (1 trial), or metformin plus nonspecified sulfonylurea (1 trial) Doses of comparators were not specified and 1 trial had 2 control groups.	MA of DB, RCTs of TZDs that reported risk estimates or frequency data for congestive heart failure and cardiovascular death Patients with prediabetes or type 2 diabetes (with and without cardiovascular disease), mean age 59.2 years, mean BMI 31 kg/m^2, mean baseline HbA_{1c} 7.72%	7 trials N=20,191 29.7 months (range, 12 to 48 months)	Primary: Development of congestive heart failure, risk of cardiovascular death Secondary: Not reported	Primary: Three hundred and sixty of 20,191 patients who had either prediabetes or type 2 diabetes had congestive heart failure events (214 with TZDs and 146 with comparators). The overall event rate for congestive heart failure was 2.3% for patients receiving TZDs and 1.4% in the comparator group. Patients given pioglitazone (RR, 1.32; 95% CI, 1.04 to 1.68; P=0.02) or rosiglitazone (RR, 2.18; 95% CI, 1.44 to 3.32; P=0.0003) had increased risk for development of congestive heart failure across a wide background of cardiac risk compared to the control agent (combined RR, 1.72; 95% CI, 1.21 to 2.42; P=0.002). The risk for congestive heart failure did not differ for rosiglitazone and pioglitazone (RR, 1.74; 95% CI, 0.97 to 3.14; P=0.07). The overall event rate for cardiovascular death was 0.7% in both groups. The risk of cardiovascular death was not increased with pioglitazone (RR, 1.01; 95% CI, 0.51 to 2.01; P=0.98), rosiglitazone (RR, 0.91; 95% CI, 0.63 to 1.32; P=0.63) or both TZDs (combined RR, 0.93; 95% CI, 0.67 to 1.29; P=0.68). The risk of cardiovascular death did not differ between both drug groups (RR, 1.01; 95% CI, 0.73 to 1.40; P=0.96). Secondary: Not reported
Nagajothi et al.[52] (2008) Pioglitazone vs active comparators (metformin and/or sulfonylurea) or placebo	MA (5 trials) Patients treated with pioglitazone	N=not reported Duration varied	Primary: MI Secondary: Stroke, revascularization, total mortality, cardiovascular mortality	Primary: The RR for MI was 0.86 (95% CI, 0.69 to 1.07; P=0.17). Secondary: The RR for stroke was 0.79 (95% CI, 0.61 to 1.02; P=0.07). The RR for total mortality was 0.94 (95% CI, 0.78 to 1.15; P=0.56). The RR for coronary revascularization was 0.40 (95% CI, 0.13 to 1.23; P=0.11.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The RR for cardiovascular mortality was 0.92 (95% CI, 0.73 to 1.16; P=0.47).
Lincoff et al.[53] (2007) Pioglitazone monotherapy vs metformin (1 trial), placebo (4 trials), sulfonylureas (6 trials) or rosiglitazone (1 trial) or pioglitazone combination therapy (7 trials) with insulin, metformin, or sulfonylureas vs active comparator or placebo	DB, MA, RCT with placebo or active comparator Adult patients with type 2 diabetes and inadequate glycemic control	N=16,390 (19 trials) 4 months to 3.5 years	Primary: Composite of death from any cause, MI or stroke Secondary: Incidence of serious heart failure	Primary: Death, MI, or stroke occurred in 375 of 8,554 patients (4.4%) receiving pioglitazone and 450 of 7,836 patients (5.7%) receiving control therapy (HR, 0.82; 95% CI, 0.72 to 0.94; P=0.005). Individual components of the primary end point were reduced with pioglitazone treatment with varying degrees of statistical significance (death: HR, 0.92; P=0.38, MI: HR, 0.81; P=0.08, death and MI: HR, 0.85; P=0.04, and stroke: HR, 0.80; P=0.09). Progressive separation of time-to-event curves became apparent after approximately one year of therapy. Secondary: Serious heart failure was reported in 2.3% of the pioglitazone-treated patients and 1.8% of the control treated patients (HR, 1.41; 95% CI, 1.14 to 1.76; P=0.002). The composite of serious heart failure and death was not significantly increased among patients receiving pioglitazone (HR, 1.11; 95% CI, 0.96 to 1.29; P=0.17).
Karter et al.[54] (2005) Patients initiated pioglitazone (15.2%), sulfonylureas (25.3%), metformin (50.9%), and insulin (8.6%) alone, or in addition to pre-existing therapies	Cohort study of all patients in the Kaiser Permanente Medical Care Program with type 2 diabetes (Kaiser Permanente Northern California Diabetes Registry) who initiated any new diabetes pharmacotherapy between October	N=23,440 10.2 months (mean)	Primary: Time-to-incident admission to hospital for congestive heart failure Secondary: Not reported	Primary: Three hundred and twenty admissions for congestive heart failure were observed during the follow-up (mean, 10.2 months) after drug initiation. Relative to patients initiating sulfonylureas, there were no significant increases in the incidence of hospitalization for congestive heart failure in those initiating pioglitazone (HR, 1.28; 95% CI, 0.85 to 1.92). There was a significantly higher incidence among those initiating insulin (HR, 1.56; 95% CI, 1.00 to 2.45) and lower incidence among those initiating metformin (HR, 0.70; 95% CI, 0.49 to 0.99). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	1999 and November 2001			
Nissen et al.[55] (2007) Rosiglitazone monotherapy or combination therapy vs placebo or active comparators (including gliclazide†, glimepiride, glipizide, glyburide, insulin, and metformin)	MA of RCTs of more than 24 weeks that had outcome data for MI and death from cardiovascular causes (included ADOPT and DREAM trials) Mean age of participants was 56 years, mean baseline HbA_{1c} 8.2%	42 trials n=15,560 for rosiglitazone ; n=12,283 for comparator 24 to 208 weeks	Primary: MI and death from cardiovascular causes Secondary: Not reported	Primary: Rosiglitazone was associated with a significant increase in the risk of MI compared to the control agent (OR, 1.43; 95% CI, 1.03 to 1.98; P=0.03). Compared to the control agent, rosiglitazone was associated with a trend toward increased cardiovascular death (OR, 1.64; 95% CI, 0.98 to 2.74; P=0.06). Although not a prespecified end point, the OR for death from any cause with rosiglitazone was 1.18 (95% CI, 0.89 to 1.55; P=0.24). Secondary: Not reported
Singh et al.[56] (2007) Rosiglitazone vs control (placebo or other non-TZD oral hypoglycemic drug including glyburide or metformin)	MA of RCTs (available up to May 2007 and included ADOPT, DREAM and RECORD trials) of rosiglitazone of at least 12 months duration Study participants with impaired glucose tolerance or type 2 diabetes, studies monitored cardiovascular adverse events and provided numerical	4 trials N=14,291 (n=6,421 rosiglitazone ; n=7,870 control) 1 to 4 years	Primary: RR of MI, heart failure, and cardiovascular mortality Secondary: Not reported	Primary: Rosiglitazone significantly increased the risk of MI (94 vs 83; RR, 1.42; 95% CI, 1.06 to 1.91; P=0.02) and heart failure (102 vs 62; RR, 2.09; 95% CI, 1.52 to 2.88; P<0.001) compared to the control. There was no significant difference in the risk of cardiovascular mortality between the rosiglitazone and control group (59 vs 72; RR, 0.90; 95% CI, 0.63 to 1.26; P=0.53). Rosiglitazone had no effect on all-cause mortality (146 vs 180; RR, 0.99; 95% CI, 0.80 to 1.23; P=0.92). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	data on all adverse events			
Richter et al.[57] (2007) Rosiglitazone monotherapy (10 trials) vs glyburide (2 trials), metformin (3 trials), pioglitazone (1 trial), placebo (5 trials), or repaglinide (1 trial) or rosiglitazone combination therapy vs a similar combination with another compound (8 trials) Some studies had more than 1 treatment arm.	MA of DB (11) or OL (5) RCTs (last search conducted in April 2007, included the ADOPT trial), PG Adults with type 2 diabetes, trial duration of at least 24 weeks	18 trials N=3,888 randomized to rosiglitazone treatment (total N not reported) 24 weeks to 4 years (median 26 weeks)	Primary: Patient-oriented outcomes including mortality, morbidity and adverse effects Secondary: Health-related QOL and metabolic control (HbA_{1c})	Primary: No study included mortality as a primary or secondary end point. While not an initial primary or secondary study end point, the ADOPT trial reported that the all-cause mortality was 2.3% in the rosiglitazone group, 2.1% in the metformin group and 2.2% in the glyburide group (P values not reported in this reference). The ADOPT trial also reported comparable hospitalization rates for any cause between rosiglitazone (11.6%), metformin (11.8%), and glyburide (10.4%) groups (P values were not reported in this reference). Cardiovascular disease was increased in the rosiglitazone group compared to the glyburide group but not the metformin group with serious/total events reported in 3.4/4.3% and 1.8/2.8% of patients receiving rosiglitazone and glyburide, respectively (events were 3.2/4.0% with metformin; P values were not reported in this reference). Congestive heart failure was observed more frequently in patients receiving rosiglitazone (1.5%) than patients receiving glyburide (0.6%) but not metformin (1.3%; P values were not reported in this reference). The percentage of overall adverse events was comparable between the intervention and control groups (which included placebo arms); serious adverse events appeared to happen more often after rosiglitazone treatment (median of 6 vs 4% in the control groups; P value not reported). Median discontinuation rate following rosiglitazone administration was also higher than after control therapy (median of 7 vs 4%; P value not reported). Three studies reported a more pronounced (apparently dose-related) decrease of hemoglobin after rosiglitazone intake in comparison to other active compounds or placebo; hemoglobin reductions ranged between 0.5 and 1.0 g/dL. Eleven studies evaluated body weight and observed an increase up to 5.0 kg after rosiglitazone treatment; four studies described a rise in BMI up to 1.5 kg/m^2. Seven of the 18 included studies showed data on hypoglycemic episodes: compared to active monotherapy control, rosiglitazone treatment resulted in somewhat lower rates of hypoglycemia, especially when compared to sulfonylureas. Occurrence of edema was significantly raised when results of nine studies were pooled (OR, 2.27; 95% CI, 1.83 to 2.81;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				P<0.00001). The ADOPT trial reported a higher incidence of fractures in women receiving rosiglitazone (9.30%) than metformin (5.08%; P<0.01) or glyburide (3.47%; P<0.01). Secondary: No study investigated health-related QOL. Active glucose-lowering compounds like metformin, glibenclamide‡ or glimepiride resulted in similar reductions of HbA_{1c} compared to rosiglitazone treatment.
Type 2 Diabetes – Combination Therapy				
Lopez-Alvarenga et al.[58] (1999) Chlorpropamide 500 mg daily, metformin 1,200 mg daily, and acarbose 100 mg TID vs chlorpropamide 500 mg daily, metformin 1,200 mg daily, and NPH insulin at bedtime vs chlorpropamide 500 mg daily, metformin 1,200 mg daily, and placebo	DB, RCT, XO Patients with type 2 diabetes 35 to 70 years of age with BMI 23 to 35 kg/m^2, with a fasting plasma glucose above 8.8 mmol/L despite maximal doses of chlorpropamide and metformin for at least 2 months	N=46 42 weeks	Primary: Change in FPG from baseline, body weight, HbA_{1c}, fasting insulin, fasting C-peptide, intravenous glucose tolerance test (incremental area), glucose meal tests (incremental area) Secondary: Not reported	Primary: Changes in FPG from baseline were not significant for placebo (P=0.62), but were significant for acarbose (P=0.05) and insulin (P=0.003). Changes in HbA_{1c} from baseline were not significant for placebo (P=0.62) and acarbose (P=0.3), but were significant for insulin (P=0.008). Changes in body weight were not significant in any group; P=0.2 for each group from baseline. Changes in fasting insulin from baseline were not significant for placebo (P=0.38), but were significant for acarbose (P=0.03) and insulin (P=0.02). Changes in fasting C-peptide from baseline were not significant in any group, placebo (P=0.7), acarbose (P=0.5), and insulin (P=0.24). Changes in intravenous glucose tolerance test (incremental area) from baseline were not significant in any group, placebo (P=0.36), acarbose (P=0.91), and insulin (P=0.94). Changes in glucose meal tests (incremental area) from baseline were not significant for placebo (P=0.84) and insulin (P=0.08), but were for acarbose (P=0.02). Changes in insulin (incremental area) from baseline were not significant for any group, placebo (P=0.92), acarbose (P=0.3), and insulin (P=0.43).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Thirty-seven percent of patients developed severe bloating during acarbose use. This was significant (P<0.05) compared to acarbose and placebo or insulin. Secondary: Not reported
Yokoyama et al.[59] (2011) Continuation of glimepiride for 3 months vs discontinuation of glimepiride for 3 months All patients received metformin and basal insulin.	OL, XO Patients with type 2 diabetes ≥5 years duration who are receiving insulin, metformin, and a sulfonylurea; BMI ≤40 kg/m^2, and HbA_{1c} ≤8.0%	N=25 6 months	Primary: Plasma glucose levels, change in baseline HbA_{1c} Secondary: Not reported	Primary: During meal tolerance tests performed at the end of each three month period, significant increases in plasma glucose were seen in patients who discontinued glimepiride at 0-, 30-, and 60-minutes, while significant decreases in serum C-peptide were observed as 60- and 120-minutes. HbA_{1c} significantly increased in patients discontinuing glimepiride (from 6.6±0.6 at baseline to 7.7±0.8 at three months; P<0.0001). Increases in HbA_{1c} were closely correlated with decreases in AUC of meal-stimulated serum C-peptide (P<0.001). Secondary: Not reported
Dhindsa et al.[60] (2003) Glimepiride 2 mg QD vs gliclazide† 80 mg BID All patients received existing metformin regimens.	DB, RCT, XO Patients 50 to 70 years of age with type 2 diabetes and inadequate glycemic control despite metformin 500 mg BID monotherapy	N=12 12 weeks	Primary: Changes in fructosamine, augmentation index, peak microvascular response to acetylcholine and sodium nitroprusside, and PD_{10} values (dose of agonist required to increase mean	Primary: Metabolic control improved following the addition of a sulfonylurea, as seen by the reductions in serum fructosamine concentrations, but there were no significant differences in the antidiabetic effect between glimepiride and gliclazide as add-on therapy. There was no change in augmentation index during treatment with either sulfonylurea. There were no differences in pressor responsiveness (PD_{10}) or microvascular responses between the two treatment groups. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			arterial BP by 10 mm Hg) Secondary: Not reported	
Cefalu et al.[61] CANTATA-SU (2013) Canagliflozin 100 mg vs canagliflozin 300 mg vs glimepiride titrated to a maximum of 6 or 8 mg/day	AC, DB, NI, RCT Patients aged 18 to 80 years with type 2 diabetes and an HbA_{1c} between 7.0 and 9.5% receiving stable metformin therapy	N=1,450 52 weeks	Primary: Change in HbA_{1c} from baseline Secondary: Percentage change from baseline in bodyweight, proportion of patients with documented hypoglycemic episodes	Primary: Both canagliflozin doses were non-inferior to glimepiride for lowering of HbA_{1c}, and canagliflozin 300 mg was superior to glimepiride for HbA_{1c} reduction. The least squares mean change from baseline was -0.81, -0.82, and -0.93% in the glimepiride, canagliflozin 100 mg, and canagliflozin 300 mg, respectively. Secondary: The proportion of patients with documented hypoglycemic episodes was significantly lower with canagliflozin 100 mg and 300 mg than with glimepiride (P<0.0001 for both). The frequency of severe hypoglycemia was also lower with canagliflozin 100 mg (two [<1%] patients) and 300 mg (three [<1%]) than with glimepiride (15 [3%]). Both canagliflozin doses significantly reduced bodyweight at week 52, whereas a slight increase occurred with glimepiride (P<0.0001 for both canagliflozin doses vs glimepiride).
Müller-Wieland et al.[62] (2018) Glimepiride 1 to 6 mg (titrated) vs dapagliflozin 10 mg plus saxagliptin 5 mg vs	DB, MC, RCT Patients with type 2 diabetes 18 to ≥75 years of age on stable metformin (≥1500 mg/day) for ≥8 weeks and HbA_{1c} concentration of 7.5 to 10.5%	N=939 52 weeks	Primary: Absolute change from baseline in HbA_{1c} Secondary: Proportion of patients reporting confirmed hypoglycemic episodes during the 52-week treatment period, changes from baseline in total body weight	Primary: Adjusted mean change from baseline in HbA_{1c} at 52 weeks was −0.82% for dapagliflozin alone and −1.20% for dapagliflozin plus saxagliptin, compared with −0.99% for glimepiride when added to baseline metformin monotherapy. Non-inferiority, based on a prespecified margin of 0.3%, was demonstrated for both dapagliflozin-containing treatment groups, relative to glimepiride, at Week 52. The change in HbA_{1c} from baseline was statistically significantly greater (P=0.001) with dapagliflozin plus saxagliptin than with glimepiride. Secondary: The proportion of patients experiencing at least one episode of confirmed hypoglycemia was low across all groups (<5%) and was significantly lower in both dapagliflozin-containing treatment groups than in the glimepiride group (P<0.001, both comparisons). Total body weight decreased from

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
dapagliflozin 10 mg Patients on metformin monotherapy (≥1500 mg/day)			and FPG at week 52, and the time to rescue during the treatment period	baseline in both dapagliflozin-containing treatment groups, whereas it increased in the glimepiride group. Reductions in FPG from baseline were statistically significantly greater with dapagliflozin plus saxagliptin than with glimepiride as add-on therapy, and dapagliflozin was non-inferior to glimepiride as add-on therapy. The proportions of patients who met rescue criteria during the treatment period were 18.6%, 8.3% and 21.4% in the dapagliflozin, dapagliflozin plus saxagliptin and glimepiride add-on to metformin groups, respectively.
Frias et al.[63] (2020) Glimepiride 1 to 6 mg (GLIM) vs Dapagliflozin 10 mg (DAPA) + saxagliptin 5 mg (SAXA)	AC, DB, MC, RCT Patients ≥18 years of age with type 2 diabetes who were inadequately controlled (HbA_{1c} 7.5 to 10.5%) on metformin monotherapy	N=443 52 weeks	Primary: Mean change in HbA_{1c} from baseline Secondary: Change from baseline in total body weight; proportion of patients achieving a therapeutic response, defined as HbA_{1c} <7.0%; change from baseline in systolic blood pressure (SBP); and time to treatment intensification	Primary: The adjusted mean change from baseline in HbA_{1c} at 52 weeks was greater with DAPA + SAXA (−1.35%) than with GLIM (−0.98%; P<0.001 vs GLIM). Secondary: The proportion of patients who achieved HbA_{1c} <7.0% at 52 weeks was greater with DAPA + SAXA than with GLIM (P=0.044). Total body weight decreased from baseline to week 52 with DAPA + SAXA, whereas it increased with GLIM (P<0.001). Similarly, SBP decreased from baseline to week 52 with DAPA + SAXA and increased with GLIM (P=0.007). Significantly fewer patients required treatment intensification with DAPA + SAXA than with GLIM (P=0.002); however, these results were not included in sequential testing, because there were <10 patients in each treatment group.
Hollander et al.[64] VERTIS SU Glimepiride titrated from 1 mg up to 6 or 8 mg QD vs	AC, DB, MC, PG, RCT Patients ≥18 years of age with type 2 DM and HbA_{1c} ≥7.0% to ≤9.0% on ≥1,500 mg/day of metformin	N=1,326 104 weeks (two 52 week phases)	Primary: Change from baseline in HbA_{1c} at week 52 Secondary: Changes from baseline in body	Primary: The least-squares mean change from baseline at week 52 in HbA_{1c} was -0.6% (95% CI, -0.7 to -0.5), -0.6% (95% CI, -0.6 to -0.5), and - 0.7% (95% CI, -0.8 to -0.7) in the ertugliflozin 15mg, ertugliflozin 5 mg, and glimepiride groups respectively. The between-group difference for ertugliflozin 15 mg and glimepiride of 0.1% (95% CI, -0.0 to 0.2) met the pre-specified non-inferiority criterion. However, the between-group difference for ertugliflozin 5 mg and glimepiride at week 52 was 0.2% (95%

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ertugliflozin 15 mg QD vs ertugliflozin 5 mg QD Glycemic rescue therapy with open-label sitagliptin was prescribed for subjects meeting progressively more stringent glycemic rescue criteria.	monotherapy for at least eight weeks at screening		weight and SBP at week 52	CI, 0.1 to 0.3) and did not satisfy the criterion for non-inferiority to glimepiride. Secondary: Greater body weight and SBP reductions from baseline at week 52 were observed with ertugliflozin compared to glimepiride. The least-squares mean changes in body weight from baseline at week 52 were -3.4 kg (95% CI, -3.7 to -3.0), -3.0 kg (95% CI, -3.3 to -2.6) and 0.9 kg (95% CI, 0.6 to 1.3) in the ertugliflozin 15 mg, ertugliflozin 5 mg and glimepiride groups, respectively. The least-squares mean differences versus glimepiride at week 52 were -4.3 kg (95% CI, -4.8 to -3.8) and -3.9 kg (95% CI, -4.4 to -3.4) for ertugliflozin 15 mg and 5 mg respectively (P<0.001). Least square mean changes in SBP from baseline at week 52 were -3.8 mmHg (95% CI, -4.9 to -2.7), -2.2 mmHg (95% CI, -3.4 to -1.1) and 1.0 mmHg (95% CI, -0.1 to 2.1) in the ertugliflozin 15 mg, ertugliflozin 5 mg and glimepiride groups, respectively. The least-squares mean differences versus glimepiride at week 52 were -4.8 mmHg (95% CI, -6.3 to -3.2) and -3.2 mmHg (95% CI, -4.7 to -1.7) for ertugliflozin 15 mg and 5 mg, respectively (P<0.001).
Derosa et al.[65] (2011) Exenatide 5 µg SC BID, titrated up to 10 µg SC BID vs glimepiride 1 mg TID, titrated up to 2 mg TID	MC, RCT, SB Patients ≥18 years of age with type 2 diabetes intolerant to metformin at the highest dosages (2,500 to 3,000 mg/day)	N=111 12 months	Primary: Change in baseline body weight, glycemic control, insulin resistance Secondary: Not reported	Primary: There was decrease of body weight and BMI after six, nine, and 12 months (*P*<0.05, *P*<0.01, *P*<0.001, respectively) with exenatide, not obtained with glimepiride. BMI reached with exenatide was significantly lower compared to glimepiride (P<0.05). A similar decrease in HbA_{1c}, FPG, and PPG after nine (*P*<0.05 for all), and after 12 months (*P*<0.01 for all) with both treatments, without significant differences between the two treatments. Exenatide resulted in a reduction of fasting plasma insulin, and HOMA-IR after 12 months (*P*<0.05 for both), not observed with glimepiride; fasting plasma insulin increased with glimepiride. Values reached with exenatide were significantly lower compared to values reached with glimepiride after 12 months (*P*<0.05). Exenatide, but not glimepiride, gave an increase of adiponectin after 12 months (*P*<0.05), and the value registered with exenatide was significantly

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				higher compared to the value recorded with glimepiride at trial end (*P*<0.05). A decrease of tumor necrosis factor-α was observed after 12 months (*P*<0.05) with exenatide, but no with glimepiride; furthermore the value obtained with exenatide was significantly better compared to the value obtained with glimepiride after 12 months (*P*<0.05). Exenatide, but not glimepiride, gave a reduction of high sensitivity CRP after nine and 12 months (*P*<.0.05 and *P*<0.01) compared to baseline and glimepiride (*P*<0.05). Secondary: Not reported
Gallwitz et al.[66] EUREXA (2012) Exenatide 5 to 10 µg BID vs glimepiride 1 mg initially, titrated to maximum tolerated dose	MC, OL, RCT Overweight patients aged 18 to 85 years with type 2 diabetes on a stable maximum tolerated dose of metformin with HbA_{1c} between 6.5 and 9.0%	N=977 Average treatment was 2 years	Primary: Time to inadequate glycemic control (HbA_{1c} >9% after the first 3 months, or >7% at 2 consecutive visits 3 months apart after the first 6 months) Secondary: Markers of β-cell function, bodyweight, hypoglycemia, surrogate markers of cardiovascular risk (blood pressure and heart rate)	Primary: Median time to inadequate HbA_{1c} control was 180 weeks with exenatide versus 142.1 weeks with glimepiride (P=0.032). In the exenatide group, 203 (41%) patients had treatment failure compared with 262 (54%) in the glimepiride group (risk difference, 12.4; 95% CI, 6.2 to 18.6; HR, 0.748; CI, 0.623 to 0.899; P=0.002). Secondary: Systolic blood pressure decreased in patients in the exenatide group (change to endpoint -1.9 mmHg; P=0.006), but not in the glimepiride group (1.1 mmHg; P=0.096). Heart rate increased at endpoint in patients given exenatide (1.2 beats per min (bpm); P=0.024), but not in those given glimepiride (0.6 bmp; P=0.282), with no difference between groups at any time. Discontinuation because of adverse events (mainly gastrointestinal) was significantly higher (P=0.0005) in the exenatide group than in the glimepiride group in the first six months of treatment, but not thereafter.
Forst et al.[67] (2010)	AC, DB, MC, PC, PG, RCT	N=333 12 weeks	Primary: Change in baseline HbA_{1c}	Primary: Placebo corrected decreases in HbA_{1c} were -0.40±0.14 (P=0.006), -4.40±0.14 (P<0.001), and -8.00±1.50% (P<0.001) with linagliptin 1, 5, and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Linagliptin 1, 5, or 10 mg/day vs placebo vs glimepiride (OL) 1 to 3 mg/day Patients were also receiving metformin.	Type 2 diabetics 21 to 75 years of age with BMI 25 to 40 kg/m^2, who had inadequate glycemic control on metformin alone (HbA_{1c} 7.5 to 10.0%)		Secondary: Change in baseline FPG and body weight, proportion of patients achieving an HbA_{1c} ≤7.0%, proportion of patients with an HbA_{1c} decrease ≥0.5%, safety	10 mg, respectively. Treatment with glimepiride significantly decreased HbA_{1c} compared to treatment with placebo -0.68% (P<0.0001). Secondary: Decreases in FPG were significantly greater with all doses of linagliptin compared to placebo. The placebo corrected FPG decrease were -1.1 (P=0.0020), -1.9 (P<0.0001), and -1.6 mmol/L (P<0.0001) with linagliptin 1, 5, and 10 mg, respectively. After 12 weeks a small decrease in body weight was observed with all doses of linagliptin (-0.15, -0.57, and -1.27 kg, respectively; P values not reported). Only one (1.4%) patient receiving placebo achieved an HbA_{1c} ≤7.0% compared to ten (approximately 15%), nine (approximately 15%), and 14 (21%) patients receiving linagliptin 1, 5, and 10 mg/day, respectively (P values not reported). A greater proportion of patients receiving linagliptin achieved an HbA_{1c} decrease ≥0.5% compared to patients receiving placebo (43.8 to 53.2 vs 12.9%; P value not reported). In addition, HbA_{1c} decreased by ≥1.0% in 14.1, 27.4, 22.7, and 7.7% with linagliptin 1 mg, linagliptin 5 mg, linagliptin 10 mg, and placebo (P values not reported). Linagliptin was well tolerated. The most commonly reported adverse events were considered to be of mild or moderate intensity; however, ten patients experienced severe adverse events. No episodes of hypoglycemia were reported. Three (4.6%) patients experienced hypoglycemia after dosing with glimepiride.
Yang et al.[68] (2011) Liraglutide 0.6, 1.2, or 1.8 mg QD vs	AC, DB, DD, RCT Adult patients with type 2 diabetes	N=929 16 weeks	Primary: Change in baseline HbA_{1c} Secondary: Proportions of patients achieving HbA_{1c} <7.0 and	Primary: Baseline HbA_{1c} was significantly reduced with all treatments. Treatment with liraglutide 1.2 and 1.8 mg was non-inferior to glimepiride (mean reduction: 1.36, 1.45, 1.39% points, respectively). Secondary: No significant difference was shown in the proportion of patients achieving HbA_{1c} <7.0 or ≤6.5% between liraglutide 1.2 and 1.8 mg and glimepiride.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
glimepiride 4 mg QD All patients received metformin.			≤6.5%, body weight, BP, hypoglycemia, adverse events	Liraglutide resulted in a mean reduction in weight of -1.8 to -2.4 kg compared to 0.1 kg weight gain with glimepiride. Liraglutide significantly reduced SBP compared to glimepiride. Two patients receiving glimepiride experienced major hypoglycemia compared to zero patients receiving liraglutide. Liraglutide was associated with a 10-fold lower incidence of minor hypoglycemia compared to glimepiride. Gastrointestinal disorders were the most commonly reported adverse events with liraglutide therapy; events were transient and resulted in few withdrawals.
Charbonnel et al.[69] (2013) Sitagliptin starting at 100 mg/day, with glimepiride added if further glucose control needed (oral) vs liraglutide starting at 0.6 mg/day, up-titrated to 1.2 mg/day after 1 week (injectable)	AC, OL, RCT Patients with type 2 diabetes mellitus aged 18 to 79 years, on a stable dose of metformin monotherapy ≥1,500 mg/day for ≥12 weeks, with an HbA_{1c} ≥7.0% and ≤11.0% and a fasting fingerstick glucose <15 mmol/L at the randomization visit, deemed capable by the investigator of using a Victoza pen injection device	N=653 (per protocol patients were analyzed, N=522) 26 weeks	Primary: Change in HbA_{1c} (non-inferiority) Secondary: FPG, plasma lipids, safety	Primary: HbA_{1c} decreased over 26 weeks in both treatment strategy groups, with a larger initial reduction at week 12 in the injectable strategy group. The mean change in HbA_{1c} at week 26 was -1.3% in the oral group and -1.4% in the injectable group. The primary hypothesis was met to declare that the oral treatment was non-inferior to the injectable in lowering HbA_{1c}. Secondary: Significant reductions in FPG at week 26 were observed in both groups, with a greater reduction observed in the injectable group. No meaningful between-group differences were found in any lipid variable or in the incidence of clinical adverse effects overall. The incidence of drug-related adverse events or adverse events leading to discontinuation was greater in the injectable group than in the oral group. These differences were mainly related to the significantly higher incidence of gastrointestinal adverse events, such as abdominal pain, diarrhea, nausea, and vomiting, in the injectable group.
Chogtu et al.[70] (2009)	OL, RCT	N=63 12 weeks	Primary:	Primary: The mean change in the FPG and PPG from baseline to week 12 was significant in both groups (P<0.05). There was no significant difference

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Glimepiride 2 mg daily and pioglitazone (variable doses) vs glimepiride 2 mg daily and rosiglitazone (variable doses)	Patients 30 to 70 years of age with type 2 diabetes who received glimepiride and required a TZD due to a lack of glycemic control, normotensive, and not on antilipemic therapy		Blood glucose levels, plasma lipids, BP Secondary: Not reported	between the groups with regard to the change in FPG (P=0.10) and PPG (P=0.95). HbA_{1c} levels also decreased from baseline to week 12. There was no significant difference between the treatment groups (P>0.05). At week 12, 37.9% of patients in the pioglitazone group and 17.8% of patients in the rosiglitazone group had HbA_{1c} <7.0% (P value not reported). TC decreased in both treatment groups; however, to a greater extent with pioglitazone compared to rosiglitazone (P=0.004). TG in the pioglitazone group (P=0.0006) decreased significantly in comparison to the rosiglitazone group (P=0.255) at 12 weeks (P=0.002 pioglitazone vs rosiglitazone). LDL-C decreased significantly (P=0.005) in the pioglitazone group compared to the rosiglitazone group. There was no significant difference in HDL-C among the treatment groups (P>0.05). There was no change in SBP with pioglitazone or rosiglitazone from baseline to week 12. There was also no significant difference in SBP between the treatment groups (P=0.45). There was an increase in the weight following treatment with pioglitazone and rosiglitazone; however, there was no difference between the groups (P=0.10). Secondary: Not reported
Chou et al.[71] (2008) Glimepiride 1mg titrated to 4 mg QD (GLIM) vs	DB, MC, PG, RCT Type 2 diabetics, HbA_{1c} 7.5 to 12.0%, fasting C-peptide ≥0.8 ng/mL, FPG ≥126 mg/dL, who had been treated with diet and/or exercise alone or	N=901 28 weeks	Primary: Change in baseline HbA_{1c} Secondary: Change in baseline FPG, proportion of patients achieving HbA_{1c} and FPG targets, HOMA-S,	Primary: Both rosiglitazone/glimepiride regimens significantly reduced HbA_{1c} to a greater extent than glimepiride or rosiglitazone monotherapy regimens (P<0.0001). Secondary: A significantly greater reduction in FPG levels was observed in the rosiglitazone/glimepiride group compared to the glimepiride or rosiglitazone monotherapy groups (P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
rosiglitazone 4 mg titrated to 8 mg QD (RSG) vs rosiglitazone/ glimepiride 4/1 mg titrated to 4/4 mg (regimen A) or titrated to 8/4 mg QD (regimen B) (RSG/GLIM)	who had not taken oral antidiabetic medication or insulin for >15 days in the preceding 4 months		HOMA-B, cardiovascular biomarkers, safety	Significantly more patients achieved HbA_{1c} target levels ≤6.5 and <7.0% with either rosiglitazone/glimepiride regimen than patients with glimepiride or rosiglitazone monotherapy regimens (P<0.0001). Improvement in CRP was also observed in patients treated with rosiglitazone/glimepiride or rosiglitazone monotherapy compared to patients treated with glimepiride monotherapy (P<0.05). There were no new safety or tolerability issues identified from its monotherapy components and a similar adverse event profile was observed across the fixed-dose regimens. The most commonly reported adverse event was hypoglycemia and the incidence of confirmed symptomatic hypoglycemia (3.6 to 5.5%) was comparable among subjects treated with a fixed-dose regimen and glimepiride monotherapy.
McCluskey et al.[72] (2004) Glimepiride 2 to 8 mg QD and rosiglitazone (existing therapy) vs rosiglitazone (existing therapy)	MC, PC, RCT Patients with type 2 diabetes poorly controlled (HbA_{1c} 7.5 to 9.5%) with rosiglitazone monotherapy	N=40 30 weeks	Primary: Effect on HbA_{1c} Secondary: Effect on FPG, body weight, lipoproteins, proportion of patients who achieved HbA_{1c} and FPG targets	Primary: Significant reductions in HbA_{1c} were observed with glimepiride (-1.2%) compared to placebo (-0.3%; P<0.001). Secondary: Significant reductions in FPG were observed with glimepiride (-24.41 mg/dL) compared to placebo (5.9 mg/dL; P<0.008). Significantly greater proportion of patients receiving glimepiride achieved the target HbA_{1c} ≤7.0% (60.0 vs 14.3%; P<0.008). There were no significant differences between treatment groups in TC, HDL-C, LDL-C, or TG at any time during study period.
Rosenstock et al.[73] (2008) <u>Study A</u> Glimepiride 3 mg QD and rosiglitazone 4 mg QD (RSG 4 mg + GLIM)	2 DB, PC, RCT Patients 40 to 80 years of age (Study A) or 18 to 75 years of age (Study B) with type 2 diabetes, HbA_{1c} ≥7.0% and FPG 126 to 270 mg/dL at	N=174 (Study A) N=391 (Study B) 26 weeks (Study A) 24 weeks	Primary: Mean change in baseline HbA_{1c} Secondary: Proportion of patients with HbA_{1c} <7.0% and/or HbA_{1c} reduction ≥0.7% at	<u>Study A</u> Primary: At week 26, the mean change in HbA_{1c} from baseline was -0.63% in the RSG 4 mg+GLIM (P=0.03 vs GLIM 3 mg), -1.17% in the RSG 8 mg+GLIM groups (P<0.0001 vs GLIM 3 mg), and -0.08% in the GLIM 3 mg group. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs glimepiride 3 mg QD and rosiglitazone 8 mg QD (RSG 8 mg + GLIM) vs glimepiride 3 mg QD (GLIM alone) <u>Study B</u> Glimepiride 2 to 4 mg QD and rosiglitazone 4 mg QD (RSG add-on) vs glimepiride 4 to 8 mg QD and placebo (GLIM)	baseline; in the 3 months prior to enrolment, eligible patients in Study A received monotherapy with an oral antidiabetic agent; eligible patients in Study B were treated with a non-TZD oral antidiabetic therapy for ≥3 months prior to screening, including metformin monotherapy, sulfonylurea monotherapy, or low-dose combination therapy with metformin and sulfonylurea	(Study B)	the end of the treatment period, mean change in baseline FPG	The mean change in FPG from baseline was -21 mg/dL in the RSG 4 mg+GLIM (P=0.09 vs GLIM alone), -43 mg/dL in the RSG 8 mg+GLIM groups (P<0.0001 vs GLIM 3 mg), and -2 mg/dL for GLIM 3 mg. At week 26, 43% of patients achieved HbA_{1c} <7.0% in the RSG 4 mg+GLIM group (P=0.0129 vs GLIM alone) and 68% achieved the same HbA_{1c} goal in the RSG 8 mg+GLIM group (P=0.0001 vs GLIM 3 mg) compared to 32% in the GLIM 3 mg. <u>Study B</u> Primary: At week 24, the mean change in HbA_{1c} from baseline was -0.68% in the RSG add-on group compared to -0.08% in the GLIM 4 to 8 mg group (P<0.0001). Secondary: The mean change in FPG from baseline was -28 mg/dL in the RSG add-on group compared to -1 mg/dL in the GLIM 4 to 8 mg group (P<0.0001). At week 24, 39% of patients achieved HbA_{1c} <7.0% in the RSG add-on group compared to 15% in the GLIM 4 to 8 mg group (P<0.0001). Insulin sensitivity increased significantly in the RSG add-on group but was unchanged with GLIM 4 to 8 mg. β-cell function increased over 24 weeks in both treatment groups but with a significantly greater increase with RSG add-on group. RSG add-on significantly reduced fasting levels of C-peptide (P=0.025), proinsulin (P=0.0006), and insulin (P=0.013) and reduced the proinsulin: insulin ratio (P<0.0001). There were no significant changes in any of these parameters with GLIM 4 to 8 mg (C-peptide; P=0.075, proinsulin; P=0.42, insulin; P=0.10 and proinsulin:insulin ratio; P=0.34).
Schernthaner et al.[74] (2015) GENERATION	DB, MC, RCT Patients with type 2 diabetes ≥65 years of age on stable	N=720 52 weeks	Primary: HbA_{1c} <7.0% without confirmed/severe hypoglycemia	Primary: The proportions of patients achieving HbA_{1c} <7.0% at week 52 without confirmed/severe hypoglycemia were similar with saxagliptin and glimepiride: 37.9 vs 38.2% (OR, 0.99; 95% CI, 0.73 to 1.34; P=0.9415);

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Glimepiride ≤6 mg/day vs saxagliptin 5 mg/day	metformin monotherapy at any dose for ≥8 weeks before enrolment and had an HbA_{1c} concentration of 7.0 to 9.0%		Secondary: Incidence of confirmed/severe hypoglycemia	however, a significant treatment-by-age interaction was detected (P=0.0389). Secondary: Fewer patients in the saxagliptin group experienced ≥1 confirmed/severe hypoglycemic event over the treatment period, compared with the glimepiride group: 1.1 vs 15.3% (OR, 0.06; 95% CI, 0.02 to 0.17; nominal P<0.0001).
Kim et al.[75] (2017) Glimepiride starting at 1 mg and titrated as needed vs sitagliptin-metformin 50-1000 mg fixed-dose combination BID	DB, MC, RCT Patients ≥ 18 years of age with type 2 diabetes with HbA_{1c} levels ranging from ≥7.0 to ≤9.5% for patients not on antihyperglycemic agents for at least 12 weeks or from ≥6.5 to ≤9.0% for patients taking antihyperglycemic agents	N=292 30 weeks	Primary: Change from baseline in HbA_{1c} Secondary: Proportion of patients achieving target goal (HbA_{1c} <7.0%) and change from baseline in FPG; safety	Primary: At Week 30, the mean HbA_{1c} fell from 8% at baseline to 6.5% in the sitagliptin-metformin group, and from 8.1% to 7.3% in the glimepiride group. The least squares mean change in HbA_{1c} from baseline was −1.49% and −0.71% in the sitagliptin-metformin and glimepiride groups, respectively. The between-group difference was −0.78% (95% CI, −0.96 to −0.59; P<0.001). Secondary: At 30 weeks, a higher proportion of patients in the sitagliptin-metformin group met the target HbA_{1c} goal compared with the glimepiride group (81.2% vs 40.1%; P<0.001; RR, 2.02). Treatment with sitagliptin-metformin provided a greater reduction (from baseline) in FPG compared with glimepiride (LS mean difference, − 23.5 mg/dL; P<0.001). Both drugs were generally well tolerated. Hypoglycemia events and weight gain were lower in patients with sitagliptin-metformin than with glimepiride (5.5% vs 20.1% and -0.83 vs +0.90 kg, respectively; both P<0.001). No serious drug-related adverse events or deaths were reported.
Schernthaner et al.[76] (2015) EUREXA TZD or glimepiride added to metformin plus exenatide twice daily vs	MC, OL, RCT Patients with type 2 diabetes with metformin failure (HbA_{1c} ≥6.5 to ≤9.0%), were 19 to 85 years of age, and had a BMI of ≥25 to ≤40 kg/m^2	N=310 Median duration of 2 years	Primary: Changes in HbA_{1c}, BMI, lipids, hypoglycemia, and vital signs Secondary: Not reported	Primary: Significant changes from baseline in HbA_{1c} were observed at 52, 78, 104 and 130 weeks with add-on TZD (all P<0.01), but only at 52 weeks with add-on glimepiride (P=0.001). Significant between-group differences favoring add-on TZD were observed at 78 (P=0.004) and 130 weeks (P=0.001). Among patients re-randomized to add-on glimepiride and add-on TZD, HbA_{1c} ≤7.0% was achieved by 26.0 and 30.7%, respectively, and HbA_{1c}

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
exenatide twice daily added to metformin plus glimepiride				≤6.5% by 8.2 and 9.3%, respectively (no significant differences between the randomized groups). BMI significantly increased from baseline at 52, 78, 104 and 130 weeks with add-on TZD (all P≤0.01), but significantly increased at 52 and 78 weeks (both P<0.05) and decreased at 130 weeks with add-on glimepiride; the between-group difference was significant at 104 (P=0.022) and 130 weeks (P=0.008). HDL cholesterol significantly increased from baseline to 130 weeks in the TZD add-on group (P<0.001), but not in the add-on glimepiride group; the between-group difference significantly favored TZD (P<0.001). For total and LDL cholesterol, there were no significant within- or between-group changes from baseline to 130 weeks. Systolic blood pressure was significantly increased at 130 weeks with add-on TZD (P=0.043), but not with add-on glimepiride; the between-group difference significantly favored glimepiride (P=0.044). The incidence of any hypoglycemia and nocturnal, non-nocturnal and documented symptomatic hypoglycemia with blood glucose ≤70 mg/dl was significantly higher for glimepiride than TZD as add-on to exenatide plus metformin. Although the proportion of patients reporting documented symptomatic hypoglycemia with blood glucose <50 mg/dl was similar in the add-on glimepiride (1/74; 1.4%) or TZD (1/76; 1.3%) groups, the exposure-adjusted mean rate/year was higher in the glimepiride group (0.10 vs 0.01 events/year of patient exposure). Secondary: Not reported
GRADE Study Research Group[77] (2022) Insulin glargine U-100 administered daily at an initial	MC, PG, RCT Participants with type 2 diabetes of less than 10 years' duration who were receiving metformin	N=5,047 5 years	Primary: Cumulative incidence of a glycated hemoglobin level of 7.0% or higher	Primary: Over the mean 5-year follow-up, 71% of the cohort had a primary metabolic outcome event, with the highest frequency in the sitagliptin group (77%), intermediate frequency in the glimepiride group (72%), and the lowest frequency in the liraglutide (68%) and glargine (67%) groups. The between-group differences in the Kaplan–Meier estimates of the cumulative

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
dose of up to 20 U and adjusted according to glucose levels vs glimepiride, increased from 1 to 2 mg to a maximum of 8 mg per day, administered in divided doses and adjusted according to glucose levels vs liraglutide initiated at a dose of 0.6 mg, with escalation to a maximum dose of 1.8 mg daily, depending on gastrointestinal side effects vs sitagliptin at a dose of 100 mg, with the dose adjusted according to kidney function	and had glycated hemoglobin levels of 6.8 to 8.5%		Secondary: Cumulative incidence of a glycated hemoglobin level of 7.5% or higher	incidence of a primary-outcome event were significant (P<0.001 by the log-rank test). Secondary: The differences among the groups with respect to a glycated hemoglobin level greater than 7.5% (the secondary outcome) paralleled those of the primary outcome. A secondary-outcome event occurred in 55% of the participants in the sitagliptin group over a mean follow-up of 5 years, followed by glimepiride (in 50%), liraglutide (in 46%), and glargine (in 39%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Metformin was supplied to all the participants				
GRADE Study Research Group[78] (2022) Insulin glargine U-100 administered daily at an initial dose of up to 20 U and adjusted according to glucose levels vs glimepiride, increased from 1 to 2 mg to a maximum of 8 mg per day, administered in divided doses and adjusted according to glucose levels vs liraglutide initiated at a dose of 0.6 mg, with escalation to a maximum dose of 1.8 mg daily, depending on gastrointestinal side effects	MC, PG, RCT Participants with type 2 diabetes of less than 10 years' duration who were receiving metformin and had glycated hemoglobin levels of 6.8 to 8.5%	N=5,047 5 years	Primary: Hypertension and dyslipidemia, confirmed moderately or severely increased albuminuria or an estimated glomerular filtration rate of less than 60 ml/min/1.73 m^2, diabetic peripheral neuropathy, cardiovascular events (major adverse cardiovascular events [MACE], hospitalization for heart failure, or an aggregate outcome of any cardiovascular event), and death Secondary: Not reported	Primary: There were no material differences among the interventions with respect to the development of hypertension or dyslipidemia or with respect to microvascular outcomes; the mean overall rate (i.e., events per 100 participant-years) of moderately increased albuminuria levels was 2.6, of severely increased albuminuria levels 1.1, of renal impairment 2.9, and of diabetic peripheral neuropathy 16.7. The treatment groups did not differ with respect to MACE (overall rate, 1.0), hospitalization for heart failure (0.4), death from cardiovascular causes (0.3), or all deaths (0.6). There were small differences with respect to rates of any cardiovascular disease, with 1.9, 1.9, 1.4, and 2.0 in the glargine, glimepiride, liraglutide, and sitagliptin groups, respectively. When one treatment was compared with the combined results of the other three treatments, the hazard ratios for any cardiovascular disease were 1.1 (95% confidence interval [CI], 0.9 to 1.3) in the glargine group, 1.1 (95% CI, 0.9 to 1.4) in the glimepiride group, 0.7 (95% CI, 0.6 to 0.9) in the liraglutide group, and 1.2 (95% CI, 1.0 to 1.5) in the sitagliptin group. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs sitagliptin at a dose of 100 mg, with the dose adjusted according to kidney function Metformin was supplied to all the participants				
Bao et al.[79] (2010) Glipizide XL vs glipizide XL plus acarbose	AC, OL, RCT Newly diagnosed type 2 diabetics, 30 to 70 years of age, with HbA_{1c} 7.0 to 9.8%, and no prior use of antidiabetic medications	N=40 8 weeks	Primary: Glycemic control, improvements in insulin secretion and sensitivity, glycemic variability, hypoglycemia Secondary: Not reported	Primary: After eight weeks, FPG, two-hour post-oral glucose tolerance test plasma glucose, mean blood glucose, HbA_{1c}, glycated albumin, and HOMA-IR were significantly decreased with both treatments. HOMA-B increased significantly compared to baseline (P<0.01 for both). Compared to glipizide XL, combination therapy had significantly lower mean blood glucose and HOMA-IR values after eight weeks (P<0.05 for both). Mean changes in mean blood glucose, HbA_{1c}, and glycated albumin were all greater with combination therapy compared to monotherapy, with only differences in mean blood glucose reaching significant. The overall glucose-lowering and -stabilizing effects were more pronounced with combination therapy. Over the duration of the trial, the decreases in mean amplitude of glycemic excursions and $AUC_{postprandial\ incremental}$ were significant with both treatments (P<0.01). There was also a significant decrease in mean of daily differences with combination therapy compared to baseline (P<0.01). Patients receiving combination therapy had significantly lower mean of daily differences, mean amplitude of glycemic outcomes, and $AUC_{postprandial\ incremental}$ values compared to patients receiving monotherapy after eight weeks (P<0.05 for all). There were no significant between-group differences in either the frequency or the duration of hypoglycemia. The mean duration of hypoglycemia was 88.8±84.7 minute per event with monotherapy and 176.3±123.5 minute per event with combination therapy (P=0.114). Patients receiving monotherapy had 0.7±0.4 events per day compared to 0.8±0.4 events per day in patients

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				receiving combination therapy (P=0.612). There was no difference in total instances of severe hypoglycemia reported. Secondary: Not reported
Rosenstock et al.[80] (2013) Alogliptin 25 mg QD vs glipizide 5 mg (titrated to 10 mg if needed)	AC, DB, PRO, RCT Patients aged 65 to 90 years of age with type 2 diabetes on diet and exercise therapy alone during the 2 months prior to screening with HbA_{1c} level of 6.5 to 9.0% or on oral antidiabetic monotherapy with HbA_{1c} of 6.5 to 8.0%	N=441 52 weeks	Primary: HbA_{1c} changes at week 52 from baseline. Secondary: Changes from baseline in HbA_{1c} at all time points, changes in FPG, 2-hour PPG, weight and lipid changes, and adverse events	Primary: Glycemic control with alogliptin was comparable to that with glipizide, with no statistically significant treatment-group differences for any of the corresponding efficacy endpoints. Secondary: Treatment with alogliptin resulted in modest body weight decreases throughout the study, which were significant when compared with the increases observed with glipizide, −0.62 vs 0.60 kg, respectively, by week 52 (P<0.001). Triglycerides also significantly improved with alogliptin (8.0% decrease) compared with glipizide (1.2% increase; P=0.046), whereas no significant differences were noted for total cholesterol (0.4 vs 0.3% decrease), high-density lipoprotein cholesterol (1.7 vs 0.6% increase) or low-density lipoprotein cholesterol (0.8% increase vs 1.3% decrease). Fewer patients discontinued from alogliptin because of adverse events (8.6 vs 12.3% from glipizide).
Del Prato et al.[81] (2014) Alogliptin 12.5 mg QD vs alogliptin 25 mg QD vs glipizide 5 mg QD, titrated to a maximum of 20 mg	DB, MC, RCT Patients 18 to 80 years of age with type 2 diabetes inadequately controlled on stable-dose metformin	N=2,639 104 weeks	Primary: Mean change from baseline in HbA_{1c} Secondary: Changes over time in HbA_{1c} and FPG, incidence of clinical response (HbA_{1c} ≤6.5 and ≤7.0%), changes in body weight, incidence of hyperglycemic	Primary: From baseline HbA_{1c} values of 7.6% in all three treatment groups, changes up to weeks 52 and 104 showed sustained glycemic response. In the analysis of mean differences between the treatment groups at week 104, the criteria for non-inferiority to glipizide were satisfied for both alogliptin 12.5 mg (P<0.001) and alogliptin 25 mg (P<0.001), and the criteria for superiority to glipizide were satisfied for alogliptin 25 mg (P=0.010). Secondary: FPG concentration decreased by 0.05 and 0.18 mmol/l for alogliptin 12.5 and 25 mg, respectively, and increased by 0.30 mmol/l for glipizide (P<0.001 for both comparisons with glipizide). Mean weight changes were −0.68, −0.89 and 0.95 kg for alogliptin 12.5 and 25 mg and glipizide, respectively (P<0.001 for both comparisons with glipizide). Hypoglycemia

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			rescue, and changes in 2-h PPG over time	occurred in 23.2% of patients in the glipizide group vs 2.5 and 1.4% of patients in the alogliptin 12.5 and 25 mg groups, respectively.
Del Prato et al.[82] (2015) Dapagliflozin vs glipizide Studied agent added on to OL dosed metformin.	DB, MC, RCT Patients with T2DM, ≥18 years of age, who were previously treated with oral anti-diabetic agents, inadequately controlled blood sugar, BMI ≤45 kg/m^2 and fasting C-peptide ≥0.34 ng/mL	N=801 4 year extension study	Primary: Therapeutic glycemic response defined as HbA_{1c} <7.0% Secondary: FPG, blood pressure, body weight, safety	Primary: At 208 weeks, dapagliflozin compared with glipizide produced sustained reductions in HbA_{1c}: −0.30% (95% CI, −0.51 to −0.09), in total body weight: −4.38 kg (95% CI, −5.31 to −3.46) and in systolic blood pressure: −3.67 mmHg (95% CI, −5.92 to −1.41). Secondary: Dapagliflozin was not associated with glomerular function deterioration, while this occurred more frequently in patients in the glipizide group. Fewer patients reported hypoglycemia in the dapagliflozin compared with the glipizide group (5.4 vs 51.5%). Genital and urinary tract infections were more common with dapagliflozin than with glipizide, but their incidence decreased with time and all events responded well to antimicrobial treatment.
Goldstein et al.[83] (2003) Glipizide 15 mg BID vs metformin 500 to 2,000 mg daily vs glipizide/ metformin 5/500 mg daily (dose titrated up to 4 tablets per day)	DB, MC, PG, RCT Patients with type 2 diabetes and inadequate glucose control (HbA_{1c} 7.5 to 12.0%) despite monotherapy with at least half the maximum labeled daily dose of a sulfonylurea, FPG <300 mg/dL, and BMI ≥25 to ≤40 kg/m^2	N=247 18 weeks	Primary: Change in HbA_{1c} Secondary: Changes in FPG, three-hour PPG, area under the concentration-time curve (AUC), three-hour postprandial insulin incremental AUC during three hours after a standard test meal, fasting insulin level, serum lipid profiles, body weight	Primary: The decreases in HbA_{1c} were significantly greater in the glipizide/metformin group compared to either of the monotherapy groups (P<0.001). A total of 36.6% of patients receiving glipizide/metformin, 8.9% of patients receiving glipizide, and 9.9% of patients receiving metformin had an HbA_{1c} <7.0% at the final visit. Secondary: Combination therapy reduced the FPG from baseline significantly more compared to glipizide and metformin monotherapies (P<0.001). Combination therapy controlled PPG more than metformin monotherapy or glipizide monotherapy, as measured using a three-hour incremental AUC (P=0.002, and P<0.001, respectively). The postprandial insulin three-hour incremental AUC increased from baseline with combination therapy, and decreased with glipizide monotherapy; the differences between these groups were not significant. There was a decrease in the postprandial insulin AUC in the metformin monotherapy group, which was significant (P<0.001 vs combination group).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Fasting insulin decreased in the combination therapy group and in the metformin monotherapy group. Fasting insulin increased in the glipizide monotherapy group. The changes in the combination therapy group did not differ significantly from either monotherapy group. There were decreases in body weight in all groups, -0.3 kg with the combination therapy group, -0.4 kg with the glipizide monotherapy group, and -2.7 kg in the metformin monotherapy group. The changes in the metformin monotherapy group were significant compared to the combination therapy group (P<0.001). There were no significant changes in the fasting lipid profile in the combination group or metformin monotherapy group. There were significant increases from baseline in TC and TG in the glipizide monotherapy group.
Göke et al.[84] (2013) Saxagliptin 5 mg/day vs glipizide 5 to 20 mg/day Both treatments as an add-on to metformin	AC, DB, MC, RCT Adults with type 2 diabetes and inadequate glycemic control on metformin alone (HbA_{1c} > 6.5 to 10%)	N=858 52 week initial phase followed by 52 week extension phase	Primary: Non-inferiority in mean change from baseline HbA_{1c}, safety and tolerability Secondary: Not reported	Primary: Improvement in HbA_{1c} at week 104 was similar with saxagliptin + metformin and glipizide + metformin. At week 104, the adjusted mean ±SE change from baseline HbA_{1c} was -0.41±0.04% with saxagliptin + metformin and -0.35±0.04% with glipizide + metformin [a between-group difference of -0.05% (95% CI, -0.17 to 0.06%)]. Over the course of the 104-week study, 896 hypoglycemic events were reported in 165 patients (38.4%) in the glipizide + metformin group, and 24 hypoglycemic events were reported in 15 patients (3.5%) in the saxagliptin + metformin group (difference, -34.9%; 95% CI for difference, -39.8 to -30.0%). Most of these events occurred during the initial 52 weeks. Over the course of the study, mean body weight decreased in the saxagliptin + metformin group and increased in the glipizide + metformin group. Secondary: Not reported
Garber et al.[85] (2002)	DB, MC, PC, PG, RCT	N=806 20 weeks	Primary: Change in HbA_{1c} Secondary:	Primary: Patients in both glyburide/metformin groups had significantly greater mean reduction from baseline HbA_{1c} (level of 8.2%) compared to the placebo group (P<0.001). The reductions in HbA_{1c} from baseline for each

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Glyburide 2.5 mg daily vs metformin 500 mg daily vs glyburide/ metformin 1.25/250 mg daily vs glyburide/ metformin 2.5/500 mg daily vs placebo Doses were titrated to a maximum of 4 tablets per day.	Patients with type 2 diabetes with inadequate glycemic control with diet and exercise, HbA_{1c} >7.0%, normal renal and liver function, and a BMI ≤38 kg/m^2		Changes in FPG, two-hour PPG, fasting and two-hour insulin levels, serum lipid concentrations, body weight	glyburide/metformin group were significantly greater than the placebo or metformin groups (P<0.001). The reduction in HbA_{1c} in the glyburide/metformin 1.25/250 mg group was significantly greater compared to the glyburide group (P<0.016), and for the glyburide/metformin 2.5/500 mg group compared to the glyburide group (P<0.004). Sixty-six percent of the patients in the glyburide/metformin 1.25/250 mg group (P=0.006 vs metformin) and 72% of the patients in the glyburide/metformin 2.5/500 mg group (P<0.001 vs metformin, P=0.037 vs glyburide) had achieved an HbA_{1c} <7.0% compared to 60% of the patients in the glyburide group, 50%of patients in the metformin group, and 20% of patients in the placebo group. Secondary: Mean decreases in FPG concentrations were significantly greater for both combination groups compared to the placebo (P<0.001) and metformin groups (P<0.001). Mean decreases in FPG were numerically greater in both combination groups compared to the glyburide group, but the differences were not significant. Glyburide/metformin 1.25/250 mg group, glyburide/metformin 2.5/500 mg group, and the glyburide group had modest changes in body weight of 1.4, 1.9, and 1.7 kg, respectively, compared to 0.7 and 0.6 kg mean decrease in patients receiving placebo and metformin, respectively. The mean changes in body weight for the glyburide/metformin groups and the glyburide group were significantly different from placebo. There were no significant changes seen in TC, LDL-C, or HDL-C, and TGs with any treatment.
Marre et al.[86] (2002) Glyburide 5 mg daily vs	DB, MC, PG, RCT Patients >18 years of age with type 2 diabetes with a FPG ≥126 mg/dL despite treatment with monotherapy	N=411 16 weeks	Primary: Change in HbA_{1c} Secondary: Changes in FPG, fructosamine levels	Primary: Mean HbA_{1c} levels improved in all groups. There were significantly greater reductions in the patients receiving combination therapy as compared to either monotherapy (P<0.05). There were no significant differences in the amount of the reductions in the HbA_{1c} between the two combination therapies or the two monotherapies.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
metformin 500 mg daily vs glyburide/ metformin 2.5/500 mg daily vs glyburide/ metformin 5/500 mg daily Doses were titrated to a maximum of 4 tablets per day.	metformin ≥850 mg BID or ≥500 mg TID, diet, and exercise for 2 months prior to enrollment, and BMI <40 kg/m^2			Seventy-five percent of the glyburide/metformin 2.5/500 mg group and 63.8% of the glyburide/metformin 5/500 mg group achieved an HbA_{1c} <7.0% as compared to the metformin (37.6%) or glyburide (41.9%) groups (P=0.001 for both). Secondary: FPG decreased in all groups. There were significant improvements in both the combination groups compared to either monotherapy (P<0.05). There were no significant differences in effects on FPG between either of the combination therapies or the monotherapies. Mean decreases in fructosamine in both combination groups were significantly greater (P<0.05) compared to the changes seen in the monotherapy groups.
DeFronzo et al.[87] (1995) <u>Protocol 1:</u> Metformin 850 to 2,550 mg daily vs placebo <u>Protocol 2:</u> Glyburide 5 to 10 mg BID vs metformin 500 to 2,500 mg daily	2 DB, PG, RCT Moderately obese patients with type 2 diabetes inadequately controlled by diet (Protocol 1) or diet plus glyburide (Protocol 2)	<u>Protocol 1</u> N=289 29 weeks <u>Protocol 2</u> N=632 29 weeks	Primary: Changes in plasma glucose, HbA_{1c}, plasma insulin, lipids, plasma lactate Secondary: Not reported	Primary: <u>Protocol 1:</u> As compared to the placebo group, the metformin group had lower mean FPG concentrations (189±5 vs 244±6 mg/dL; P<0.001). HbA_{1c} levels were also lower in the metformin group (7.1±0.1 vs 8.6±0.2%; P<0.001). The changes from baseline for TC and LDL-C for metformin were significant compared to placebo (P=0.001 and P=0.019, respectively). Fasting plasma lactate levels were similar at all times during the active-treatment in both groups. <u>Protocol 2:</u> Patients in the metformin plus glyburide combination group, compared to the glyburide alone group, had lower mean FPG concentrations (187±4 vs 261±4 mg/dL; P<0.001), and HbA_{1c} values (7.1±0.1 vs 8.7±0.1%; P<0.001). The effect of metformin alone was similar to that of glyburide alone.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs glyburide plus metformin				The changes from baseline were significant compared to glyburide for the following: TC, metformin (P=0.011) and metformin plus glyburide (P=0.001); LDL-C, metformin (P=0.009) and metformin plus glyburide (P=0.001); and TG, each glyburide and metformin plus glyburide (P=0.001) Fasting plasma lactate did not change in any of the groups in the course of treatment. Secondary: Not reported
Chien et al.[88] (2007) Glyburide 5 mg BID vs metformin 500 mg BID vs glyburide/ metformin 2.5/500mg BID vs glyburide/ metformin 5/500 mg BID Doses were titrated to a maximum of 4 tablets per day.	DB, MC, PG, RCT Patients 30 to 75 years of age with type 2 diabetes, BMI 18.5 to 35.0 kg/m^2, FPG 140 to 250 mg/dL, and HbA_{1c} 7.0 to 12.0% at the screening visit and FPG ≥140 mg/dL at the second visit, maintained stable sulfonylurea regimen, with or without metformin use	N=100 16 weeks	Primary: Change in baseline HbA_{1c} Secondary: Change in baseline FPG, adverse events	Primary: After 16 weeks, the HbA_{1c} increased in patients receiving glyburide (0.52%; P=0.0018) and there was no change in patients receiving metformin (0.09%; P value not significant). After 16 weeks, treatment with glyburide/metformin 2.5/500 mg resulted in a greater reduction in HbA_{1c} compared to glyburide or metformin (-1.77%; P<0.001 and -1.34%; P=0.002). Treatment with glyburide/metformin 5/500 mg resulted in a greater reduction in HbA_{1c} compared to glyburide or metformin alone (-1.73%; P<0.001 and -1.30%; P=0.005). After 16 weeks, 19 and 24% of patients in the glyburide/metformin groups (2.5/500 mg and 5/500 mg, respectively) had an HbA_{1c} <7.0% compared to 12.0% in the metformin monotherapy group and 6% in the glyburide monotherapy group. Secondary: Mean changes in FPG from baseline were -43 mg/dL in the glyburide group, -41 mg/dL in the metformin group, -98 mg/dL in the glyburide/metformin 2.5/500mg group, and -101 mg/dL in the glyburide/metformin 5/500 mg group. The two glyburide/metformin groups had significant reductions from baseline compared to the monotherapy groups (P<0.0125 compared to glyburide and metformin). Treatment with glyburide/metformin 2.5/500 mg resulted in a 55 mg/dL reduction in FPG compared to glyburide (P=0.001) and a 57 mg/dL reduction in FPG compared to metformin (P=0.001). Treatment with

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				glyburide/metformin 5/500 mg resulted in a in a 58 mg/dL reduction in FPG compared to glyburide (P<0.001) and a 60 mg/dL reduction in FPG compared to metformin (P=0.001). Ninety-eight episodes of adverse events were reported from the screening visit to the end of the study. Four (14.3%) patients reported adverse events associated with hypoglycemia in the glyburide/metformin 2.5/500 mg group, and two (8.3%) patients reported adverse events associated with gastrointestinal disease among all patients who took metformin during the entire course of the study. The highest incidence of gastrointestinal adverse effects was 32.0% in metformin group, and the lowest was 7.7% in the glyburide/metformin 2.5/500 mg group (P=0.021).
Lewin et al.[89] (2007) Glyburide 15 mg QD and metformin XR (Glumetza®) 1,500 mg QD, 2,000 mg QD, or 1,000 mg BID vs glyburide 15 mg QD	DB, MC, RCT Type 2 diabetic patients 18 to 79 years of age, drug naïve or previously treated with oral antidiabetic medications (monotherapy with any oral antidiabetic medications up to half the maximum therapeutic dose), HbA_{1c} 7.5 to 12.0% in drug-naïve patients or 6.5 to 12.0% in prior drug treatment patients, FPG 200 to 400 mg/dL (drug naïve patients) or 120 to 250 mg/dL (prior drug treatment patients) and C-	N=607 30 weeks	Primary: Change baseline HbA_{1c} Secondary: Changes in HbA_{1c} and FPG at week eight, fructosamine, TC, HDL-C, LDL-C, TG, weight, BMI, discontinuation rates, adverse events	Primary: There were significant reductions in HbA_{1c} from baseline to week 30 in all combined metformin and sulfonylurea groups compared to the sulfonylurea monotherapy group (-0.74 vs 0.08%, respectively; P<0.001). Secondary: There were significant reductions from baseline in mean FPG and in mean HbA_{1c} at week eight in all combined metformin and sulfonylurea groups compared to the sulfonylurea monotherapy group (P<0.001). There were significant differences between the combined metformin and sulfonylurea groups and the monotherapy group for mean changes in fructosamine, TC, HDL-C, and LDL-C (P<0.001 for all). There were significant increases from baseline in mean weight and BMI in the monotherapy sulfonylurea group (P<0.001). In comparison, there was no significant change in weight and a smaller increase in mean BMI in the combined metformin and sulfonylurea groups (P=0.028). There was a significant difference in the rates of hypoglycemia between groups, which were 11.6% in the combined metformin and sulfonylurea groups and 4.2% in the monotherapy sulfonylurea group (P=0.007). However, no significant difference between these two groups was observed for gastrointestinal events.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	peptide levels >0.8 ng/mL			Forty patients (9.3%) in the combined metformin and sulfonylurea groups and three patients (2.1%) in the monotherapy sulfonylurea group discontinued treatment due to an adverse event, mainly hypoglycemia (P=0.001).
Nauck et al.[90] (2009) LEAD-2 Liraglutide 0.6, 1.2, and 1.8 mg SC QD vs placebo vs glimepiride 4 mg/day All patients also received metformin 1,500 to 2,000 mg/day.	AC, DB, DD, MC, PG, RCT Type 2 diabetic patients 18 to 80 years of age with HbA_{1c} 7.0 to 11.0% (pre-trial oral glucose lowering agent monotherapy ≥3 months) or 7.0 to 10.0% (pre-trial oral glucose lowering agent combination therapy ≥3 months), and BMI ≤40 kg/m2	N=1,091 26 weeks	Primary: Change in baseline HbA_{1c} Secondary: Changes in baseline body weight, FPG, seven-point self-monitored glucose concentrations, and β cell function	Primary: HbA_{1c} decreased by -0.7±0.1% with liraglutide 0.6 mg, -1.0±0.1% with liraglutide 1.2 and 1.8 mg, and increased by 0.1±0.1% with glimepiride and placebo. Based on the estimated treatment differences, liraglutide had more efficacious glycemic control compared to placebo (liraglutide 0.6 mg vs placebo, -0.8%; 95% CI, -1.0 to -0.6 and liraglutide 1.2 and 1.8 mg vs placebo, -1.1%; 95% CI, -1.3 to -0.9; P values not reported). Analysis of the estimated treatment difference in HbA_{1c} between liraglutide and glimepiride demonstrated that liraglutide 1.2 and 1.8 mg were noninferior to treatment with glimepiride. Secondary: Weight loss was dose-dependent with liraglutide (liraglutide 0.6 mg, -1.8±0.2 kg; liraglutide 1.2 mg, -2.6±0.2 kg; liraglutide 1.8 mg, -2.8±0.2 kg). Reductions in weight with liraglutide were significantly different compared to glimepiride (-1.0±0.2 kg; P<0.001). Weight loss with liraglutide 1.2 and 1.8 mg was significantly greater compared to placebo (1.5±0.3 kg; P≤0.01). Decreases in FPG with liraglutide (-1.1, -1.6, and -1.7 mmol/L with liraglutide 0.6, 1.2, and 1.8 mg) were significantly greater compared to the increase with placebo (0.4 mmol/L; P<0.0001). Decreases with liraglutide were similar to glimepiride (-1.3 mmol/L; P value not reported). Mean baseline PPG values decreased with all liraglutide doses and glimepiride (liraglutide 0.6 mg, -1.7 mmol/L; liraglutide 1.2 mg, -2.3 mmol/L; liraglutide 1.8 mg, -2.6 mmol/L; glimepiride, -2.5 mmol/L; placebo, -0.6 mmol/L; P<0.001 for comparisons of all liraglutide doses vs placebo). The decreases observed with liraglutide 1.2 and 1.8 mg were comparable to glimepiride (P values not reported). No differences in the fasting C-peptide values were observed between liraglutide and glimepiride or placebo (P values not reported).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Decreases in the proinsulin: insulin ratio with all three liraglutide doses (-0.1) were comparable to glimepiride (P value not reported), and were significantly greater compared to placebo (0.1; P<0.0001). Liraglutide 0.6, 1.2, and 1.8 mg had improvements in HOMA-B of 63, 70, and 71%. Glimepiride had similar improvements, and there were no improvements with placebo. No differences were observed between any of the treatments (P values not reported).
Marre et al.[91] (2009) LEAD-1 Liraglutide 0.6, 1.2, and 1.8 mg SC QD plus glimepiride 2 to 4 mg/day and placebo vs placebo plus glimepiride 2 to 4 mg/day vs placebo plus glimepiride 2 to 4 mg/day and rosiglitazone 4 mg/day	AC, DB, DD, MC, PG, RCT Type 2 diabetic patients 18 to 80 years of age treated with an oral glucose-lowering agent for ≥3 months, HbA_{1c} 7.0 to 11.0% (previously on oral glucose lowering agent monotherapy) or 7.0 to 10.0% (previously on oral glucose lowering agent combination therapy), and BMI ≤45 kg/m^2	N=1,041 26 weeks	Primary: Change in baseline HbA_{1c} Secondary: Proportion of patients reaching HbA_{1c} (<7.0 and ≤6.5%), FPG (5.0 to ≤7.2 mmol/L), and PPG (10.0 mmol/L) targets; change in baseline body weight, FPG, mean PPG, β cell function, and BP	Primary: After 26 weeks, HbA_{1c} decreased by -1.1% with both liraglutide 1.2 and 1.8 mg, respectively, compared to placebo (0.2%) and rosiglitazone (-0.4%). Estimated treatment differences compared to placebo were: liraglutide 1.8 mg, -1.4% (95% CI, 1.6 to -1.1; P<0.0001); liraglutide 1.2 mg, -1.3% (95% CI, 1.5 to -1.1; P<0.0001); liraglutide 0.6 mg, -0.8% (95% CI, -1.1 to -0.6; P<0.0001); and rosiglitazone, -0.7% (95% CI, -0.9 to -0.4; P<0.0001). Additionally, the two higher doses of liraglutide (1.2 and 1.8 mg) were more efficacious compared to treatment with rosiglitazone (P<0.0001 for both measures). Decreases in HbA_{1c} were greater in patients previously on an oral glucose lowering agent monotherapy. Secondary: The proportion of patients reaching HbA_{1c} targets with liraglutide was dose-dependent. At week 26, 42, and 21% of patients receiving liraglutide 1.8 mg reached HbA_{1c} <7.0 and ≤6.5% compared to 8 and 4% of patients receiving placebo. Estimated proportions of patients receiving liraglutide 1.2 and 1.8 mg reaching HbA_{1c} targets were greater compared to patients receiving placebo (P<0.0001) and rosiglitazone (P<0.0003), respectively. More patients reached <7.0% with liraglutide 1.8 mg compared to 1.2 mg (P=0.018). The proportions of patients achieving FPG targets were significantly greater with liraglutide 0.6 mg (19%; P=0.002), 1.2 mg (37%; P<0.001), and 1.8 mg (38%; P=0.002) compared to placebo (7%). Compared to patients receiving rosiglitazone (26%), significantly more patients receiving liraglutide 1.2 and 1.8 mg achieved FPG targets (P=0.007 and P=0.01, respectively).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The proportion of patients with one, two, or three PPG target measurements were significantly greater for all doses of liraglutide compared to placebo (P<0.05), but not rosiglitazone (P value not reported). Mean decreases in weight were -0.2 kg with liraglutide 1.8 mg and -0.1 kg with placebo. Mean increases in weight were 0.7 kg with liraglutide 0.6 mg, 0.3 kg with liraglutide 1.2 mg, and 2.1 kg with rosiglitazone. Differences between rosiglitazone and liraglutide were significant (P<0.0001), although there were no differences compared to placebo (P value not reported). Decreases in the proinsulin:insulin ratio were significantly greater with liraglutide 1.2 and 1.8 mg compared to rosiglitazone and placebo (P≤0.02). HOMA-B increased with liraglutide 1.2 and 1.8 mg compared to rosiglitazone (P<0.05), and increases were only significant compared to placebo with liraglutide 1.2 mg (P=0.01). No differences between treatments were observed for changes in HOMA-IR. Decreases in SBP with liraglutide 1.2 and 1.8 mg (-2.6 to -2.8 mm Hg) were not different compared to placebo or rosiglitazone (-0.9 to -2.3 mm Hg; P values not reported).
Chacra et al.[92] (2010) Glyburide 7.5 to 15 mg daily and saxagliptin 2.5 mg QD vs glyburide 7.5 to 15 mg daily and saxagliptin 5 mg QD vs	DB, MC, RCT Type 2 diabetics 18 to 77 years of age with inadequate glycemic control (HbA_{1c} ≥7.5 to ≤10.0%), on a submaximal sulfonylurea dose for ≥2 months before screening, fasting C-peptide ≥1 ng/mL, and BMI ≤40 kg/m^2	N=768 24 weeks	Primary: Change in baseline HbA_{1c} Secondary: Change in baseline FPG and PPG AUC_{0-3hr}, proportion of patients achieving an HbA_{1c} <7.0%, safety	Primary: Saxagliptin significantly decreased HbA_{1c} compared to placebo (-0.54 and -0.64 vs 0.08%; P<0.0001 for both). Secondary: Saxagliptin significantly decreased FPG compared to placebo (2.5 mg; P=0.0218 and 5 mg; P=0.002). Saxagliptin significantly decreased PPG AUC_{0-3hr} compared to placebo (-4,296 and -5,000 vs 1,196 (mg/minute)/(dL); P<0.0001 for both). A significantly greater proportion of patients receiving saxagliptin achieved an HbA_{1c} <7.0% compared to patients receiving placebo (22.4 and 22.8 vs 9.1%; P<0.0001 for both). Overall saxagliptin was well tolerated. The proportion of patients reporting any adverse event was similar across all treatments; with no evidence of a

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
glyburide 2.5 to 15 mg daily and placebo				dose-response relationship. The proportion of patients reporting at least one adverse event and at least one treatment-related adverse event was 75.0 and 19.8, 72.3 and 21.3, and 76.8 and 14.2% with saxagliptin 2.5 mg, saxagliptin 5 mg, and placebo. No events of Stevens-Johnson syndrome or angioedema were reported. Cardiac disorder events were: 2.0, 4.0 and 3.7% with saxagliptin 2.5 mg, saxagliptin 5 mg, and placebo. Hypertension was reported in 3.6, 6.3, and 2.2% with saxagliptin 2.5 mg, saxagliptin 5 mg, and placebo; however, mean SBP and DBP decreased with all treatments. There was no difference in the incidence of reported and confirmed hypoglycemic events with saxagliptin compared to placebo (P>0.05). Confirmed hypoglycemia occurred in 2.4, 0.8, and 0.7% of patients receiving saxagliptin 2.5 mg, saxagliptin 5 mg, and placebo.
Goke et al.[93] (2010) Saxagliptin 5 mg/day vs glipizide 5 mg/day, titrated up to 20 mg/day	DB, NI, RCT Patients ≥18 years of age with type 2 diabetes with type 2 diabetes, HbA_{1c} >6.5 to 10.0%, and inadequate glycemic control on metformin alone	N=858 52 weeks	Primary: Change in baseline HbA_{1c} Secondary: Hypoglycemia, safety	Primary: The per protocol analysis demonstrated non-inferiority of saxagliptin vs glipizide; adulated mean changes from baseline HbA_{1c} were -0.74 vs -0.80%, respectively; the between-group difference was 0.06% (95% CI, -0.05 to 0.16). There was a significantly smaller risk in HbA_{1c} (%/week) from week 24 to 52 with saxagliptin vs glipizide (0.001 vs 0.004%; *P*=0.04) indicating a sustained glycemic effect beyond week 24. Secondary: Treatment with saxagliptin vs glipizide was associated with a significantly smaller proportion of patients with hypoglycemic events (3.0 vs 36.3%; *P*<0.0001) and a divergent impact on body weight (adjusted mean change from baseline, -1.1 vs 1.1 kg; *P*<0.0001). Excluding hypoglycemic events, the proportion of patients reporting adverse events was smaller with glipizide (60.0 vs 56.7%); however, treatment-related adverse events were less common with saxagliptin (9.8 vs 31.2%), attributable to the higher frequency of hypoglycemia with glipizide. Discontinuation rates resulting from adverse events were similar (approximately 4%).
Arechavaleta et al.[94] (2011)	DB, NI, RCT	N=1,035 30 weeks	Primary: Change in baseline HbA_{1c}	Primary: After 30 weeks, the least squares mean change in HbA_{1c} from baseline was -0.47% with sitagliptin compared to -0.54% with glimepiride, with a

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Sitagliptin 100 mg/day vs glimepiride 1 mg/day, titrated up to 6 mg/day	Patients with type 2 diabetes, HbA_{1c} 6.5 to 9.0%, and on a stable dose of metformin (≥1,500 mg/day) combined with diet and exercise for ≥12 weeks		Secondary Proportions of patients achieving HbA_{1c} <7.0%, change in baseline FPG, hypoglycemia, body weight	between-group difference of 0.07% (95% CI, -0.03 to 0.16). This result met the prespecified criterion for declaring non-inferiority. Secondary: The proportions of patients with HbA_{1c} <7.0% at week 30 were 52 and 60% with sitagliptin and glimepiride, respectively. The least squares mean change in FPG from baseline was -0.8 mmol/L (95% CI, -1.0 to -0.6) with sitagliptin compared to -1.0 mmol/L (95% CI, -1.2 to -0.8) with glimepiride, for a between-group difference of 0.2 mmol/L (95% CI, -0.1 to 0.4). The proportions of patients who reported hypoglycemia were 7 and 22% with sitagliptin and glimepiride (percentage-point difference, -15; P<0.001). Relative to baseline, sitagliptin was associated with a mean weight loss compared to a mean weight gain with glimepiride (-0.8 vs 1.2 kg), yielding a between-group difference of -2.0 kg (*P*<0.001).
Srivastava et al.[95] (2012) Sitagliptin 50 mg/day, titrated up to 100 mg/day vs glimepiride 1 mg/day, titrated up to 2 mg/day	PG, RCT Patients with type 2 diabetes inadequately controlled with metformin alone	N=50 18 weeks	Primary: Change in baseline HbA_{1c} Secondary: Change in baseline FPG and two-hour PPG, body weight, hypoglycemia	Primary: At 18 weeks, both treatments significantly (*P*<0.001) reduced baseline HbA_{1c} (-0.636 vs -1.172%), with 12% of patients receiving sitagliptin and 36% of patients receiving glimepiride achieving target HbA_{1c}. Secondary: Reductions were significant (*P*<0.001) for both treatments in FPG (-15.49 vs -26.84 mg, respectively) and two-hour PPG (-34.28 vs -44.83 mg, respectively). Sitagliptin showed a net decrease in body weight by 0.102 kg, whereas glimepiride showed net increase in body weight by 0.493 kg. Incidence of hypoglycemia was 4 and 8% with sitagliptin and glimepiride.
Seck et al.[96] (2011) Sitagliptin	DB, RCT Patients with type 2 diabetes receiving metformin	N=803 1 year	Primary: Composite endpoint of HbA_{1c} reduction, lack of	Primary: Both treatments provided similar degrees of glycemic efficacy (least squares mean difference, -0.67%; between-group difference, -0.01; 95% CI, -0.09 to 0.08); however, significantly more patients receiving sitagliptin achieved an HbA_{1c} reduction >0.5% without hypoglycemia and without an increase in

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vs glimepiride			hypoglycemia, and no body weight Secondary: Not reported	body weight (least squares mean difference, -1.5 vs 1.1 kg; *P*<0.001; between-group difference, -2.5 kg; 95% CI, -3.1 to -2.0). Patients receiving glipizide reported more than 10 times as many events of hypoglycemia compared to patients receiving sitagliptin. Secondary: Not reported
Hermansen et al.[97] (2007) Sitagliptin 100 mg QD, glimepiride 4 to 8 mg daily, and metformin 1,500 to 3,000 mg daily vs sitagliptin 100 mg QD plus glimepiride 4 to 8 mg daily vs glimepiride 4 to 8 mg daily, metformin 1,500 to 3,000 mg daily, and placebo vs glimepiride 4 to 8 mg daily plus placebo	DB, DD, MC, PC, PG, RCT Type 2 diabetics 18 to 75 years of age, HbA_{1c} 6.7 to 10.6%, and inadequately controlled on glimepiride with or without metformin	N=441 24 weeks	Primary: Change in baseline HbA_{1c} Secondary: Change in baseline FPG, plasma lipids, β cell function, and insulin resistance; safety and tolerability	Primary: Sitagliptin significantly decreased HbA_{1c} (P<0.001) compared to placebo (treatment difference, -0.74%; 95% CI, -0.90 to -0.57). Patients who were receiving triple therapy (-0.89%; 95% CI, -1.10 to -0.68) had a significantly greater decrease in HbA_{1c} compared to patients receiving combination therapy (-0.57%; 95% CI, -0.82 to -0.32). A significantly greater proportion of patients receiving sitagliptin achieved an HbA_{1c} <7.0% compared to patients receiving placebo (17.1 vs 4.8%; P<0.001). A significantly greater proportion of patients receiving triple therapy achieved an HbA_{1c} <7.0% compared to patients receiving combination therapy with glimepiride plus metformin (22.6 vs 1.0%; P<0.001). No difference was observed between combination therapy with glimepiride plus sitagliptin compared to glimepiride (10.8 vs 8.7%; P<0.638). Secondary: Sitagliptin significantly decreased FPG compared to placebo (treatment difference, -20.1 mg/dL; 95% CI, -28.4 to -11.8; P<0.001). Sitagliptin demonstrated neutral effects on plasma lipids compared to placebo (specific figures not reported). A significant increase in HOMA-B was achieved with sitagliptin compared to placebo (11.3 [95% CI, 4.4 to 18.1] vs -0.7% [95% CI, -8.2 to 6.8]; P<0.001). There were no differences in fasting proinsulin, proinsulin:insulin ratio, HOMA-IR, and QUICKI between the treatments.

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				Sitagliptin significantly increased fasting insulin compared to placebo (1.8 vs 0.1 μIU/mL; P<0.001). Sitagliptin was well tolerated, both in combination with glimepiride and in triple therapy. There was a higher incidence of overall adverse events (difference of 8.0%; 95% CI, 2.2 to 13.9) observed with sitagliptin compared to placebo, with the majority of that difference due to rates of minor to moderate hypoglycemia. A significant increase in body weight of 0.8 kg (95% CI, 0.4 to 1.2) was noted with sitagliptin compared to a slight decrease in weight with placebo (-0.4 kg; 95% CI, -0.8 to 0.1).
Nauck et al.[98] (2007) Sitagliptin 100 mg QD vs glipizide 5 to 20 mg QD All patients received metformin ≥1,500 mg daily.	AC, DB, MC, NI, PG, RCT Patients 18 to 78 years of age with type 2 diabetes who were inadequately controlled (HbA_{1c} ≥6.5 and ≤10%) on metformin monotherapy	N=1,172 52 weeks	Primary: Change in baseline HbA_{1c} Secondary: FPG, fasting insulin, proinsulin, and lipid parameters, β-cell function, insulin resistance and sensitivity, safety and tolerability, change in body weight	Primary: In both treatments, the least squares mean HbA_{1c} change from baseline was -0.67% (95% CI, -0.75 to -0.59). A similar proportion of patients reached an HbA_{1c} level <7.0% in each group (63 vs 59%; difference, 3.9%; 95% CI, -2.8 to 10.7). Secondary: The change in FPG was not significantly different between the two treatments. The least squares change from baseline for sitagliptin was -0.56 mmol/L (95% CI, -0.81 to -0.30) and -0.42 mmol/L for glipizide (95% CI, -0.67 to -0.17). Sitagliptin led to a decrease in fasting proinsulin compared with an increase with glipizide. Patients receiving glipizide demonstrated a higher rate of hypoglycemia as compared to patients receiving sitagliptin (32 vs 5%; P<0.001). No meaningful differences in overall serious clinical adverse events were observed between the two treatments. Body weight significantly decreased with sitagliptin; the least squares mean change from baseline was -1.5 kg (95% CI, -2 to -0.9). Body weight significantly increased with glipizide with a least squares mean change from baseline of 1.1 kg (95% CI, 0.5 to 1.6). The between-treatment difference was -2.5 kg (95% CI, -3.1 to -2.0; P<0.001).
Schwarz et al.[99]	AC, DB, MC, RCT	N=69	Primary:	Primary:

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(2008) Glyburide 10 mg QD and metformin 2,000 mg QD vs metformin 2,000 mg QD and nateglinide 120 mg TID before meals	Men and women ≥65 years of age with type 2 diabetes, drug naïve, HbA_{1c} 7.0 to 11.0%, FPG ≤15 mmol/L, BMI 22 to 45 kg/m^2	104 weeks	Change in HbA_{1c} from baseline Secondary: Change from baseline to week 104 in FPG, two-hour PPG using the incremental area under the curve ($AUC_{0\text{-}120\ min}$) of glucose during oral glucose tolerance tests, the proportion of patients achieving a target HbA_{1c} <7.0 or ≤6.5%, adverse events	Similar reductions in HbA_{1c} were seen with both treatments. The average change in HbA_{1c} from baseline to week 104 in the nateglinide plus metformin group (–1.2±0.2%) was similar (P=0.310) to that in the glyburide plus metformin group (–1.2±0.1%). The changes in HbA_{1c} were significant for both groups as compared to baseline (P<0.001) after two years of treatment and there was no significant difference between the groups. Secondary: Mean change in FPG was –26 ±6 mg/dl in patients receiving nateglinide plus metformin (P<0.001 vs baseline) and –36±6 mg/dL in patients receiving glyburide plus metformin (P<0.001 vs baseline) (P=0.234 between the groups). A non-significant reduction in two-hour PPG from baseline was reported in both nateglinide plus metformin and glyburide plus metformin groups (–15±7 mg/dL; P=0.071 and –8±8 mg/dL; P=0.385, respectively). The proportion of patients who achieved a target HbA_{1c} <7.0% in the nateglinide plus metformin group was not significantly different compared to the glyburide plus metformin group (70 vs 65%, respectively; P=0.736). Similar proportions of patients in the nateglinide plus metformin group and the glyburide plus metformin group maintained a target HbA_{1c} ≤6.5% (40 and 60%, respectively; P=0.206). Approximately 94% of patients in the nateglinide plus metformin group and 88% of patients in the glyburide plus metformin group reported one or more adverse events. One mild hypoglycemic event occurred with nateglinide plus metformin treatment vs 8 mild-to-severe hypoglycemic events with glyburide plus metformin treatment (P<0.023).
Derosa et al.[100] (2009) Glyburide 7.5 to 12.5 mg daily and metformin 1,500 to 3,000 mg daily	MC, DB, PG, RCT Patients ≥18 years of age with type 2 diabetes mellitus, HbA_{1c} >7.0%), BMI 25 to 28 kg/m^2, and	N=248 12 months	Primary: Changes in BMI, FPG and PPG, HbA_{1c}, fasting and postprandial plasma insulin, HOMA index, and	Primary: BMI did not show any significant change during the study. A significant reduction in HbA_{1c} was shown after nine months (P<0.05) and 12 months (P<0.01) in the nateglinide group compared to the baseline value. A significant reduction in HbA_{1c} was seen with glyburide after 12 months

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vs nateglinide 60 mg TID and metformin 1,500 to 3,000 mg daily	hypertensive (SBP/DBP, >130/≥85 mm Hg)		lipid profile (TC, LDL-C, HDL-C, TG, apolipoprotein A-I, and apolipoprotein B), SBP, and DBP Secondary: Not reported	(P<0.05) compared to baseline. The HbA_{1c} at 12 months was 6.4% in the nateglinide group compared to 7.3% in the glyburide group (P<0.05). After nine and 12 months, mean FPG levels were significantly decreased in the nateglinide and glyburide groups (P<0.05 and P<0.01, respectively) compared to baseline. Significant changes in PPG were found at nine months (P<0.05) in the nateglinide group and after 12 months in glyburide and nateglinide groups (P<0.05 and P<0.01, respectively) compared to baseline. Fasting plasma insulin and PPI did not show any significant change after three, six, nine and 12 months in both groups compared to the baseline. HOMA index decrease was obtained only at 12 months (P<0.05) compared to the baseline value in both groups, No significant change was observed in TC, LDL-C, HDL-C, TG, apolipoprotein A-I, apolipoprotein B, SBP, DBP and heart rate in either group after three, six, nine and 12 months. Secondary: Not reported
Gerich et al.[101] (2003) Nateglinide 120 mg TID before meals and metformin 500 to 2,000 mg daily vs glyburide 1.25 to 10 mg daily and metformin 500 to 2,000 mg daily	DB, MC, RCT (PRESERVE-β Study) Men and women 18 to 77 years of age with type 2 diabetes, drug naïve, HbA_{1c} 7.0 to 11.0%, FPG ≤15 mmol/L, BMI 22 to 45 kg/m^2 and inadequately	N=428 104 weeks	Primary: Change in HbA_{1c} from baseline (average of weeks -2 and 0) to week 104 Secondary: Change from baseline to week 104 in FPG, and body weight	Primary: Both treatments maintained similar reductions in HbA_{1c}. The mean change in HbA_{1c} from baseline to week 104 in the nateglinide plus metformin group (–1.2±0.1%) was similar (P=0.1730) to that in the glyburide plus metformin group (–1.5±0.1%). The changes in HbA_{1c} were significant for both groups as compared to baseline (P<0.0001) after one and two years of treatment and there was no significant difference between the groups. Secondary: Mean change in FPG was –1.6±0.2 mmol/L in patients in the nateglinide plus metformin group (P<0.0001 vs baseline) and –2.4±0.2 mmol/L in patients in the glyburide plus metformin group (P<0.0001 vs baseline; P=0.0078 vs nateglinide plus metformin).

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	controlled on diet and exercise			Body weight decreased in the nateglinide plus metformin group (–0.4±0.4 kg) and increased in the glyburide plus metformin group (0.8±0.5 kg). The change from baseline was significant for the glyburide plus metformin group (P=0.0011) only (P=0.8413 for the nateglinide plus metformin group). The difference between groups was statistically significant (P=0.0115).
Wolffenbuttel et al.[102] (1999) Repaglinide 0.5 to 4 mg TID before each meal vs glyburide 1.75 to 10.5 mg daily	DB, MC, PG, RCT Patients 40 to 75 years of age with type 2 diabetes who were being treated with oral blood glucose-lowering agents and/or diet, BMI 21 to 35 kg/m^2, and an HbA_{1c} >6.5% when treated with diet only and <12.0% when treated with diet plus oral blood glucose-lowering agents	N=424 12 months	Primary: Change in HbA_{1c} and FPG from baseline to the final visit Secondary: Change in fasting insulin and lipid levels and four-point blood glucose levels (fasting, before lunch, before supper, and at bedtime) from baseline to the final visit	Primary: Change in HbA_{1c} levels was not different between groups when compared to baseline. HbA_{1c} levels increased by 0.58% (95% CI, 0.41 to 0.76) in the repaglinide group and by 0.45% (95% CI, 0.22 to 0.69) in the glyburide group. In a subset of patients who were treated previously with diet only, HbA_{1c} decreased significantly more during glyburide treatment (–2.4%) vs repaglinide (–1%; P<0.05). The changes in HbA_{1c} in patients who were already being treated with oral agents were similar, 0.6% in the repaglinide group and 0.7% in the glyburide group. Changes in fasting plasma glucose from baseline showed a similar trend as the HbA_{1c}. Secondary: Mean fasting insulin levels decreased in the repaglinide group (–3 pmol/L) and increased in the glyburide group (+1 pmol/L). There was no treatment difference. Changes from baseline in four-point glucose levels were small for both treatment groups. Lipid levels (TC, HDL, and TG) did not change during the study.
Cesur et al.[103] (2007) Repaglinide up to 4 mg QD vs	MC, OL, OS, PRO Patient 33 to 67 years of age with type 2 diabetes, HbA_{1c} 6.0 to 8.0% taking oral diabetes agents, who were	N=65 Duration not specified	Primary: FBG, PPG, HbA_{1c}, fructosamine, BMI, lipid metabolism and hypoglycemia in pre-Ramadan and	Primary: In the fasting group, both FPG and PPG levels showed no significant changes at post-Ramadan and one-month post-Ramadan compared to pre-Ramadan. In the nonfasting group, FPG levels did not change significantly throughout the study, whereas PPG levels increased at post-Ramadan (P<0.05 and P<0.01, respectively). At post-Ramadan and one-month post-Ramadan,

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glimepiride up to 8 mg QD vs insulin glargine up to 36 U QD	willing to fast throughout Ramadan month		post-Ramadan fasting Secondary: Not reported	changes in PPG values in the fasting group were lower compared to the nonfasting group (P<0.01 for both time periods). There was no significant change in HbA_{1c} levels between the nonfasting and fasting groups. There was a significant increase in fructosamine levels in both fasting group and non-fasting group at one-month post-Ramadan (P<0.01 for both). BMI did not change during the study in fasting group but a gradual increase in BMI was seen in the nonfasting group (P<0.05 between pre-Ramadan and post-Ramadan in nonfasting group). TC, LDL and TG did not change throughout the study period but HDL levels significantly increased at post-Ramadan in the fasting group (P<0.01). In nonfasting group, LDL and TG levels significantly increased at post-Ramadan (P<0.05 for both). At least one hypoglycemia episode was reported in 12.2% of patients in the fasting group and 12.5% of patients in the nonfasting group. Hypoglycemia was seen in 14.3% of patients in the glimepiride group, 11.1% in the repaglinide group and 10.0% in the insulin group. There was no significant difference between three drug groups regarding the rate of hypoglycemia. Secondary: Not reported
Standl et al.[104] (2001) Glyburide 3.5 to 5 mg BID to QID, metformin 500 to 850 mg daily, and miglitol 25 mg to 100 mg TID vs	DB, MC, PC, PG, RCT Patients 30 to 70 years of age with type 2 diabetes for at least 3 years, HbA_{1c} ≥7.5 to ≤10.5%, BMI ≤35 kg/m^2, stable body weight over the	N=154 24 weeks	Primary: Change in HbA_{1c} from baseline Secondary: FPG, PPG, fasting and postprandial serum insulin and TG levels, and urinary glucose	Primary: Addition of miglitol to sulfonylureas and metformin produced a significant reduction in HbA_{1c} (–0.55%; P=0.04) and PPG (–2.6 mmol/L; P=0.0009) from baseline to end point when compared to placebo. Secondary: FPG decreased in the miglitol group and was almost unchanged from baseline with placebo, the difference was not significant (P=0.10). Fasting insulin levels were unchanged for both groups throughout the study, the difference was not significant (P=0.79).

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glyburide 3.5 to 5 mg BID to QID, metformin 500 to 850 mg daily, and placebo	previous 3 months, and inadequately controlled on combination therapy of diet, glibenclamide* and metformin			Postprandial insulin decreased from baseline to end point, but the difference between the groups was not significant (P=0.26). Postprandial TG decreased slightly in the miglitol group and remained unchanged in the placebo group, the difference was not significant (P=0.47).
Pantalone et al.[105] (2012) glimepiride and metformin vs glipizide and metformin glimepiride and metformin vs glyburide (glibenclamide) and metformin glipizide and metformin vs glyburide (glibenclamide) and metformin	RETRO Patients ≥18 years with type 2 diabetes who had a prescription for glyburide (glibenclamide), glipizide, or glimepiride, in combination with metformin	N=7,320 Median follow-up 2.4 years	Primary: Overall mortality Secondary: Not reported	Primary: No difference in overall mortality risk was found among the different combinations of sulfonylureas and metformin. Post-propensity adjustment results were: glimepiride and metformin vs glipizide and metformin (HR, 1.03; 95% CI, 0.89 to 1.20; P=0.69); glimepiride and metformin vs glyburide and metformin (HR, 1.08; 95% CI, 0.90 to 1.30; P=0.42); and glipizide and metformin vs glyburide and metformin (HR, 1.05; 95% CI, 0.95 to 1.15; P=0.34). Secondary: Not reported
Kabadi et al.[106] (2003) Tolazamide 1 gram daily plus premixed 70% NPH and 30% regular insulin daily vs	PC, RCT Patients with type 2 diabetes mellitus with a lapse of glycemic control, established by documentation of HbA_{1c} >7.4% on ≥2 occasions at an interval of ≥3	N=40 7 months	Primary: Changes in body weight, HbA_{1c}, and fasting C-peptide concentrations Secondary: Changes in daily insulin dose and the number of hypoglycemic	Primary: Changes in body weight were 2.5±0.8 kg for the tolazamide group, 2.6±1.0 kg for the glyburide group, 2.4±0.9 kg for the glipizide XL group, and 2.2±0.7 kg for the glimepiride group, all were significant compared to placebo (P<0.01) after the addition of insulin. All groups achieved optimal glycemic control as expressed by HbA_{1c} <7.4%, 1% above the highest normal level of 6.4% in our laboratory as recommended by the American Diabetes Association after the addition of insulin. HbA_{1c} was 6.8±0.4% for tolazamide, 6.9±0.4% for glyburide,

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glyburide 20 mg daily plus premixed 70% NPH and 30% regular insulin daily vs glipizide XL plus premixed 70% NPH and 30% regular insulin daily vs glimepiride 8 mg daily plus premixed 70% NPH and 30% regular insulin daily vs placebo plus premixed 70% NPH and 30% regular insulin daily	months in each patient while taking oral sulfonylureas consisting of one of these drugs in the maximum recommended daily dose: tolazamide 1 g daily, glyburide 20 mg daily, glipizide XL 20 mg daily, or glimepiride 8 mg daily		episodes confirmed by finger stick blood glucose <60 mg/ dL	6.7±0.4% for glipizide XL, 6.7±0.3% for glimepiride, and 7.0±0.3% for placebo. C-peptide levels decreased in all groups. The reduction in the C-peptide level was significantly greater (P<0.05) in the placebo group compared to the sulfonylurea groups. There were no significant differences among the sulfonylurea groups. Secondary: Patients receiving sulfonylureas required a significantly lower (P<0.01) daily insulin dose, as well as dose per kilogram of body weight in comparison to patients receiving placebo (P<0.01). The daily insulin dose and units per kilogram of body weight was significantly lower (P<0.05) in patients receiving glimepiride in comparison to those receiving tolazamide, glyburide, or glipizide XL. The number of hypoglycemic episodes during the last four weeks of the study were significantly lower in the sulfonylurea groups as compared to the placebo group (P<0.01). The differences among the individual sulfonylurea groups were not significantly different.
Ligvay et al.[107] (2009) Pioglitazone 15 to 45 mg QD plus glyburide 1.25 mg BID vs insulin aspart protamine and	RCT, OL Patients 21 to 70 years of age with type 2 diabetes who were treatment naïve	N=58 36 months	Primary: HbA_{1C}, rate of treatment failures (defined as HbA_{1c} >8.0%), hypoglycemia, weight gain, compliance, QOL, and patient satisfaction Secondary:	Primary: After 36 months, HbA_{1c} was 6.1 % in the insulin-treated group compared to 6.0% in the triple oral group (P=0.26). The percentage of patients achieving HbA_{1c} <7.0% was 100% in both groups at baseline; 92% of patients in the insulin group and 76% of patients in the triple oral group met the HbA_{1c} goal at the end of 36 months. Three patients in each group reached the “treatment failure” end point. The insulin group had 0.51 mild hypoglycemia events/person month and the triple oral group had 0.68 event/person-month (P=0.18). The insulin group

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insulin aspart (NovoLog Mix 70/30) 0.2 units/kg divided twice daily All patients were receiving metformin 1,000 mg BID Doses of medications could be titrated at the investigator's discretion.			Not reported	averaged 0.04 severe hypoglycemic event/person-year, and the triple oral group averaged 0.09 event/ person-year (P=0.53). In the completer analysis, the triple oral group experienced more weight gain than the insulin group: 10.10 kg (95% CI, 4.46 to 15.74) versus 3.36 kg (-0.47 to 7.20; P=0.04). Compliance was high throughout the trial: 93% in the insulin-treated group and 90% in the triple oral group. There were differences between the groups for any of the 12 QoL domains evaluated. All patients receiving insulin reported satisfaction with insulin treatment and willingness to continue insulin at 18 months after randomization. Secondary: Not reported
Bayraktar et al.[108] (1996) Sulfonylurea and acarbose 50 to 100 mg TID vs sulfonylurea and metformin 500 mg TID	RCT, XO Patients from 30 to 63 years of age with type 2 diabetes for 2 to 20 years, HbA_{1c} >8.5%, FPG >7.7 mmol/L, or a PPG >10 mmol/L on maximum doses of gliclazide† (240 mg daily)	N=18 20 weeks	Primary: Changes in FBG, PPG, HbA_{1c}, TGs, cholesterol, fibrinogen, insulin levels, and C-peptide levels from baseline Secondary: Not reported	Primary: Mean FPG, PPG, and HbA_{1c} decreased at the end of each combination treatment period as compared with baseline levels (P<0.05). PPG level in the acarbose group was lower than the level achieved by the group using metformin (P<0.05). Each saw a statistically significant decrease between pre- and posttreatment two-hour postprandial blood glucose levels (–5.3±0.4 for acarbose vs –2.9±0.3 for metformin; P<0.05). There were small reductions in fibrinogen, insulin, and C-peptide levels in each group, but the differences were not statistically significant. Cholesterol levels remained unchanged with both treatment groups. Secondary: Not reported
Abbasi et al.[109]	RCT	N=31	Primary:	Primary:

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(2004) Sulfonylurea (existing therapy) and metformin 500 to 1,000 mg BID vs dietary therapy and metformin 500 to 1,000 mg BID	Patients with type 2 diabetes with relatively poor glycemic control with FPG >9.5 mmol/L on dietary therapy alone or sulfonylurea monotherapy, BMI <40 kg/m^2, and no apparent cardiovascular disease	12 weeks	Changes in fasting glucose, HbA_{1c}, lipid concentrations Secondary: Not reported	FPG decreased to a similar degree with diet therapy (metformin) (12.45±0.48 vs 9.46±0.47 mmol/L; P<0.001) and combined sulfonylurea plus metformin (14.09±0.51 vs 10.57±0.85 mmol/L; P=0.001). The changes in the diet therapy (metformin) group compared to the combined sulfonylurea plus metformin group was not significant (P=0.58). Changes in fasting HbA_{1c} from baseline were significant for diet therapy (metformin) (P<0.001) and combined sulfonylurea plus metformin (P<0.002). The changes were not significant when compared to each other (P=0.30). Fasting TC, TG, HDL-C, and LDL-C did not change significantly in either treatment group (P=0.64, P=0.34, P=0.48, and P=0.85, respectively) for diet therapy (metformin) compared to combined sulfonylurea plus metformin. Fasting remnant lipoprotein cholesterol concentrations were significantly lower in the diet therapy (metformin) group as compared to baseline (0.43±0.09 vs 0.34±0.07 mmol/L; P=0.02). The changes were not significant for diet therapy (metformin) compared to combined sulfonylurea plus metformin (P=0.06). Concentrations of FFA and remnant lipoprotein cholesterol concentrations were lower to a similar degree in both groups, whereas day long plasma insulin concentrations were unchanged. Changes in LDL particle diameter and percent of small dense LDL particles between the groups were not significant at end point (P=0.28 and P=0.73, respectively). Secondary: Not reported
Seufert et al.[110] (2008) <u>Study 1</u> Gliclazide† 80 to 320 mg daily and metformin (existing therapy)	2 MC, RCT Patients 35 to 75 years of age with type 2 diabetes who were inadequately controlled on either metformin or	N=1,269 104 weeks	Primary: Change in HbA_{1c} from baseline, FPG, glucose excursions using three-hour oral glucose tolerance	Primary: <u>Study 1</u> The mean change in HbA_{1c} from baseline to week 104 was -0.89% with pioglitazone and metformin compared to -0.77% with gliclazide and metformin (P=0.20).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs pioglitazone 15 to 45 mg QD and metformin (existing therapy) <u>Study 2</u> Sulfonylurea (existing therapy) and pioglitazone 15 to 45 mg QD vs sulfonylurea (existing therapy) and metformin 850 to 2,550 mg daily	sulfonylurea monotherapy (HbA_{1c} 7.5 to 11.0%), and fasting C-peptide >1.5 ng/mL)		test and insulin sensitivity Secondary: Not reported	The mean change in FPG from baseline to week 104 was -1.8 mmol/L with pioglitazone and metformin compared to -1.1 mmol/L with gliclazide and metformin (P<0.001). Pioglitazone therapy in patients failing metformin therapy achieved decreases in glucose excursions at the end of the 2-year treatment period. This effect was not seen in the patients receiving gliclazide for two years as add-on therapy to failing metformin. Insulin sensitivity increased when pioglitazone was added to metformin therapy (+13.8%) compared with a decrease when gliclazide was added to metformin (-7.2%; P<0.0001). <u>Study 2</u> The mean change in HbA_{1c} from baseline to week 104 was -1.03% for patients receiving pioglitazone and sulfonylurea compared to -1.16% for patients receiving metformin and sulfonylurea (P=0.173). The mean change in FPG from baseline to week 104 was -2.0 mmol/L with pioglitazone and sulfonylurea compared to -1.9 mmol/L with metformin and sulfonylurea (P=0.506). The addition of pioglitazone to failing sulfonylurea therapy for two years resulted in a decrease of post-load glucose excursions which was not seen when metformin was added to sulfonylurea treatment. Insulin sensitivity increased when pioglitazone was added to sulfonylurea, (+5.8%) compared to an increase of +3.9% when metformin was added to sulfonylurea (P=0.581 between treatments). Secondary: Not reported
Matthews et al.[111] (2005) Gliclazide† 80 to 320 mg QD and	DB, RCT Patients with type 2 diabetes that was poorly controlled	N=630 12 months	Primary: Effect on HbA_{1c} Secondary:	Primary: Similar reductions in HbA_{1c} were observed in pioglitazone- (–0.99%) and gliclazide-treated groups (–1.01%; P=0.837). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
metformin (existing therapy) vs pioglitazone 15 to 45 mg QD and metformin (existing therapy)	(HbA_{1c} 7.5 to 11.0%) with metformin monotherapy		Effect on FPG, insulin, lipoproteins, and C-peptide	Similar reductions in FPG were observed in pioglitazone- (–2.1 mmol/L) and gliclazide- (–1.6 mmol/L) treated groups (P=0.506). Gliclazide significantly reduced LDL-C compared to pioglitazone (–4.2 vs +10.4 mg/dL; P=0.001). Pioglitazone significantly reduced TG (–53.1 vs –19.5 mg/dL; P<0.001) and increased HDL-C (6.9 vs no change; P<0.001) compared to gliclazide.
Charbonnel et al.[112] (2005) Gliclazide† 80 to 320 mg QD and metformin (existing therapy) vs pioglitazone 15 to 45 mg QD and metformin (existing therapy)	DB, RCT Patients with type 2 diabetes that was poorly controlled (HbA_{1c} 7.5 to 11.0%) with metformin monotherapy	N=630 24 months	Primary: Effect on HbA_{1c} Secondary: Effect on FPG, insulin, lipoproteins, and C-peptide	Primary: Similar reductions in HbA_{1c} were observed with pioglitazone add-on therapy (–0.89%) and with gliclazide add-on therapy (–0.77%; P=0.200) after 2 years. Secondary: Significant reductions in FPG were observed with pioglitazone add-on therapy (–1.8 mmol/L) compared to gliclazide add-on therapy (–1.1 mmol/L; P<0.001) after two years. Gliclazide add-on therapy had significantly reduced LDL-C compared to pioglitazone add-on therapy (–6 vs +2 mg/dL; P<0.001). Pioglitazone add-on therapy significantly reduced TG (–23 vs –7 mg/dL; P<0.001) and increased HDL-C (22 vs 7 mg/dL; P<0.001) compared to gliclazide add-on therapy. No significant difference between treatment groups in number of adverse events or discontinuation due to adverse events was reported. Less weight gain was observed with gliclazide add-on therapy to metformin (1.2 kg) compared to pioglitazone add-on therapy (2.5 kg).
Hanefeld et al.[113] (2004) Sulfonylurea (existing therapy)	DB, MC, PG, RCT Patients with type 2 diabetes inadequately controlled on	N=639 12 months	Primary: Change in HbA_{1c} Secondary: FPG, fasting plasma insulin,	Primary: HbA_{1c} was reduced by 1.20 and 1.36% in the pioglitazone and metformin groups, respectively (P=0.065 for differences between treatments). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
and pioglitazone 15 to 45 mg QD vs sulfonylurea (existing therapy) and metformin 850 to 2,250 mg	sulfonylurea monotherapy		lipids, urinary albumin and creatinine (to determine albumin-to-creatinine ratio)	FPG (P=0.528) and fasting plasma insulin (P=0.199) were also reduced but the between-treatment differences were not statistically significant. Pioglitazone addition to sulfonylurea significantly reduced TG (–16 vs –9%; P=0.008) and increased HDL-C (14 vs 8%; P<0.001) compared with metformin addition. LD-C was increased 2% by the addition of pioglitazone and decreased 5% by the addition of metformin to sulfonylurea monotherapy (P<0.001). Urinary albumin-to-creatinine ratio was reduced by 15% in the pioglitazone group and increased 2% in the metformin group (P=0.017). Both combinations were well tolerated with no evidence of hepatic or cardiac toxicity in either group.
Vaccaro et al.[114] (2017) TOSCA.IT Sulfonylurea (5 to 15 mg glibenclamide, 2 to 6 mg glimepiride, or 30 to 120 mg gliclazide) vs pioglitazone (15 to 45 mg)	MC, OL, RCT Patients 50 to 75 years of age with type 2 diabetes inadequately controlled with metformin monotherapy (2 to 3 g per day)	N=3,028 Median follow-up of 57.3 months	Primary: Composite of first occurrence of all-cause death, non-fatal MI, non-fatal stroke, or urgent coronary revascularization, assessed in the modified intention-to-treat population (all randomly assigned participants with baseline data available and without any protocol violations in relation to inclusion or exclusion criteria)	Primary: The primary cardiovascular composite outcome occurred in 105 patients (7%; 1.5 per 100 person-years) who were given pioglitazone and 108 patients (7%; 1.5 per 100 person-years) who were given sulfonylureas. There were no significant between-group differences in the composite primary outcome (HR, 0.96; 95% CI, 0.74 to 1.26; P=0.79) or in its components. On the basis of a futility analysis, the study was stopped when the median follow-up was 57.3 months. Secondary: The key secondary outcome occurred in 74 patients (5%; 1.1 per 100 person-years) in the pioglitazone group and in 83 patients (6%; 1.2 per 100 person-years) in the sulfonylureas group (HR, 0.88; 0.65 to 1.21; P=0.44).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Secondary: Composite of ischemic cardiovascular disease, which included first occurrence of sudden death, fatal and non-fatal MI (including silent MI), fatal and non-fatal stroke, leg amputation above the ankle, and any revascularization of the coronary, leg, or carotid arteries	
Comaschi et al.[115] (2008) Metformin/ glibenclamide* fixed dose combination 400/2.5 mg 1 to 3 tablets daily vs Pioglitazone 15 to 30 mg QD as add-on to existing oral hypoglycemic therapy (either metformin or sulfonylurea)	MC, OL, PG, RCT Patients aged ≥35 years with type 2 diabetes who had received treatment with a stable dose of either metformin or a sulfonylurea as monotherapy for at least 3 months before study entry, HbA_{1c} 7.5 to 11.0%, and fasting C-peptide >0.33 nmol/L	N=250 6 months	Primary: Change in HbA_{1c} from baseline to six months Secondary: Change in lipid profiles after six months of treatment	Primary: Pioglitazone-based and fixed-dose metformin/glibenclamide resulted in similar reductions in HbA_{1c} (-1.11 vs -1.29%, respectively; P=0.192) and FPG (-2.13 vs -1.81 mmol/L, respectively; P=0.370). Secondary: No changes in TC were observed with pioglitazone-based therapy (-0.017 mmol/L) compared to the fixed-dose combination of metformin/glibenclamide (-0.099 mmol/L; P=0.479). The addition of pioglitazone to metformin or a sulfonylurea led to a slight increase in HDL-C (+0.04 mmol/L) compared to a reduction in HDL-C with metformin/glibenclamide (-0.09 mmol/L; P<0.001). There was no significant change in non-HDL-C in patients treated with pioglitazone-based therapy (-0.06 mmol/L) or the fixed-dose combination of metformin/glibenclamide (-0.01 mmol/L; P=0.677).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				There was no significant change in LDL-C in patients treated with pioglitazone-based therapy (+0.06 mmol/L) or the fixed-dose combination of metformin/glibenclamide (-0.03 mmol/L; P=0.425) There was a significant reduction in TGs with pioglitazone-based therapy (-0.25 mmol/L) compared to no change with the fixed-dose combination of metformin/glibenclamide (0.03 mmol/L; P=0.045).
Home et al.[116] (2007) Sulfonylurea plus metformin vs rosiglitazone plus either metformin or a sulfonylurea	MC, OL, RCT Patients with type 2 diabetes between 40 and 75 years of age, BMI >25.0 kg/m^2, HbA_{1c} 7.1 to 9.0% while receiving maximum permitted or tolerated doses of metformin or a sulfonylurea; exclusion criteria were the current use of other glucose-lowering agents, hospitalization for a major cardiovascular event in the previous 3 months, a planned cardiovascular intervention, heart failure, clinically significant hepatic disease, renal impairment, and uncontrolled hypertension	N=4,447 (n=1,117 rosiglitazone plus metformin; n=1,103 rosiglitazone plus sulfonylurea; n=2,227 metformin plus sulfonylurea) Mean follow-up 3.75 years for the unplanned interim analyses (study was designed to be 6 years)	Primary: Hospitalization or death from cardiovascular causes Secondary: Death from cardiovascular causes and from any cause, MI, congestive heart failure, and composite of death from cardiovascular causes, MI and stroke	Primary: For adjudicated primary end points (hospitalization or death from cardiovascular causes), the HR was 1.08 (95% CI, 0.89 to 1.31; P=0.43) with 217 events in the rosiglitazone group and 202 events in the control group. An additional 91 patients (50 in the rosiglitazone group and 41 in the control group) had potential primary events reported by investigators, but these events were pending adjudication. Secondary: There was no statistically significant difference between the rosiglitazone group and the control group for the following secondary end points: death from cardiovascular causes (HR, 0.83; 95% CI, 0.51 to 1.36; P=0.46) or any cause (HR, 0.93; 95% CI, 0.67 to 1.27; P=0.63), MI (HR, 1.16; 95% CI, 0.75 to 1.81; P=0.50), or the composite of cardiovascular death, MI and stroke (HR, 0.97; 95% CI, 0.73 to 1.29; P=0.83). However, the power to detect significant differences was low, as reflected by the wide 95% CI. Patients in the rosiglitazone group had a significantly higher risk of congestive heart failure than did patients in the control group, with 38 vs 17 adjudicated events (HR, 2.24; 95% CI, 1.27 to 3.97; P=0.006).
Home et al.[117]	MC, OL, RCT	N=4,458	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2009) Sulfonylurea plus metformin vs rosiglitazone plus either metformin or a sulfonylurea	Patients 40 to 75 years of age with type 2 diabetes and BMI ≥25 kg/m^2, on maximum tolerated doses of metformin or a sulfonylurea monotherapy, and inadequate glycemic control (HbA_{1c} 7.0 to 9.0%)	5.5 years (mean follow-up)	Time to first cardiovascular hospitalization or cardiovascular death Secondary: Cardiovascular death, all-cause mortality, MI, stroke, composite of cardiovascular death, MI, and stroke	The primary end point (cardiovascular hospitalization or cardiovascular death) occurred in 321 and 323 patients receiving rosiglitazone and active control, respectively (HR, 0.99; 95% CI, 0.85 to 1.16; P=0.93). Secondary: There was no significant difference between rosiglitazone and active controls for the following end points: cardiovascular death (HR, 0.84; 95%, CI 0.59 to 1.18; P=0.32), all-cause mortality (HR, 0.86; 95% CI, 0.68 to 1.08; P=0.19), MI (HR, 1.14; 95% CI, 0.80 to 1.63; P=0.47), stroke (HR, 0.72; 95% CI, 0.49 to 1.06; P=0.10), and the composite of cardiovascular death, MI, or stroke (HR, 0.93; 95% CI, 0.74 to 1.15; P=0.50). Heart failure occurred in 61 patients receiving rosiglitazone compared to 29 patients receiving active control (HR, 2.10; 95% CI, 1.35 to 3.27; P=0.0010). There were no serious adverse event reports of macular edema. The incidence of bone fractures was higher with rosiglitazone compared to active control (RR, 1.57; 95% CI, 1.26 to 1.97; P<0.0001). The risk was higher in women than in men (RR, 1.82; 95% CI, 1.37 to 2.41 vs RR, 1.23; 95% CI, 0.85 to 1.77; P=0.10). The excess of fractures in patients on rosiglitazone was primarily in the upper limb (RR, 1.57; 95% CI, 1.12 to 2.19; P=0.0095) and distal lower limb (RR, 2.60; 95% CI, 1.67 to 4.04; P<0.0001). Hip and femur fracture did not increase with rosiglitazone treatment. There was a nonsignificant increase in spinal fractures.
Home et al.[118] (2007) Sulfonylurea plus metformin vs rosiglitazone plus either metformin or a sulfonylurea	MC, OL, PG, RCT Patients 40 to 75 years of age with type 2 diabetes and BMI ≥25 kg/m^2, on maximum tolerated doses of metformin or a sulfonylurea monotherapy, and inadequate glycemic	N=1,122 18 months	Primary: Change in baseline HbA_{1c} Secondary: FPG, serum lipids, HOMA basal insulin sensitivity and islet β-cell function (HOMA %β), body weight, inflammatory/	Primary: At 18 months, HbA_{1c} reduction on background metformin was similar with rosiglitazone and sulfonylurea (difference, 0.07%; 95% CI, -0.09 to 0.23; P value not significant), as was the change when rosiglitazone or metformin was added to sulfonylurea (difference, 0.06%; 95% CI, -0.09 to 0.20; P value not significant). Secondary: Differences in FPG were not significant at 18 months (rosiglitazone vs sulfonylurea, -0.36 mmol/L; P=0.062 and rosiglitazone vs metformin, -0.34 mmol/L; P=0.089).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	control (HbA_{1c} 7.0 to 9.0%)		thrombotic markers, CRP	Rosiglitazone increased TC (P≤0.001) and LDL-C (P=0.000) and reduced nonesterified fatty acids (P=0.000) at 18 months compared to the control. An increase in HDL-C and TG was observed with rosiglitazone compared to sulfonylurea (0.08 vs 0.02 mmol/L; P=0.001, 0.40 vs 0.15 mmol/L; P=0.016, respectively), but not with metformin (P value not significant for both). HOMA-estimated basal insulin sensitivity was substantially increased with rosiglitazone compared to the respective controls (P<0.001 for both). Both rosiglitazone and sulfonylurea when added to metformin increased HOMA %β, but this increase was greater with the sulfonylurea (P<0.001). Rosiglitazone or metformin added to background sulfonylurea also increased HOMA %β, to a similar extent (P value not significant). Rosiglitazone was associated with a significant increase in body weight compared to metformin (P<0.001) and a sulfonylurea (P=0.003). At 18 months, plasminogen activator inhibitor-1 antigen decreased from baseline with rosiglitazone, with a significant difference compared to sulfonylureas (-5.7 vs 7.0%; P=0.047); rosiglitazone and metformin did not differ (P value not significant). There was a significant reduction in CRP with rosiglitazone compared to a sulfonylurea (P<0.001) and metformin (P=0.001).
Mahaffey et al.[119] (2013) RECORD re-evaluation Metformin plus a sulfonylurea vs rosiglitazone plus either metformin or a sulfonylurea	RETRO Patients 40 to 75 years of age with type 2 diabetes and BMI ≥25 kg/m^2, on maximum tolerated doses of metformin or a sulfonylurea monotherapy, and inadequate glycemic control (HbA_{1c} 7.0 to 9.0%)	N=4,458 5.5 years (mean follow-up)	Primary: Time to first cardiovascular hospitalization or cardiovascular death Secondary: Cardiovascular death, all-cause mortality, MI, stroke, composite of cardiovascular	Primary: For the primary end point (time to first occurrence of CV (or unknown cause) death, MI, or stroke) no statistically significant difference was observed between rosiglitazone and metformin/sulfonylurea using the original RECORD end point definitions (HR, 0.95; 95% CI, 0.78 to 1.17). For the primary end point, no meaningful difference between rosiglitazone and metformin/sulfonylurea was observed using the original RECORD end point definitions (HR, 0.95; 95% CI 0.78 to 1.17) or new FDA end point definitions (HR, 0.97; 95% CI, 0.79 to 1.18). Furthermore, these results are similar to results from the original RECORD study (HR, 0.93; 95% CI, 0.74 to 1.15).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			death, MI, and stroke	Secondary: The original RECORD study results and the Duke Clinical Research Institute clinical events classification results were also similar for the individual components of the composite end point. These findings and the additional sensitivity analyses performed support the original RECORD results and suggest that when using essentially the same data, the observations were not affected by different clinical events classification processes, physician adjudicators, or end point definitions.
Komajda et al.[120] (2008) Sulfonylurea plus metformin vs rosiglitazone plus either metformin or a sulfonylurea	RCT, MC, OL, (RECORD) Patients 40 to 75 years of age with type 2 diabetes and BMI ≥25 kg/m^2, on maximum tolerated doses of metformin or a sulfonylurea monotherapy, and inadequate glycemic control (HbA_{1c} 7.0 to 9.0%)	N=668 12 months	Primary: Change from baseline in 24-hour ambulatory BP at six months and 12 months Secondary: Not reported	Primary: For patients receiving rosiglitazone and a sulfonylurea, the reduction in 24-hour SBP was greater at six months (-3.8 mm Hg) and 12 months (-3.8 mm Hg) than with metformin and sulfonylurea therapy (-1.2 mm Hg and -1.3 mm Hg, respectively; six months, P=0.015; 12 months, P=0.031). Reductions in 24-hour DBP were greater at six months and 12 months for patients receiving rosiglitazone and a sulfonylurea (-3.1 mm Hg and -3.7 mm Hg) compared to metformin and sulfonylurea (-0.4 mm Hg and -0.6 mm Hg; both P<0.001). At 12 months, the reduction in 24-hour SBP was greater for rosiglitazone and metformin (-4.9 mm Hg) than for metformin and sulfonylurea (-2.2 mm Hg; P=0.016). At 12 months, the reduction in DBP was greater for rosiglitazone and metformin (-3.8 mm Hg) than for metformin and sulfonylurea (-1.7 mm Hg; P=0.003). At six months, the reductions in SBP and DBP were not significantly different for rosiglitazone and metformin compared to metformin and sulfonylurea (SBP; P=not significant; DBP; P=0.049). Secondary: Not reported
Hamann et al.[121] (2008) Glibenclamide*	RCT, DB, PG Overweight patients (BMI ≥25 kg/m^2)	N=596 52 weeks	Primary: Change in HbA_{1c} from baseline to week 52	Primary: At week 52, mean change in HbA_{1c} from baseline was -0.78% for RSG+MET compared to -0.86% with SU+MET (95% CI, -0.08 to 0.25).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
5 mg or gliclazide† 80 mg and metformin 2,000 mg daily (SU+MET) vs rosiglitazone/ metformin FDC 4 mg/2,000 mg daily (RSG+MET)	with type 2 diabetes, HbA_{1c} 7.0 to 10.0%, who received metformin ≥850 mg/day for at least 8 weeks		Secondary: Change in FPG, β-cell function, insulin resistance, hypoglycemia, BP	Secondary: Reductions in FPG from baseline to week 52 was -2.29 mmol/L with RSG+MET compared to -2.25 mmol/L with SU+MET (P=0.8095). The degree of β-cell failure was significantly greater with SU+MET compared to RSG+MET as measured by the coefficient of failure (0.543 vs 0.055 HbA_{1c}%/year, respectively; P=0.0002). Insulin sensitivity increased 55% with RSG+MET compared to 12.3% with SU+MET (P<0.0001). Hypoglycemia occurred in 30% of patients receiving SU+MET compared to 6% of patients receiving RSG+MET (P<0.0001). After 52 weeks, 24-hour diastolic and systolic ambulatory BP were reduced with RSG+MET, but not with SU+MET. The difference between treatments was significant for diastolic ambulatory BP (-2.9 mm Hg; P=0.0013), but not for systolic ambulatory BP (-2.6 mm Hg; P=0.0549).
Duckworth et al.[122] (2003) Glyburide/ metformin	RETRO Patients 18 to 80 years of age with type 2 diabetes were eligible if they had received a combination product with glyburide and metformin for ≥90 days and had been treated with glipizide or glyburide plus metformin for ≥6 months prior to switching to the combination	N=72 196 days (mean follow-up)	Primary: Changes in HbA_{1c}, lipid parameters, weight Secondary: Not reported	Primary: The mean baseline HbA_{1c} in the total population was 8.3±1.7%. The mean reduction in HbA_{1c} was 0.6% (P=0.002) with a mean follow-up of 196 days after the initiation of glyburide/metformin. The mean daily doses of glyburide and metformin at baseline and at final follow-up were 17.2 and 1,607 mg and 14.7 and 1,750 mg, respectively. The greatest decrease in HbA_{1c} was observed in patients with a baseline HbA_{1c} ≥8.0% (n=37). This group had a mean reduction of HbA_{1c} of 1.3% (P=0.0002) with similar doses of glyburide (14.7 vs 16.9 mg; P=0.077) and metformin (1,743 vs 1,624 mg; P=0.11) in both treatment periods. There were no significant changes in TC, HDL-C, LDL-C, or TG from baseline. There were no significant changes in body weight from a baseline level of 104.3 kg to the last follow-up weight of 104.0 kg (P=0.0645).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	product of glyburide/ metformin			There were no significant differences in patient adherence to the regimen (92.4% before vs 90.9% after). Secondary: Not reported
Blonde et al.[123] (2003) Glyburide coadministered with metformin vs glyburide/ metformin	RETRO Patients with type 2 diabetes new to the combination product glyburide/ metformin or glyburide coadministered with metformin between August 2000 and July 2001 and had HbA_{1c} levels at baseline within 79 to 194 days of initiating combination therapy	N=1,421 ~ 6 month (follow-up period)	Primary: Change in HbA_{1c} Secondary: Not reported	Primary: The mean HbA_{1c} for the two groups at baseline were similar, 9.1% for the combination product and 9.2% for the individual agents coadministered. During the follow-up period, patients taking the combination product had a lower mean daily dose of glyburide and metformin than patients receiving the individual agents coadministered regardless of baseline HbA_{1c}. Fifty-six percent of patients in the combination group achieved an HbA_{1c} <7.0% compared to 31.2% of patients receiving the individual agents coadministered. The mean HbA_{1c} decrease from baseline in the combination group was -2.02% and -1.49% when the individual agents were coadministered. The regression results indicated that patients taking the combination product had a significantly greater (P<0.0001) reduction in HbA_{1c} than patients receiving the individual agents coadministered. Patients receiving the combination product with baseline HbA_{1c} ≥8.0% experienced a significantly (P<0.0001) greater decrease in HbA_{1c} of 2.93% compared to 1.92% for the individual agents coadministered. For patients with baseline HbA_{1c} <8.0%, the difference between the HbA_{1c} responses remained significant. The reductions in HbA_{1c} were smaller for both the combination product and the individual agents coadministered (-0.54 and -0.23%; P=0.0017). Patients were more adherent with the combination product than the individual agents coadministered (84% days with drug supply vs 76% days with drug supply, respectively; P<0.0001). The mean decreases in HbA_{1c} were similar for those patients ≥80% adherent and <80% adherent for the combination product (2.12 vs 2.19%; P value not significant) and the individual agents coadministered (1.47 vs 1.24%; P value not significant). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Not reported
Johnson et al.[124] (2005) Sulfonylurea monotherapy vs metformin monotherapy vs combination therapy of sulfonylureas and metformin	RETRO Patients ≥30 years of age who were new users of oral antidiabetic drugs (sulfonylurea monotherapy, metformin monotherapy, or combination therapy of sulfonylureas and metformin)	N=4,124 N=2,138 sulfonylurea monotherapy N=923 metformin monotherapy N=1,081 combination therapy Duration not reported	Primary: Composite end point of fatal or nonfatal cardiovascular related events Secondary: Not reported	Primary: A total of 381 patients died from cardiovascular causes and 715 were hospitalized at least once for cardiovascular reasons. Patients in the metformin monotherapy group had the lowest nonfatal hospitalization rate for cardiovascular causes (53.7 hospitalizations per 1,000 person years) compared to sulfonylurea monotherapy patients (75.3 per 1,000 person years; P<0.05) and compared to combination therapy patients (90.2 per 1,000 person years; P<0.05). Nonfatal cardiovascular related hospitalization rates were similar for sulfonylurea monotherapy patients and combination therapy patients (P=0.08). Metformin monotherapy was associated with a lower risk of the composite end point (adjusted HR, 0.81; 95% CI, 0.68 to 0.97) as compared to sulfonylurea monotherapy. Cardiovascular hospitalizations were similar for sulfonylurea monotherapy and combination therapy (P=0.32). Secondary: Not reported
Swinnen et al.[125] (2010) Continuation of secretagogues (sulfonylureas or meglitinides) vs discontinuation of secretagogues (sulfonylureas or meglitinides)	PRO Patients 40 to 75 years of age with type 2 diabetes, HbA_{1c} 7.0 to 10.5% receiving oral glucose-lowering drugs	N=865 24 weeks	Primary: Change in HbA_{1c} Secondary: Hypoglycemia, body weight, insulin dose	Primary: In patients continuing secretagogue treatment, HbA_{1c} decreased to 7.0±0.8% at week 12 compared to 7.4±0.9% in patients discontinuing their secretagogues. Endpoint HbA_{1c} level was 7.2±0.9% in both treatment groups. The difference in mean HbA_{1c} reduction during the trial was not significant (-1.59±1.08% for patients continuing secretagogues and -1.30±1.14% for patients discontinuing secretagogues; P=0.382). Secondary: Compared to patients who discontinued secretagogues, patients who continued secretagogues experienced significantly more hypoglycemia (40.0 vs 24.5%; P<0.001) and gained significantly more weight (1.44±3.04 vs 0.43±3.00 kg; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
All patients received existing metformin regimens and initiated insulin therapy.				End of trial insulin doses, were significantly lower in patients who continued secretagogues compared to patients who discontinued secretagogues (P<0.001).
Hollander et al.[126] (2015) Insulin glargine+ one oral antidiabetes drug (metformin or sulfonylurea) wherein previous TZD therapy was dropped and replaced with insulin glargine (GLAR +1 OAD) vs three oral antidiabetes drugs (3OAD) wherein patients receiving TZD and metformin received add-on sulfonylurea (glyburide) and patients receiving TZD and sulfonylurea received add-on metformin (3OAD)	MC, OL, RCT Type 2 diabetes patients 18 to 79 years of age with a HbA_{1c} of 7.5 to 12.0% despite ≥3 months of treatment with a TZD plus metformin or a sulfonylurea	N=337 48 weeks	Primary: Change in HbA_{1c} Secondary: Changes in FPG, weight, BMI, and serum lipid profile	Primary: Substitution of insulin glargine for a TZD and addition of a third OAD resulted in an adjusted mean change in HbA_{1c} from baseline of −1.66% and −1.86%, respectively (adjusted mean difference 0.20; 95% CI, −0.11 to 0.51). The upper limit of the 95% CI for the difference in the adjusted mean changes from baseline to endpoint for HbA_{1c} was 0.51%; therefore, the primary efficacy analysis did not demonstrate equivalent glycemic control during treatment with GLAR + 1 OAD and 3OAD as measured by HbA_{1c} levels. In patients originally taking sulfonylurea, there was a significantly greater reduction in HbA_{1c} in those adding metformin to TZD and sulfonylurea versus those switching the TZD for GLAR + SU at weeks 12, 24, and 48. Secondary: Adjusted mean FPG at baseline was similar between the two treatment arms (GLAR + 1 OAD 193.0 mg/dL vs 3OAD 199.5 mg/dL; P=0.4299). FPG reduced significantly from baseline to endpoint (P<0.0001 for both arms). Weight gain was observed in both treatment arms at each study visit and at endpoint. At each visit, patients in the GLAR + 1 OAD arm gained less weight than those in the 3OAD arm; this difference was significant at week 12 (P=0.0035). A similar pattern was observed for BMI. Overall, insulin glargine + metformin was as effective as 3OAD in achieving glycemic control but with greater improvements in lipid parameters, less weight gain, and lower hypoglycemia rates.
Kheirbek et al.[127] (2013)	OS, RETRO	N=17,773	Primary: All-cause mortality	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Hypoglycemic medications (metformin, glyburide, glipizide, rosiglitazone, acarbose, chlorpropamide, glimepiride, pioglitazone, tolazamide, repaglinide, troglitazone, insulin, and DPP-4 inhibitors) *Defined as any use of the medication independent of dose or days of use	Veterans with diabetes cared for at a Veterans Administration Capital area medical center	Variable duration	Secondary: Not reported	After adjustments were made for severity of illness and patient demographics, the remaining variance in mortality was explained by exposure to five medications, listed in order of impact on risk-adjusted mortality: glipizide (OR=1.566), glyburide (OR=1.804), rosiglitazone (OR=1.805), insulin (OR=2.382), and chlorpropamide (OR=3.026). None of the other medications (metformin, acarbose, glimepiride, pioglitazone, tolazamide, repaglinide, troglitazone, and DPP-4 inhibitors) were associated with excess mortality beyond what could be expected from the patients' severity of illness or demographic characteristics. Insulin, glyburide, glipizide, and rosiglitazone continued to be associated with statistically significant increased mortality after controlling for possible drug interactions. Secondary: Not reported
Mearns et al.[128] (2015) Hypoglycemic medications (Alpha-glucosidase inhibitors, DPP-4 inhibitors, colesevelam, meglitinides, GLP-1 analogs, long-acting, once-daily basal insulin, SGLT2 inhibitors, sulfonylureas, TZDs, and	Network MA (62 RCTs) Patients with inadequately controlled type 2 diabetes on metformin alone	N=32,185 3 to 12 months	Primary: Changes in HbA_{1c}, body weight, and SBP; risk of developing hypoglycemia and urinary and genital tract infection Secondary: Not reported	Primary: All agents significantly reduced HbA_{1c} vs placebo; although not to the same extent (range, 0.43% for miglitol to 1.29% for glibenclamide). Glargine, sulfonylureas, and nateglinide were associated with increased hypoglycemia risk vs placebo. SGLT2 inhibitors, GLP-1 analogs, miglitol, and empagliflozin/linagliptin significantly reduced body weight (range, 1.15 to 2.26 kg) whereas sulfonylureas, TZDs, glargine, and alogliptin/pioglitazone caused weight gain (range, 1.19 to 2.44 kg). SGLT2 inhibitors, empagliflozin/linagliptin, liraglutide, and sitagliptin decreased SBP (range, 1.88 to 5.43 mmHg). No therapy increased UTI risk vs placebo; however, SGLT2 inhibitors were associated with an increased risk of genital tract infection (RR range, 2.16 to 8.03). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
combinations of the above agents)				
Gestational Diabetes				
Moore et al.[129] (2010) Glyburide 2.5 to 10 mg BID vs metformin 500 to 2,000 mg daily (divided doses) Insulin was started in treatment failures and oral medication was discontinued.	DB, PG, RCT Women with gestational diabetes between 11 and 33 weeks gestation at the time of randomization	N=149 Variable duration	Primary: Glycemic control Secondary: Medication failure rate, macrosomia, admission to the neonatal intensive care unit, five-minute Apgar score <7, birth trauma, preeclampsia, maternal and neonatal hypoglycemia, and route of delivery	Primary: There was no difference between the glyburide or metformin groups in mean fasting (P=0.23) or two-hour PPG concentrations (post-breakfast, P=0.15; post-lunch, P=0.28; post-dinner, P=0.32). Secondary: Twenty-six patients (34.7%) in the metformin group and 12 patients (16.2%) in the glyburide group did not meet glycemic goals and required insulin therapy (P=0.01). The failure rate of metformin was 2.1 times higher than the failure rate of glyburide (95% CI, 1.2 to 3.9; OR, 2.7). Macrosomia occurred in 5.4% of patients in the glyburide group and 1.3% of patients in the metformin group (P=0.20). The mean birth weight of babies in the metformin group was smaller than the mean birth weight of babies in the glyburide group (P=0.02). Other neonatal outcomes did not differ between the two groups. There were four neonatal intensive care unit admissions in the metformin group and one neonatal intensive care unit admission in the glyburide group (P=0.37). There were no five-minute Apgar scores <7 in either group. There was one shoulder dystocia in the glyburide group and one third-degree tear in the metformin group (P=0.49). The incidence of maternal hypoglycemia and preeclampsia was not different between the two treatment groups (P=0.56 and P>0.50, respectively). One infant in the metformin group experienced hypoglycemia with blood glucose less than 40 mg/dL. Excluding elective repeat cesarean deliveries, there were 11 cesarean deliveries in the metformin group compared with two cesarean deliveries in the glyburide group (P=0.02).
Nachum et al.[130] (2017)	OL, PRO, RCT	N=104	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Glyburide 2.5 to 20 mg daily vs metformin 850 to 2,550 mg daily (divided doses) If optimal glycemic control was not achieved, the other drug was added	Women 18 to 45 years of age with gestational diabetes diagnosed between 13 to 33 weeks gestation and whose blood glucose was poorly controlled by diet	Recruitment until delivery	Rate of treatment failure (defined as patients needing additional oral hypoglycemic or a second-line therapy either because of poor glycemic control or adverse effects of the first-line medication) Secondary: The rate of participants requiring second-line therapy as a result of poor glycemic control or medication-associated adverse effects, the rate of participants requiring third-line therapy with insulin, preprandial and postprandial glucose values, obstetric outcomes, and neonatal hypoglycemia and metabolic complications	Rates of treatment failure were comparable between the groups (glyburide, 34%; metformin, 29%; P=0.6). Secondary: The rate of adverse effects did not differ significantly between the treatments (P=0.11). The adverse effect requiring medication discontinuation was hypoglycemia in the glyburide group and gastrointestinal discomfort in the metformin group. Treatment success after second-line therapy was higher in the metformin group than in the glyburide group (13 of 15 patients [87%] vs 9 of 18 patients [50%], respectively; P=0.03). In the glyburide group, nine (17%) patients eventually were treated with insulin compared with two (4%) in the metformin group (P=0.03). Mean daily blood glucose and other obstetrical and neonatal outcomes were comparable between groups, including macrosomia, neonatal hypoglycemia, and electrolyte imbalance.
Mirzamoradi et al.[131] (2015)	RCT	N=96	Primary: Glycemic index control	Primary: Time from beginning the treatment to control the glycemic index was 28.30 ± 20.60 days in the insulin group and 22.56 ± 18.86 in the glyburide group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Glyburide vs insulin	Pregnant women 18 to 45 years of age with singleton pregnancies and in week 24 to 36 of gestation with gestational diabetes	Variable duration	Secondary: Fetal and maternal outcome, adverse events	There was no statistically significant difference in time-to-control the blood glucose level in two studied group (P=0.17). Secondary: Time, between beginning the treatment of GDM and delivery, was 53.22 ± 28.96 days in the insulin group and 56.67 ± 30.47 in the glyburide group. There was no statistically significant difference between the time of treatment-to-delivery in two studied groups (P=0.57). The incidence of preeclampsia in the insulin group was higher than glyburide group (13.6 vs 8.1%) but this difference was not statistically significant (P=0.41). There was no statistically significant difference in birth weights between two groups (P=0.84). Eleven neonates needed NICU admission. All NICU admissions were due to respiratory distress syndrome. There were no cases of hypoglycemia, hypocalcemia and polycythemia in both groups.
Poolsup et al.[132] (2014) Pool A: metformin vs insulin Pool B: glyburide vs insulin	MA Women with gestational diabetes mellitus	N=2,151 (13 RCTs) Variable duration	Primary: Safety and efficacy of oral antidiabetic agents compared to insulin Secondary: Not reported	Primary: <u>Pool A</u> There was a nonsignificant difference in the risk of macrosomia (RR, 0.93; 95% CI, 0.61 to 1.41) and large for gestational age (LGA) births (RR, 0.88; 95% CI, 0.70 to 1.12) between the two study groups. A significant increase in the risk of preterm births occurred in the metformin group as compared to insulin (RR, 1.51; 95% CI, 1.04 to 2.19; P=0.03). Rate of neonatal/perinatal mortality was very low in both groups and results remained statistically non-significant. Risk of shoulder dystocia, neonatal hypoglycemia, congenital abnormality, and small for gestational age (SGA) births tended to be lower with metformin but statistical significance was not achieved. A non-significant decrease in risk of caesarean section, pre-eclampsia, and labor induction was noticed with metformin compared to insulin. A significant decrease in the risk of gestational hypertension was observed in the metformin arm (RR, 0.54; 95% CI, 0.31 to 0.91; P=0.02). A significant decrease in PPG levels occurred (mean difference, -2.47 mg/dL; 95% CI, -4.00 to -0.94, P=0.002) in metformin group compared to insulin, while results were statistically nonsignificant between the two groups for FPG levels (mean difference, 0.74 mg/dL; 95% CI, -0.52 to -2.01). <u>Pool B</u> Glyburide significantly increased the risk of macrosomia (RR, 3.07; 95% CI, 1.14 to 8.23; P=0.03) and neonatal hypoglycemia (RR, 2.30; 95% CI, 1.28

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				to 4.11; P=0.005) compared to insulin. There was no difference between glyburide and insulin with regard to risk for LGA births; statistically significant heterogeneity was detected for this outcome. There were no significant differences in the risk of preterm births, neonatal mortality, congenital abnormality, or SGA births for glyburide versus insulin. None of the maternal outcomes (caesarean section, pre-eclampsia, maternal hypoglycemia, glycemic levels) displayed a significant difference between glyburide and insulin. The effect estimate for fasting glucose levels (mean difference, 1.90 mg/dL; 95% CI, -0.38 to 4.18) and postprandial glucose levels (mean difference, 3.42 mg/dL; 95% CI, -1.17 to 8.02) favored the insulin group, but results remained nonsignificant. Secondary: Not reported

*Synonym for glyburide.
†Agent not available in the United States.
Drug regimen abbreviations: BID=twice daily, ER=extended-release, QD=once daily, SC=subcutaneous, TID=three times daily, XL=extended-release, XR=extended-release
Study abbreviations: AC=active-comparator, DB=double-blind, DD=double-blind, ES=extension study, MA=meta-analysis, MC=multicenter, NI=non-inferiority, OL=open-label, OS=observational, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, SB=single-blind, SR=systematic review, XO=cross-over
Miscellaneous abbreviations: AUC=area under the curve, BMI=body mass index, BP=blood pressure, CI=confidence interval, CRP=C-reactive protein, DBP=diastolic blood pressure, DPP-4=dipeptidyl peptidase-4, EQ-5D=EuroQol questionnaire**,** FFA=free fatty acid, FPG=fasting plasma glucose, GLP-1=glucagon-like peptide-1, HbA_{1c}= glycosylated hemoglobin, HDL-C=high density lipoprotein cholesterol, HOMA-B=homeostasis model assessment-beta cell function, HOMA-IR=homeostasis model assessment-estimated insulin resistance, HOMA-S=homeostasis model assessment-insulin sensitivity, HR=hazard ratio, ITT=intention-to-treat, IWQOL=Impact of Weight on Quality of life Questionnaire, LDL-C=low density lipoprotein cholesterol, MI=myocardial infarction, NPH=neutral protamine Hagedorn, NYHA=New York Heart Association, OR=odds ratio, PPAR=peroxisome proliferator-activated receptors**,** PPG=postprandial plasma glucose, QOL=quality of life, RR=relative risk, SBP=systolic blood pressure, TC=total cholesterol, TG=triglyceride, TZD=thiazolidinedione, WMD=weighted mean difference

Additional Evidence

Dose Simplification
Dezii et al. evaluated the differences in adherence and persistence with a once-daily extended-release formulation of glipizide gastrointestinal therapeutic system (GITS) and a twice-daily immediate-release formulation of glipizide. After one year of treatment, adherence rates were 60.5% in the once-daily group compared to 52.0% in the twice-daily group (P=0.027). Persistence rates were 44.4% in the once-daily group and 35.8% in the twice-daily group (P=0.016).[133] Donnan et al. evaluated the patterns and predictors of adherence in patients with type 2 diabetes receiving treatment with a single antidiabetic agent. Adherence was ≥90% in 31.3% of the patients prescribed sulfonylureas and 33.9% of patients prescribed metformin. Patients with better adherence tended to be younger and had a shorter duration of diabetes. There were linear trends of poorer adherence with each increase in the daily number of tablets taken for both sulfonylurea (P=0.001) and metformin (P=0.074) indices. There were significant trends of decreasing adherence with the number of concomitant medications for the sulfonylurea group (P=0.0001) and metformin group (P=0.007).[134]

Several retrospective database analyses have been conducted to assess adherence rates with various antidiabetic agents. Blonde et al. evaluated adherence rates in patients beginning treatment with a sulfonylurea and metformin. The first group consisted of patients who were receiving glyburide/metformin as a fixed-dose combination. The second group consisted of patients who were receiving the combination of glyburide and metformin as separate formulations. The investigators found that patients were more adherent with the fixed-dose combination product than with the agents administered in separate formulations (84% days with drug supply vs 76% days with drug supply, respectively, P<0.0001).[123] Duckworth et al. evaluated patients who were taking glipizide or glyburide in combination with metformin (administered as separate formulations) for at least six months. Patients were then switched to a fixed-dose combination of glyburide/metformin. The investigators found no significant difference in adherence (92.4% before vs 90.9% after the switch).[122] Melikian et al. evaluated adherence rates in newly treated or previously treated patients with type 2 diabetes. The investigators found no difference in adherence rates during the initial six months of therapy among patients who were receiving metformin monotherapy, glyburide monotherapy, or metformin and glyburide combination therapy (administered as separate formulations) as compared to patients who received a fixed-dose combination of glyburide/metformin. Significantly lower adherence rates were seen in patients receiving metformin monotherapy and glyburide monotherapy who had a second agent added at their regimen (54%; 95% CI, 0.52 to 0.55) compared to patients who were switched to a fixed-dose combination of glyburide/metformin (77%; 95% CI, 0.72 to 0.85).[135]

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

Relative Cost Index Scale	
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 10. Relative Cost of the Sulfonylureas

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Single Entity Agents				
Glimepiride	tablet	N/A	$$$$	$
Glipizide	extended-release tablet, tablet	Glucotrol®*, Glucotrol XL®*	$$	$
Glyburide	tablet	N/A	N/A	$
Glyburide, micronized	tablet	Glynase®*	$$$$	$
Combination Products				
Glipizide and metformin	tablet	N/A	N/A	$$
Glyburide, micronized and metformin	tablet	N/A	N/A	$

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

X. Conclusions

The sulfonylureas are approved for use as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.[1-7] All of the sulfonylureas are available in a generic formulation, including the fixed-dose combination products.

The goal of treatment for type 2 diabetes is to control hyperglycemia and reduce the risk of long-term complications. A notable new theme in diabetes treatment guidelines is an emphasis on a complication-centric approach, beyond glucose levels, to frame decisions regarding first-line pharmacologic choices for the treatment of persons with diabetes. Pharmacologic therapy should be guided by person-centered treatment factors, including comorbidities and treatment goals. In adults with type 2 diabetes and established/high risk of atherosclerotic cardiovascular disease, heart failure, and/or chronic kidney disease, the treatment regimen should include agents that reduce cardiorenal risk. Pharmacologic approaches that provide adequate efficacy to achieve and maintain treatment goals should be considered, such as metformin or other agents, including combination therapy.[9-12] Clinical guidelines note that sulfonylureas are associated with weight gain and a greater risk of inducing hypoglycemia compared to other available antidiabetic medications. Among all current clinical guidelines, preference of one sulfonylurea over another is not stated.[9-14]

The sulfonylureas have been evaluated in numerous clinical trials.[15-132] In monotherapy studies, glipizide and glyburide were found to be equally efficacious, regardless of the dosage form used.[23-26,28,32] Several studies evaluated the efficacy of sulfonylureas in dual therapy regimens compared to monotherapy regimens. In these studies, the more aggressive treatment regimens improved glycemic parameters to a greater extent than the less-intensive treatment regimens.[71-73,83-88,91] However, in studies that directly compared various dual therapy regimens, there were no differences in efficacy noted.[99,110-115,118,121]

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

Therefore, all brand products 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 sulfonylurea 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 Thiazolidinediones
AHFS Class 682028
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I. Overview

Diabetes mellitus is a chronic condition which results in hyperglycemia. It is differentiated into four main classes: 1) type 1 diabetes; 2) type 2 diabetes; 3) gestational diabetes; and 4) other types (drug- or chemical-induced, genetic defects in β-cell function or insulin action, and diseases of the exocrine pancreas). Type 2 diabetes is the most prevalent form of the disease in the United States. Inadequate glycemic control may lead to both acute and long-term complications, including microvascular and macrovascular events. There are a variety of oral and injectable antidiabetic agents currently available to treat diabetes. The antidiabetic agents are categorized into 12 different American Hospital Formulary Service (AHFS) classes, which differ with regards to their mechanism of action, efficacy, safety profiles, tolerability, and ease of use.

The thiazolidinediones are approved for use as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.[1-3] They are selective agonists of the peroxisome proliferator-activated receptor-gamma (PPARγ). PPAR receptors are found in tissues important for insulin action. When activated, PPARγ regulates the transcription of insulin-responsive genes responsible for glucose production, transportation, and utilization. PPARγ also plays a role in the regulation of fatty acid metabolism. The thiazolidinediones increase the insulin sensitivity of adipose tissue, skeletal muscle, and the liver. This results in increased glucose uptake and metabolism, suppression of hepatic glucose production, and decreased plasma free fatty acid concentrations.[1-5]

Pioglitazone is available in combination with either metformin or glimepiride. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization.[1-3] Glimepiride improves glycemic control by stimulating the release of insulin from pancreatic beta cells.[1-3]

The thiazolidinediones that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. All agents are available in generic formulations. Metformin and glimepiride are also available generically in separate formulations. Pioglitazone is also available in combination with the dipeptidyl peptidase-4 (DPP-4) inhibitor alogliptin and is included in AHFS class 682005. This class was last reviewed in November 2021.

Table 1. Thiazolidinediones Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Single Entity Agents			
Pioglitazone	tablet	Actos®*	pioglitazone
Combination Products			
Pioglitazone and glimepiride	tablet	Duetact®*	pioglitazone and glimepiride
Pioglitazone and metformin	tablet	Actoplus Met®*	pioglitazone and metformin

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

II. Evidence-Based Medicine and Current Treatment Guidelines

Current clinical guidelines are summarized in Table 2. Please note that guidelines addressing the treatment of type 2 diabetes are presented globally, addressing the role of various medication classes.

Table 2. Treatment Guidelines Using the Thiazolidinediones

Clinical Guideline	Recommendation(s)
American Diabetes Association: **Standards of Care in Diabetes (2023)**[6]	Current criteria for the diagnosis of diabetes • The following are the criteria for a diagnosis of diabetes: glycosylated hemoglobin (HbA_{1c}) ≥6.5%, or a fasting plasma glucose (FPG) ≥126 mg/dL, or a two-hour plasma glucose ≥200 mg/dL during an oral glucose tolerance test or patients with classic symptoms of hyperglycemia, or classic symptoms of hyperglycemia or hyperglycemic crisis (random plasma glucose ≥200 mg/dL). Prevention or delay of type 2 diabetes • Refer adults with overweight/obesity at high risk of type 2 diabetes, as typified by the Diabetes Prevention Program (DPP), to an intensive lifestyle behavior change program to achieve and maintain a weight reduction of at least 7% of initial body weight through healthy reduced-calorie diet and ≥150 minutes/week of moderate-intensity physical activity. • A variety of eating patterns can be considered to prevent diabetes in individuals with prediabetes. • Metformin therapy for prevention of type 2 diabetes should be considered in adults at high risk of type 2 diabetes, as typified by the DPP, especially those aged 25 to 59 years with BMI ≥35 kg/m^2, higher FPG) (e.g., ≥110 mg/dL), and higher A1C (e.g., ≥6.0%), and in individuals with prior gestational diabetes mellitus (GDM). • Long-term use of metformin may be associated with biochemical vitamin B12 deficiency; consider periodic measurement of vitamin B12 levels in metformin-treated individuals, especially in those with anemia or peripheral neuropathy. Glycemic goals in adults • An A1C goal for many nonpregnant adults of <7% (53 mmol/mol) without significant hypoglycemia is appropriate. • If using ambulatory glucose profile (AGP)/glucose management indicator (GMI) to assess glycemia, a parallel goal for many nonpregnant adults is time in range (TIR) of >70% with time below range (TBR) <4% and time <54 mg/dL <1%. For those with frailty or at high risk of hypoglycemia, a target of >50% TIR with <1% TBR is recommended. • On the basis of health care provider judgment and patient preference, achievement of lower A1C levels than the goal of 7% may be acceptable and even beneficial if it can be achieved safely without significant hypoglycemia or other adverse effects of treatment. • Less stringent A1C goals (such as <8% [64 mmol/mol]) may be appropriate for patients with limited life expectancy or where the harms of treatment are greater than the benefits. HCPs should consider deintensification of therapy if appropriate to reduce the risk of hypoglycemia in patients with inappropriate stringent A1C targets. Pharmacologic therapy for type 1 diabetes • Most individuals with type 1 diabetes should be treated with multiple dose insulin injections (three to four injections per day of basal and pre-prandial insulin) or continuous subcutaneous (SC) insulin infusion therapy. • Most patients should use rapid-acting insulin analogs to reduce hypoglycemia risk. • Patients with type 1 diabetes should receive education on how to match prandial insulin doses to carbohydrate intake, premeal blood glucose, and anticipated physical activity. Pharmacologic therapy for type 2 diabetes

Clinical Guideline	Recommendation(s)
	• Healthy lifestyle behaviors, diabetes self-management education and support, avoidance of clinical inertia, and social determinants of health should be considered in the glucose-lowering management of type 2 diabetes. Pharmacologic therapy should be guided by person-centered treatment factors, including comorbidities and treatment goals. • In adults with type 2 diabetes and established/high risk of atherosclerotic cardiovascular disease, heart failure, and/or chronic kidney disease, the treatment regimen should include agents that reduce cardiorenal risk. • Pharmacologic approaches that provide adequate efficacy to achieve and maintain treatment goals should be considered, such as metformin or other agents, including combination therapy. • Weight management is an impactful component of glucose-lowering management in type 2 diabetes. The glucose-lowering treatment regimen should consider approaches that support weight management goals. • Metformin should be continued upon initiation of insulin therapy (unless contraindicated or not tolerated) for ongoing glycemic and metabolic benefits. • Early combination therapy can be considered in some individuals at treatment initiation to extend the time to treatment failure. • The early introduction of insulin should be considered if there is evidence of ongoing catabolism (weight loss), if symptoms of hyperglycemia are present, or when A1C levels (>10% [86 mmol/mol]) or blood glucose levels (≥300 mg/dL [16.7 mmol/L]) are very high. • A person-centered approach should guide the choice of pharmacologic agents. Consider the effects on cardiovascular and renal comorbidities, efficacy, hypoglycemia risk, impact on weight, cost and access, risk for side effects, and individual preferences. • Among individuals with type 2 diabetes who have established atherosclerotic cardiovascular disease or indicators of high cardiovascular risk, established kidney disease, or heart failure, a sodium–glucose cotransporter 2 inhibitor and/or glucagon-like peptide 1 receptor agonist with demonstrated cardiovascular disease benefit is recommended as part of the glucose-lowering regimen and comprehensive cardiovascular risk reduction, independent of A1C and in consideration of person-specific factors. • In adults with type 2 diabetes, a glucagon-like peptide 1 receptor agonist is preferred to insulin when possible. • If insulin is used, combination therapy with a glucagon-like peptide 1 receptor agonist is recommended for greater efficacy, durability of treatment effect, and weight and hypoglycemia benefit. • Recommendation for treatment intensification for individuals not meeting treatment goals should not be delayed. • Medication regimen and medication-taking behavior should be reevaluated at regular intervals (every three to six months) and adjusted as needed to incorporate specific factors that impact choice of treatment. • Clinicians should be aware of the potential for over-basalization with insulin therapy. Clinical signals that may prompt evaluation of over-basalization include basal dose more than ~0.5 units/kg/day, high bedtime–morning or post-preprandial glucose differential, hypoglycemia (aware or unaware), and high glycemic variability. Indication of over-basalization should prompt reevaluation to further individualize therapy.
American Diabetes Association/ European Association for the Study of Diabetes:	Consensus recommendations • All people with type 2 diabetes should be offered access to ongoing diabetes self-management education and support programs. • Providers and health care systems should prioritize the delivery of person-centered care.

Clinical Guideline	Recommendation(s)
Management of Hyperglycemia in Type 2 Diabetes. A consensus report by the American Diabetes Association and the European Association for the Study of Diabetes (2022)[7]	• Optimizing medication adherence should be specifically considered when selecting glucose-lowering medications. • Medical nutrition therapy focused on identifying healthy dietary habits that are feasible and sustainable is recommended in support of reaching metabolic and weight goals. • Physical activity improves glycemic control and should be an essential component of type 2 diabetes management. • Adults with type 2 diabetes should engage in physical activity regularly (>150 min/week of moderate- to vigorous-intensity aerobic activity) and be encouraged to reduce sedentary time and break up sitting time with frequent activity breaks. • Aerobic activity should be supplemented with two to three resistance, flexibility, and/or balance training sessions/week. Balance training sessions are particularly encouraged for older individuals or those with limited mobility/poor physical function. • Metabolic surgery should be considered as a treatment option in adults with type 2 diabetes who are appropriate surgical candidates with a BMI ≥40.0 kg/m^2 (BMI ≥37.5 kg/m^2 in people of Asian ancestry) or a BMI of 35.0 to 39.9 kg/m^2 (32.5 to 37.4 kg/m^2 in people of Asian ancestry) who do not achieve durable weight loss and improvement in comorbidities (including hyperglycemia) with nonsurgical methods. • In people with established CVD, a GLP-1 RA with proven benefit should be used to reduce MACE, or an SGLT2i with proven benefit should be used to reduce MACE and HF and improve kidney outcomes. • In people with CKD and an eGFR ≥20 ml/min per 1.73 m^2 and a urinary albumin/creatinine ratio >3.0 mg/mmol (>30 mg/g), an SGLT2i with proven benefit should be initiated to reduce MACE and HF and improve kidney outcomes. Indications and eGFR thresholds may vary by region. If such treatment is not tolerated or is contraindicated, a GLP-1 RA with proven cardiovascular outcome benefit could be considered to reduce MACE and should be continued until kidney replacement therapy is indicated. • In people with HF, SGLT2i should be used because they improve HF and kidney outcomes. • In individuals without established CVD but with multiple cardiovascular risk factors (such as age ≥55 years, obesity, hypertension, smoking, dyslipidemia, or albuminuria), a GLP-1 RA with proven benefit could be used to reduce MACE, or an SGLT2i with proven benefit could be used to reduce MACE and HF and improve kidney outcomes. • In people with HF, CKD, established CVD, or multiple risk factors for CVD, the decision to use a GLP-1 RA or SGLT2i with proven benefit should be independent of background use of metformin. • SGLT2i and GLP-1 RA reduce MACE, which is likely to be independent of baseline HbA1c. In people with HF, CKD, established CVD, or multiple risk factors for CVD, the decision to use a GLP-1 RA or an SGLT2i with proven benefit should be independent of baseline HbA1c. • In general, selection of medications to improve cardiovascular and kidney outcomes should not differ for older people. • In younger people with diabetes (<40 years), consider early combination therapy. • In women with reproductive potential, counseling regarding contraception and taking care to avoid exposure to medications that may adversely affect a fetus are important.
American Association of Clinical Endocrinologists/	Antihyperglycemic Pharmacotherapy for Persons with Type 2 Diabetes • Individualized pharmacotherapy for persons with T2D should be prescribed based on evidence for benefit that includes glucose lowering, avoidance of hypoglycemia and weight gain, and reduction of cardio-renal risk.

Clinical Guideline	Recommendation(s)
American College of Endocrinology: **Clinical Practice Guidelines for Developing a Diabetes Mellitus Comprehensive Care Plan (2022)**[8]	• Persons with T2D and their health care professionals should use patient-centered shared decision-making to agree on therapy targets and treatments as well as a regimen for glucose monitoring (i.e., BGM, structured BGM, or CGM). • Glycemic targets include A1C, BGM, and, for those using CGM, achievement of CGM targets such as time in range (TIR), percentage in low and very low range, time above range, and glycemic variability. Nonglycemic targets include avoidance of hypoglycemia, control of BP, lipids, other CVD risk factors, and achieving and maintaining a healthy body weight. • Independent of glycemic control, targets, or treatment, if there is established or high risk for ASCVD, HF, and/or CKD, clinicians should prescribe a GLP-1 RA or an SGLT2i with proven efficacy for the specific condition(s) of the person with T2D being treated. • DM therapy should be individualized based on level of glycemia and the presence of comorbidities, complications, and access. Metformin is often the preferred initial therapy. Other agents may be appropriate as first line or in addition to metformin to reduce BG and/or to address specific comorbidities (such as ASCVD, HF, CKD, obesity, NAFLD), independent of glucose-lowering effects. • For some recently diagnosed individuals with T2D and more severe hyperglycemia (A1C ≥7.5%), unlikely to attain the A1C target with a single agent, early combination pharmacotherapy should be considered, usually to include metformin plus another agent that does not cause hypoglycemia, especially a GLP-1 RA, SGLT2i, or dipeptidyl peptidase 4 (DPP-4) inhibitor. • For newly diagnosed persons with T2D and an entry A1C >9.0% and/or ≥1.5% above target, one should initiate, along with lifestyle modifications, dual- or possibly triple-combination pharmacotherapy usually including metformin. Basal insulin along with noninsulin therapy is recommended if there are significant signs or symptoms of hyperglycemia, especially including catabolism (e.g., weight loss) or a very high A1C >10% (86 mmol/mol) or BG levels (≥300 mg/dL [16.7 mmol/L]). • Clinicians should discuss with persons with T2D the likelihood that most persons with T2D ultimately require a combination of multiple complementary antihyperglycemic agents, in addition to lifestyle interventions, to attain and maintain optimal glycemic control. • The DM care team should assess medication adherence and safety and glycemic control in persons with T2D quarterly or more frequently as needed. Subsequent visits will depend upon the metabolic targets achieved and the stability of metabolic control. • Persons with T2D who start on metformin should continue it unless intolerance or contraindications occur. When intensification of antihyperglycemic treatment is needed, other agents should be added to metformin. • Most persons with T2D who require intensification of antihyperglycemic therapy with a GLP-1 RA or insulin should initially be prescribed a GLP-1 RA. If further intensification is required, one should prescribe a basal insulin or a switch to a fixed-ratio combination of a basal insulin and a GLP-1 RA (insulin glargine U100 + lixisenatide [GlarLixi] or insulin degludec + liraglutide [IdegLira]). • Insulin should be prescribed for persons with T2D when noninsulin antihyperglycemic therapy fails to achieve target glycemic control or when a person has symptomatic hyperglycemia. • Long-acting basal insulin analogs are the recommended initial choice of insulin therapy for persons with T2D. The insulin analogs glargine (U100 or U300), degludec (U100 or U200), or detemir are preferred over intermediate-acting Neutral Protamine Hagedorn (NPH) insulin because analog insulins have

Clinical Guideline	Recommendation(s)
	demonstrated less hypoglycemia in some studies. Glargine U300 and degludec can be associated with less hypoglycemia than glargine U100 or detemir. • Many persons with T2D receiving basal insulin and not at goal A1C can have significantly improved glycemia by the addition of a GLP-1 RA or being switched to a fixed-ratio combination basal insulin–GLP-1 RA (GlarLixi or IdegLira). One of these changes should be considered before adding a meal-time insulin for postprandial glycemic control. • When control of postprandial hyperglycemia is needed and a basal insulin and a GLP-1 RA are already being used, preference should be given to rapid-acting insulins (the analogs lispro, aspart, and glulisine or the rapid-acting inhaled human insulin powder) over regular human insulin. The former have a more consistent and a more rapid onset and offset of action with less risk of hypoglycemia. • Ultra-rapid-acting insulins (faster-acting insulin aspart, lispro aabc, and [human insulin] inhalation powder) may allow a decrease in the time between insulin administration and food intake and reduce the postprandial peak of PG as compared with rapid-acting insulins. The significance of this on long-term complications is unknown. • Basal-bolus insulin regimens or continuous subcutaneous insulin infusion (CSII) (i.e., insulin pump) allow for adjustment of insulin doses according to carbohydrate intake and activity levels and are recommended for intensive insulin therapy in persons with T2D. • Premixed insulin formulations (fixed combinations of shorter- and longer-acting components) of human or analog insulin may be considered for persons with T2D who have consistent dietary and exercise patterns and in whom adherence to more intensive insulin regimens is problematic. However, these preparations have reduced dosage flexibility and may increase the risk of hypoglycemia compared with basal insulin or basal-bolus regimens. • In persons with T2D who are treated with basal-bolus insulin therapy, adding a GLP-1 RA, or switching to a fixed-ratio combination of a GLP-1 RA and a basal insulin, or adding an SGLT2i or pramlintide (less commonly used) may be able to reduce postprandial hyperglycemia, A1C, and weight. GLP-1 RAs may also allow reduction or discontinuation of bolus insulin in some individuals. <u>How should insulin therapy be used for management of persons with type 1 diabetes?</u> • Insulin must be used to treat all persons with T1D. • Physiologic insulin replacement regimens, which provide both basal and prandial (meal-related or bolus) insulin, are recommended for most persons with T1D. • Achievement of glucose targets using either MDI of insulin or CSII, is needed to prevent development of life-threatening crises, such as acute hyperglycemic crises (DKA and hyperglycemic hyperosmolar state) and catabolic state. • A multi-component self-management DM education program is recommended for persons with T1D. Ideally, this is provided by a professional with expertise (i.e., certified diabetes care and education specialist) in the topics of healthy lifestyle, insulin technique including prandial insulin dosing guided by carbohydrate counting and diet adjustments for special situations, such as physical activity and prolonged fasting. Instruction is also needed in how to deal with sick days and prevention of DKA and hypoglycemia, and other relevant issues. Due to changes in DM self-management practices and each individual's medical history, personal and cultural background, and educational needs, specific education topics may need to be repeated at regular intervals. • The ideal insulin regimen should be personalized to an individual's needs and glycemic targets, attempting to better emulate physiological insulin replacement to maintain near normoglycemia, to prevent the development and progression of DM complications, while minimizing hypoglycemia and providing flexibility

Clinical Guideline	Recommendation(s)
	for specific daily life situations/scenarios such as: exercise, sleep, acute illness, psychological stress, etc. • Insulin regimens usually should involve the use of insulin analogs for most persons with T1D and include the following approaches: o MDI, which usually involve 1 to 2 subcutaneous injections daily of basal insulin to suppress ketogenesis and gluconeogenesis and to control glycemia between meals and overnight, and subcutaneous injections of prandial insulin or use of inhaled insulin before each meal to control meal-related glycemic excursions. CGM is the preferred method of glucose monitoring for all individuals with T1D. o Insulin pump therapy (CSII) provides constant/continuous infusion of fast-acting insulin driven by mechanical force and delivered via a cannula inserted under the skin. CSII can improve (or enhance) glycemic control and should be an option for insulin delivery for appropriate persons with DM. Ideally, these individuals should also use CGM as stated in R13.6.a. o Automated insulin delivery systems (AIDs), which include an insulin pump, an integrated CGM, and computer software algorithm, aim to better emulate physiological insulin replacement and achieve glycemic targets. This technology is recommended for many persons with T1D since its use has been shown to increase TIR while often reducing hypoglycemia or at least without causing increased hypoglycemia. o Open-loop (use of a pump and sensor which do not communicate) and sensor-augmented pump (SAP) systems: (CGM communicates with pump facilitating needed adjustments to basal rate; temporary interruption of insulin delivery when glucose levels are low or forecast to be low within 30 min). Insulin pump with a CGM or an SAP is recommended to manage persons with DM treated with intensive insulin management who prefer not to use AIDs or have no access to them. How should diabetes mellitus in pregnancy be managed? • For women with GDM, the following treatment goals are recommended: preprandial glucose concentration ≤95 mg/dL and either a 1-h post-meal glucose ≤140 mg/dL or a 2-h post-meal glucose ≤120 mg/dL to decrease adverse fetal outcomes. • All women with preexisting DM (T1D, T2D, or previous GDM) need access to preconception care and counseling to ensure adequate nutrition, healthy weight, and glucose control before conception, during pregnancy, and in the postpartum period. • Rapid-acting insulin analogs (insulin-lispro, insulin-aspart) should be used to treat postprandial hyperglycemia in pregnant women. • Options for basal insulin include long-acting insulin (e.g., NPH, detemir, or glargine) or rapid-acting insulin via a CSII. Regular insulin, although not recommended as first-line therapy, is acceptable to use in managing pregnant women with DM when rapid-acting insulin analogs are not available. • Insulin is the preferred therapeutic choice for pregnant women with GDM or T2D, but metformin has been given a category B for pregnancy with accumulating clinical evidence of metformin's safety during the first trimester and beyond. Metformin has been shown to improve pregnancy and fetal outcomes except for increased rates of infants with SGA and later onset of obesity. The prescriber should discuss the potential risks and benefits of oral agent therapy during pregnancy as well as the need for longer-term outcome studies.
American Association of Clinical Endocrinologists/	Principles underlying the algorithm • Lifestyle modification underlies all therapy. • Maintain or achieve optimal weight.

Clinical Guideline	Recommendation(s)
American College of Endocrinology: **Consensus Statement on the Comprehensive Type 2 Diabetes Management Algorithm (2023)[9]**	• Choice of antihyperglycemic therapy reflects glycemic targets, atherosclerotic cardiovascular disease (ASCVD), congestive heart failure (CHF), chronic kidney disease (CKD), overweight/obesity, and nonalcoholic fatty liver disease (NAFLD). • Choice of therapy includes ease of use and access. • Optimal hemoglobin A1c (A1C) is ≤6.5% or as close to normal as is safe and achievable for most patients. • Individualize all glycemic targets (A1C, glucose management indicator [GMI], time in range [TIR], fasting blood glucose [FBG], and PPG). • Get to goal as soon as possible (adjust ≤3 months). • Avoid hypoglycemia. Hypoglycemia, defined as blood glucose (BG) <70 mg/dL, is associated with an increased risk for adverse outcomes including mortality. • CGM is highly recommended to assist persons with diabetes in reaching goals safely. • Comorbidities must be managed for comprehensive care. <u>Algorithm summative information</u> • The algorithm is intended as a more concise document than the guideline, providing easily accessible, visual guidance for decision-making in the clinic setting. • In this 2023 algorithm, there continues to be an emphasis on lifestyle modification and treatment of overweight/obesity as key pillars of the management of prediabetes and DM. • The importance of appropriate management of the atherosclerotic risk factors of dyslipidemia and hypertension is highlighted. • One notable new theme is an obvious emphasis on a complication-centric approach, beyond glucose levels, to frame decisions regarding first-line pharmacologic choices for the treatment of persons with diabetes. • The algorithm is divided into discrete graphic sections that outline the principles for management of T2D and guide management of adiposity-based chronic disease (ABCD), prediabetes, and atherosclerotic risk factors of dyslipidemia and hypertension. In addition, the algorithms for antihyperglycemic agents include both complication-centric and glucose-centric approaches, and there is direction for insulin initiation and titration. Tables summarizing the benefits and risks of antihyperglycemic medications (updated) and weight-loss pharmacotherapy (new) are provided.

American Academy of Pediatrics: **Management of Newly Diagnosed Type 2 Diabetes Mellitus (T2DM) in Children and Adolescents (2013)[10]**	• Clinicians must ensure that insulin therapy is initiated for children and adolescents with T2DM who are ketotic or in diabetic ketoacidosis and in whom the distinction between types 1 and 2 diabetes mellitus is unclear and, in usual cases, should initiate insulin therapy for patients.
	  ○ Who have random venous or plasma blood glucose (BG) concentrations ≥250 mg/dL.
	  ○ Whose HbA_{1c} is >9%.
	• In all other instances, clinicians should initiate a lifestyle modification program, including nutrition and physical activity, and start metformin as first-line therapy for children and adolescents at the time of diagnosis of T2DM.
	• Monitoring of HbA_{1c} concentrations is recommended every three months and intensifying treatment is recommended if treatment goals for finger-stick BG and HbA_{1c} concentrations are not being met.
	• Advise patients to monitor finger-stick BG concentrations in patients who:
	  ○ Are taking insulin or other medications with a risk of hypoglycemia; or
	  ○ Are initiating or changing their diabetes treatment regimen; or
	  ○ Have not met treatment goals; or
	  ○ Have intercurrent illnesses.

Clinical Guideline	Recommendation(s)
	• Incorporate the Academy of Nutrition and Dietetics' *Pediatric Weight Management Evidence-Based Nutrition Practice Guidelines* in dietary or nutrition counseling of patients with T2DM at the time of diagnosis and as part of ongoing management. • Encourage children and adolescents with T2DM to engage in moderate-to-vigorous exercise for at least 60 minutes daily and to limit nonacademic "screen time" to less than two hours a day.

American Diabetes Association: **Type 1 Diabetes in Children and Adolescents: A Position Statement by the American Diabetes Association (2018)[11]**	<u>Blood Glucose Management: Monitoring and Treatment</u>
	• Most children with type 1 diabetes should be treated with intensive insulin regimens via either multiple daily injections of prandial insulin and basal insulin or continuous subcutaneous insulin infusion.
	• An HbA_{1c} target of <7.5% should be considered in most children and adolescents but should be individualized based on the needs and situation of the patient and family.
	• Children and adolescents with type 1 diabetes should have blood glucose levels monitored up to six to ten times/day including premeal, pre-bedtime, and as needed for safety (e.g. exercise, driving, illness, or the presence of symptoms of hypoglycemia).
	• Continuous blood glucose monitoring should be considered in all children and adolescents whether using insulin injections or an insulin pump.
	• In pediatric patients with type 1 diabetes automated insulin delivery systems can improve glycemic control and reduce hypoglycemia.
	
	<u>Lifestyle Management</u>
	• Individualized medical nutrition therapy is recommended for children and adolescents with type 1 diabetes.
	• Monitoring carbohydrate intake, whether by carbohydrate counting or experience-based estimation, is key to achieving optimal glycemic control.
	• Exercise if recommended for all children and adolescents with type 1 diabetes. The suggested goal is 60 minutes of moderate to vigorous aerobic activity daily with muscle-strengthening and bone-strengthening activities three times a week.
	• Children and adolescents with type 1 diabetes should be educated about prevention and management of potential hypoglycemia during and after exercise.
	• Strategies to prevent hypoglycemia during exercise, after exercise, and overnight following exercise include reducing prandial insulin dosing for the meal/snack preceding exercise, increasing carbohydrate intake, eating bedtime snacks, using continuous blood glucose monitoring, and/or reducing basal insulin doses.
	
	<u>Behavioral Aspects of Self-Management</u>
	• Children and adolescents with diabetes should be assessed for psychosocial issues and family stresses that could impact diabetes management at diagnosis and routine follow-up.
	• Consider including children in consent processes as early as cognitive development indicates understanding of health consequences of behavior.
	• Offer adolescents time by themselves with their care provider(s) starting at age 12 years, or when developmentally appropriate.
	
	<u>Complications and Comorbidities</u>
	• Diabetic Ketoacidosis
	  ○ All individuals with type 1 diabetes should have access to an uninterrupted supply of insulin. Lack of access and insulin omissions are major causes of diabetic ketoacidosis.
	  ○ Patients with type 1 diabetes should have continuous access to medical support for sick-day management.
	• Hypoglycemia

Clinical Guideline	Recommendation(s)
	○ The recommended treatment of hypoglycemia (blood glucose <70 mg/dL) in conscious patients is 15 g of glucose, although any form of carbohydrate can be used. If hypoglycemia continues after 15 minutes, treatment should be repeated. Once blood glucose has returned to normal patients should consider consuming a meal/snack and/or reduce insulin. ○ All individuals with type 1 diabetes should be prescribed glucagon and families/caregivers should be educated on administration. ○ Treatment regimens should be reevaluated in those with hypoglycemia unawareness or one or more episodes of severe hypoglycemia. • Diabetic Kidney Disease ○ Annual screening for albuminuria with a random spot urine sample for albumin-to-creatinine ratio should be considered at puberty or at age >10 years, whichever is earlier, once the child has had diabetes for 5 years. ○ An angiotensin-converting-enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB), titrated to normalization of albumin excretion, may be considered when elevated urinary albumin-to-creatinine ratio is documented. • Retinopathy ○ An initial dilated and comprehensive eye examination is recommended at age 10 years or after puberty has started, whichever is earlier, once the patient has had diabetes for three to five years. ○ Annual routine follow-up is recommended but may be given every two years based on the advice of an eye care professional. • Neuropathy ○ Consider an annual comprehensive foot exam for adolescents at the start of puberty or at age 10 years, whichever is earlier, once the patient has had type 1 diabetes for 5 years. • Hypertension ○ Children and adolescents with type 1 diabetes should have blood pressure monitored at each visit. Elevated blood pressure should be confirmed on three separate days. ○ Initial treatment of high-normal blood pressure should include dietary modification and increased exercise. Pharmacologic treatment should be considered if blood pressure is not controlled after three to six months. ○ In patients with conformed hypertension pharmacologic treatment should be added to lifestyle modification at diagnosis. ○ ACE inhibitors and ARBs should be considered for initial treatment. • Dyslipidemia ○ A fasting lipid profile should be taken in children ≥10 years of age or older after the diagnosis of diabetes. Obtain a fasting lipid profile in children 10 years of age or older as soon as convenient after the diagnosis of diabetes ○ If lipids are abnormal, initial therapy should consist of optimizing glucose control and medical nutrition therapy using a Step 2 American Heart Association diet that restricts saturated fat to 7% of total calories and dietary cholesterol to 200 mg/day. ○ If lipids remain abnormal after six months of lifestyle intervention, consider adding a statin in children at least 10 years of age.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the thiazolidinediones are noted in Table 3.

Table 3. FDA-Approved Indications for the Thiazolidinediones[1-5]

Indication	Single Entity Agents	Combination Products	
	Pioglitazone	Pioglitazone and Glimepiride	Pioglitazone and Metformin
Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes	✔		
Adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus when treatment with both pioglitazone and metformin is appropriate			✔
Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes who are already treated with a thiazolidinedione and a sulfonylurea or who have inadequate glycemic control on a thiazolidinedione alone or a sulfonylurea alone		✔	

IV. Pharmacokinetics

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

Table 4. Pharmacokinetic Parameters of the Thiazolidinediones[4]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Single Entity Agents					
Pioglitazone	50*	>99	Liver, extensive (% not reported)	Renal (15 to 30)	3 to 7
Combination Products					
Pioglitazone and glimepiride	50*/100	>99	Liver, extensive (% not reported)	Renal (15 to 30)/ Renal (60), Feces (40)	3 to 7/9
Pioglitazone and metformin	50*/50 to 60†	>99/Negligible (% not reported)	Liver, extensive (% not reported)	Renal (15 to 30)/ Renal (90)	3 to 7/ 1.5 to 6.2

*Animal studies.
†Immediate-release.

V. Drug Interactions

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

Table 5. Major Drug Interactions with the Thiazolidinediones[4]

Generic Name(s)	Interaction	Mechanism
Metformin	Iodine-containing radiopaque agents	Iodinated contrast materials-induced renal failure can interfere with the renal elimination of metformin; therefore, there is an increased risk of metformin-induced lactic acidosis.
Sulfonylureas	Azole antifungals	Azole antifungals may inhibit cytochrome P450 2C9-mediated metabolism of sulfonylureas. The hypoglycemic effects of sulfonylureas may be increased by azole antifungals.
Sulfonylureas	Quinolones	The hypoglycemic effect of sulfonylureas may be increased by quinolones especially in elderly patients with renal compromise. Hypoglycemia symptoms including lightheadedness, diaphoresis, tachycardia and various neurologic and psychiatric disturbances may occur. The mechanism of this interaction is unknown.
Thiazolidinediones	Fluoroquinolones	Concurrent use of fluoroquinolones and antidiabetic agents may result in changes in blood glucose and increased risk of hypoglycemia or hyperglycemia.
Pioglitazone	Ifosfamide	Concurrent use of ifosfamide and pioglitazone may result in increased neurotoxic and nephrotoxic effects.
Pioglitazone	Tolvaptan	Concurrent use of pioglitazone and tolvaptan may result in decreased tolvaptan plasma concentrations.

VI. Adverse Drug Events

The most common adverse drug events reported with the thiazolidinediones (TZDs) are listed in Table 6. The boxed warnings for the thiazolidinediones are listed in Tables 7 through 9. The TZDs are associated with a boxed warning regarding the risk of development or exacerbation of congestive heart failure.[1-3]

Table 6. Adverse Drug Events (%) Reported with the Thiazolidinediones[1-5]

Adverse Event	Single Entity Agents	Combination Products	
	Pioglitazone	Pioglitazone and Glimepiride*	Pioglitazone and Metformin*
Cardiovascular			

Adverse Event	Single Entity Agents	Combination Products	
	Pioglitazone	Pioglitazone and Glimepiride*	Pioglitazone and Metformin*
Congestive heart failure	✔	-	-
Central Nervous System			
Dizziness	-	-	4.8 to 5.4
Headache	7 to 9	4.0 to 7.1	4.6 to 6.0
Endocrine and Metabolic			
Aggravated diabetes	5	-	-
Edema	5 to 15	5.7 to 12.3	2.9 to 11.3
Hypoglycemia	✔	13.4 to 15.7	-
Weight gain	✔	9.1 to 13.4	2.9 to 6.7
Gastrointestinal			
Diarrhea	-	4.3 to 6.0	4.8 to 5.8
Nausea	-	4.0 to 5.1	3.6 to 5.8
Tooth disorder	5	-	-
Genitourinary	-	-	-
Ovulation	✔	-	-
Hematologic			
Anemia	≤2	-	-
Hematocrit decreased	✔	-	-
Hemoglobin decreased	✔	-	-
Musculoskeletal			
Fracture	5	-	-
Myalgia	3 to 5	-	-
Respiratory			
Dyspnea	✔	-	-
Pharyngitis	5	-	-
Sinusitis	6	-	4.4 to 5.0
Upper respiratory tract infection	13	12.3 to 16.6	12.4 to 15.5
Other			
Bladder carcinoma	✔	✔	✔
Blurred vision	✔	-	-
Hepatotoxicity	Rare	-	-
Injury	-	3.5	-
Macular edema	✔	-	-
Pain in limb	-	4.0 to 5.4	-
Urinary tract infection	-	5.7 to 6.8	5.3 to 5.8

*Adverse reactions for combination therapy only are reported.
-Event not reported.
✔ Percent not specified.

Table 7. Boxed Warning for Actos® (pioglitazone)[3]

WARNING
Thiazolidinediones, including pioglitazone, cause or exacerbate congestive heart failure in some patients. After initiation of pioglitazone, and after dose increases, monitor patients carefully for signs and symptoms of heart failure (e.g., excessive, rapid weight gain, dyspnea, and/or edema). If heart failure develops, it should be managed according to current standards of care and discontinuation or dose reduction of pioglitazone must be considered. Pioglitazone is not recommended in patients with symptomatic heart failure. Initiation of pioglitazone in patients with established New York Heart Association class III or IV heart failure is contraindicated.

Table 8. Boxed Warning for Duetact® (pioglitazone and glimepiride)[1]

WARNING
Thiazolidinediones, including pioglitazone, which is a component of Duetact®, cause or exacerbate congestive heart failure in some patients. After initiation of Duetact®, observe patients carefully for signs and symptoms of heart failure (including excessive, rapid weight gain, dyspnea, and/or edema). If these signs and symptoms

develop, the heart failure should be managed according to the current standards of care. Furthermore, discontinuation of Duetact® must be considered. Duetact® is not recommended in patients with symptomatic heart failure. Initiation of Duetact® in patients with established New York Heart Association Class III or IV heart failure is contraindicated.

Table 9. Boxed Warning for Actoplus Met® (pioglitazone and metformin)[2]

WARNING
Congestive Heart Failure: Thiazolidinediones, including pioglitazone, which is a component of Actoplus Met® and Actoplus Met XR®, cause or exacerbate congestive heart failure in some patients. After initiation of Actoplus Met® or Actoplus Met XR®, and after dose increases, observe patients carefully for signs and symptoms of heart failure (including excessive, rapid weight gain, dyspnea, and/or edema). If these signs and symptoms develop, the heart failure should be managed according to the current standards of care. Furthermore, discontinuation or dose reduction of Actoplus Met® or Actoplus Met XR® must be considered. Actoplus Met® and Actoplus Met XR® are not recommended in patients with symptomatic heart failure. Initiation of Actoplus Met® or Actoplus Met XR® in patients with established New York Heart Association Class III or IV heart failure is contraindicated. Lactic Acidosis: Post-marketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias. The onset of metformin-associated lactic acidosis is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, somnolence, and abdominal pain. Metformin-associated lactic acidosis was characterized by elevated blood lactate levels (greater than 5 mmol/L), anion gap acidosis (without evidence of ketonuria or ketonemia), an increased lactate:pyruvate ratio; and metformin plasma levels generally greater than 5 mcg/mL. Risk factors for metformin-associated lactic acidosis include renal impairment, concomitant use of certain drugs (e.g., carbonic anhydrase inhibitors such as topiramate), age 65 years old or greater, having a radiological study with contrast, surgery and other procedures, hypoxic states (e.g., acute congestive heart failure), excessive alcohol intake, and hepatic impairment. If metformin-associated lactic acidosis is suspected, immediately discontinue Actoplus Met® or Actoplus Met XR® and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended.

VII. Dosing and Administration

The usual dosing regimens for the thiazolidinediones are listed in Table 10.

Table 10. Usual Dosing Regimens for the Thiazolidinediones[1-5]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Single Entity Agents			
Pioglitazone	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes: Tablet: initial, 15 or 30 mg QD; maximum, 45 mg QD	Safety and efficacy in pediatric patients have not been established.	Tablet: 15 mg 30 mg 45 mg
Combination Products			
Pioglitazone and glimepiride	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes who are already treated with a thiazolidinedione and a sulfonylurea or who have inadequate glycemic control on a thiazolidinedione alone or a sulfonylurea alone: Tablet: initial, based on patient's current regimen of pioglitazone and/or sulfonylurea, administer QD; maximum, 45-8 mg/day	Safety and efficacy in pediatric patients have not been established.	Tablet: 30-2 mg 30-4 mg
Pioglitazone and metformin	Adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus when treatment with both pioglitazone and metformin is appropriate: Tablet: initial, based on patient's current regimen of pioglitazone and/or metformin; maximum, 45-2,550 mg/day	Safety and efficacy in pediatric patients have not been established.	Tablet: 15-500 mg 15-850 mg

QD=once daily

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the thiazolidinediones are summarized in Table 11.

Table 11. Comparative Clinical Trials with the Thiazolidinediones

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Cardiovascular Outcomes Trials				
Dormandy et al.[12] (2005) PROactive Pioglitazone 15 mg (month 1) QD titrated to 30 mg QD (month 2) and to 45 mg QD (month 3) if tolerated vs placebo Study drugs were taken in addition to the patients' glucose-lowering drugs and other medications.	DB, MC, PC, PRO, RCT Patients 35 to 75 years of age with type 2 diabetes and an HbA_{1c} >6.5% despite treatment with diet alone or with oral glucose-lowering agents with or without insulin and evidence of extensive macrovascular disease as defined by ≥1 of the following: MI or stroke at least 6 months prior to enrollment, percutaneous coronary intervention or coronary artery bypass surgery at least 6 months prior to enrollment, acute coronary syndrome at least 3 months prior to enrollment,	N=5,238 (n=2,605 for pioglitazone; n=2,633 for placebo) 34.5 months (average time of observation)	Primary: Composite of all-cause mortality, nonfatal MI (including silent MI), nonfatal stroke, acute coronary syndrome, endovascular or surgical intervention on coronary or leg arteries, or amputation above the ankle Secondary: Composite of all-cause mortality, nonfatal MI (excluding silent MI) and nonfatal stroke (main secondary end point); cardiovascular death; and time to individual components of the	Primary: At least one event in the primary composite end point occurred in 514 patients taking pioglitazone and 572 patients taking placebo (HR, 0.90; 95% CI, 0.80 to 1.02; P=0.095). Secondary: Fewer patients on pioglitazone reached the main secondary end point (composite of all-cause mortality, MI and stroke) compared to patients on placebo (301 vs 358 patients; HR, 0.84; 95% CI, 0.72 to 0.98; P=0.027). Significantly more reports of heart failure were noted in patients treated with pioglitazone compared to patients treated with placebo (281 vs 198 patients; P<0.0001). Deaths due to heart failure did not differ significantly between the two study groups (25 for pioglitazone vs 22 for placebo; P=0.634). A greater number of patients on pioglitazone reported edema without heart failure compared to those on placebo (562 vs 341; P value not reported).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	or objective evidence of coronary artery disease or obstructive arterial disease in the leg; patients were excluded if they had type 1 diabetes; were taking insulin only; had planned coronary or peripheral revascularization; had NYHA class II heart failure or above; had ischemic ulcers, gangrene or rest pain in the leg; had had hemodialysis; or had 2.5 times or greater the upper limit of normal concentrations of ALT		primary composite end point	
Erdmann et al.[13] (2016) Pioglitazone vs placebo Study drugs were taken in addition to	MC, OBS Patients who had previously completed the final visit of PROactive (see above) were eligible for enrolment	N=3,599 Mean 7.8 years	Primary: Composite of all-cause mortality, non-fatal MI (including silent MI), stroke, endovascular or surgical intervention in the coronary or leg arteries, and	Primary: During follow-up (mean 7.8 years), there were no statistically significant differences in the primary or main secondary (death, MI, stroke) endpoints for subjects originally randomized to pioglitazone and placebo, except for leg amputations during follow-up (4.1% pioglitazone, 5.6% placebo; HR, 0.74; 95% CI, 0.55 to 0.99; P=0.046). Secondary: During follow-up, the incidence of total malignancies was similar between groups; bladder cancer was reported in 0.8% of patients (n = 14) in the pioglitazone versus 1.2% (n = 21) in the placebo group (RR, 0.65; 95% CI,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
the patients' glucose-lowering drugs and other medications.			amputation above the ankle Secondary: Composite endpoint comprised non-adjudicated all-cause mortality, non-fatal MI and non-fatal stroke; incidence of malignancies	0.33 to 1.28), and prostate cancer was reported in 44 men (3.7%) in the pioglitazone versus 29 men (2.5%) in the placebo group (RR, 1.47; 95% CI, 0.93 to 2.34).
Wilcox et al.[14] (2007) Pioglitazone 15 mg (month 1) QD titrated to 30 mg QD (month 2) and to 45 mg QD (month 3) if tolerated vs placebo Study drugs were taken in addition to the patients' glucose-lowering drugs and other medications.	DB, MC, PC, PRO, RCT Comparison of patients with and without prior stroke enrolled in the PROactive Study (see above)	N=5,238 (n=984 patients with prior stroke; n=4,254 patients without prior stroke) 34.5 months (average time of observation)	Primary: Composite of all-cause mortality, nonfatal MI (including silent MI), nonfatal stroke, acute coronary syndrome, endovascular or surgical intervention on coronary or leg arteries, or amputation above the ankle Secondary: Composite of all-cause mortality, nonfatal MI (excluding silent MI) and nonfatal stroke	Primary: In patients with prior stroke (n=486 pioglitazone and n=498 placebo), there was a trend of benefit with pioglitazone compared to placebo for the primary end point of all-cause mortality, nonfatal MI, nonfatal stroke, acute coronary syndrome, endovascular or surgical intervention on coronary or leg arteries, or amputation above the ankle (event rate, 20.2% pioglitazone vs 25.3% placebo; HR, 0.78; 95% CI, 0.60 to 1.02; P=0.0670). Secondary: In patients with prior stroke, there was a trend of benefit with pioglitazone compared to placebo for the main secondary end point of all-cause mortality, nonfatal MI or nonfatal stroke (event rate, 15.6% with pioglitazone vs 19.7% with placebo; HR, 0.78; 95% CI, 0.58 to 1.06; P=0.1095). In patients with prior stroke, pioglitazone reduced fatal or nonfatal stroke (event rate, 5.6% pioglitazone vs 10.2% placebo; HR, 0.53; 95% CI, 0.34 to 0.85; P=0.0085) and the composite of cardiovascular death, nonfatal MI or nonfatal stroke (event rate, 13.0% with pioglitazone vs 17.7% with placebo; HR, 0.72; 95% CI, 0.52 to 1.00; P=0.0467).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Higher event rates were observed in patients with prior stroke compared to those without prior stroke. In patients without prior stroke, no treatment effect was observed for a first stroke. In a subgroup analysis from PROactive, pioglitazone reduced the risk of recurrent stroke significantly in high-risk patients with type 2 diabetes.
Erdmann et al.[15] (2007) Pioglitazone 15 mg (month 1) QD titrated to 30 mg QD (month 2) and to 45 mg QD (month 3) if tolerated vs placebo Study drugs were taken in addition to the patients' glucose-lowering drugs and other medications.	DB, MC, PC, PRO, RCT Patients who qualified for entry into the PROactive Study on the basis of a previous MI 6 months or more before randomization (see above)	N=2,445 patients with prior MI (n=1,230 in the pioglitazone group; n=1,215 in the placebo group) 34.5 months (average time of observation)	Primary: Fatal or nonfatal MI (excluding silent MI); cardiovascular death or nonfatal MI; cardiovascular death, nonfatal MI or stroke; see PROactive Study Secondary: Acute coronary syndrome; composite of nonfatal MI (excluding silent MI), coronary revascularization, acute coronary syndrome, or cardiac death; see PROactive Study	Primary: Pioglitazone significantly reduced the risk of fatal and nonfatal MI (RR, 28%; P=0.045). There were no significant differences in the end point of cardiovascular death or nonfatal MI (P=0.201) or the end point of cardiovascular death, nonfatal MI or stroke (P=0.149). Secondary: Pioglitazone significantly reduced the risk of acute coronary syndrome (RR, 37%; P=0.035). Pioglitazone significantly reduced the risk of the cardiac composite end point of nonfatal MI, coronary revascularization, acute coronary syndrome and cardiac death (RR, 19%; P=0.033). PROactive: The differences in the primary and main secondary end points defined in the main PROactive study did not reach significance in the MI population (P=0.135 and P=0.0585, respectively); however, there was a consistently lower number of events in the pioglitazone-treated patients for all of the end points. The rate of heart failure and heart failure requiring hospitalization (in patients with a previous MI) were significantly higher in the pioglitazone group compared to the placebo group (13.5 vs 9.6%; P=0.003 and 7.5 vs 5.2%; P=0.022, respectively). The rates of fatal heart failure were similar (1.4% with pioglitazone vs 0.9% with placebo; P=0.283).
Erdmann et al.[16] (2007)	DB, MC, PC, PRO, RCT	N=5,238	Primary: Composite of all-cause mortality,	Primary: Among patients with a serious heart failure event, subsequent all-cause mortality was proportionately lower with pioglitazone (40 of 149 [26.8%]

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Pioglitazone 15 mg (month 1) QD titrated to 30 mg QD (month 2) and to 45 mg QD (month 3) if tolerated vs placebo Study drugs were taken in addition to the patients' glucose-lowering drugs and other medications.	Patients enrolled into the PROactive study who developed serious heart failure (defined as heart failure that required hospitalization or prolonged a hospitalization stay, was fatal or life threatening, or resulted in persistent significant disability or incapacity) (see above); patients with NYHA Class II-IV heart failure at screening were excluded	34.5 months (average time of observation)	nonfatal MI (including silent MI), nonfatal stroke, acute coronary syndrome, endovascular or surgical intervention on coronary or leg arteries, or amputation above the ankle Secondary: Composite of all-cause mortality, nonfatal MI and nonfatal stroke	vs 37 of 108 [34.3%] with placebo; P=0.1338). Proportionately fewer pioglitazone patients with serious heart failure went on to have an event in the primary end point (47.7% with pioglitazone vs 57.4% with placebo; P=0.0593). Secondary: More pioglitazone (5.7%) than placebo patients (4.1%) had a serious heart failure event during the study (P=0.007). However, mortality due to heart failure was similar (25 of 2,605 [0.96%] for pioglitazone vs 22 of 2,633 [0.84%] for placebo; P=0.639). Significantly fewer pioglitazone patients with serious heart failure went on to have an event in the main secondary end point (34.9% with pioglitazone vs 47.2% with placebo; P=0.025).
Wilcox et al.[17] (2008) Pioglitazone 15 mg (month 1) QD titrated to 30 mg QD (month 2) and to 45 mg QD (month 3) if tolerated vs placebo Study drugs were taken in addition to	DB, MC, PC, RCT (PROactive 10 Study) Patients 35 to 75 years of age with type 2 diabetes, HbA_{1c} >6.5% despite treatment with diet or oral antidiabetic agents with or without insulin, and extensive macrovascular disease	N=5,238 34.5 months (average time of observation)	Primary: Analysis of the prespecified main secondary end point (MACE) and additional MACE end points (MACE1 through MACE 7) (MACE=all-cause mortality, nonfatal MI, nonfatal stroke; MACE1=cardio-vascular mortality, nonfatal MI, or	Primary: Pioglitazone was associated with a 16% reduction in the main secondary end point of MACE compared to placebo (P=0.027). In the pioglitazone group, 9.9% of patients experienced an event from the MACE1 composite end point compared to 11.9% of patients receiving placebo (HR, 0.82; 95% CI, 0.70 to 0.97; P=0.0201). Fewer patients receiving pioglitazone experienced an event from the MACE2 end point compared to placebo (HR, 0.83; 95% CI, 0.72 to 0.96; P=0.0103). A similar result was observed for other end points, including MACE3 (P=0.0051), MACE4 (P=0.0120), MACE5 (P=0.0132), and MACE6 (P=0.0034). There was no significant difference in the MACE7 end point. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
the patients' glucose-lowering drugs and other medications.			nonfatal stroke; MACE2=all-cause mortality, nonfatal MI, nonfatal stroke, acute coronary syndrome; MACE3=cardio-vascular mortality, nonfatal MI, nonfatal stroke, acute coronary syndrome; MACE4=cardiac mortality, nonfatal MI, nonfatal stroke; MACE5=cardiac mortality, nonfatal MI, acute coronary syndrome; MACE6=cardiac mortality, nonfatal MI, nonfatal stroke, acute coronary syndrome; MACE7=cardiac mortality, nonfatal MI Secondary: Not reported	Not reported
Home et al.[18] (2007)	MC, OL, RCT Patients with type 2 diabetes between 40	N=4,447 (n=1,117 rosiglitazone plus	Primary: Hospitalization or death from	Primary: For adjudicated primary end points (hospitalization or death from cardiovascular causes), the HR was 1.08 (95% CI, 0.89 to 1.31; P=0.43) with 217 events in the rosiglitazone group and 202 events in the control

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Rosiglitazone plus either metformin or a sulfonylurea vs metformin plus a sulfonylurea	and 75 years of age, BMI >25.0 kg/m^2, HbA_{1c} 7.1 to 9.0% while receiving maximum permitted or tolerated doses of metformin or a sulfonylurea; exclusion criteria were the current use of other glucose-lowering agents, hospitalization for a major cardiovascular event in the previous 3 months, a planned cardiovascular intervention, heart failure, clinically significant hepatic disease, renal impairment, and uncontrolled hypertension	metformin; n=1,103 rosiglitazone plus sulfonylurea; n=2,227 metformin plus sulfonylurea) Mean follow-up 3.75 years for the unplanned interim analyses (study was designed to be 6 years)	cardiovascular causes Secondary: Death from cardiovascular causes and from any cause, MI, congestive heart failure, and composite of death from cardiovascular causes, MI and stroke	group. An additional 91 patients (50 in the rosiglitazone group and 41 in the control group) had potential primary events reported by investigators, but these events were pending adjudication. Secondary: There was no statistically significant difference between the rosiglitazone group and the control group for the following secondary end points: death from cardiovascular causes (HR, 0.83; 95% CI, 0.51 to 1.36; P=0.46) or any cause (HR, 0.93; 95% CI, 0.67 to 1.27; P=0.63), MI (HR, 1.16; 95% CI, 0.75 to 1.81; P=0.50), or the composite of cardiovascular death, MI and stroke (HR, 0.97; 95% CI, 0.73 to 1.29; P=0.83). However, the power to detect significant differences was low, as reflected by the wide 95% CI. Patients in the rosiglitazone group had a significantly higher risk of congestive heart failure than did patients in the control group, with 38 vs 17 adjudicated events (HR, 2.24; 95% CI, 1.27 to 3.97; P=0.006).
Home et al.[19] (2009) RECORD Rosiglitazone plus either metformin or a sulfonylurea vs metformin plus a sulfonylurea	MC, OL, RCT Patients 40 to 75 years of age with type 2 diabetes and BMI ≥25 kg/m^2, on maximum tolerated doses of metformin or a sulfonylurea monotherapy, and inadequate glycemic	N=4,458 5.5 years (mean follow-up)	Primary: Time to first cardiovascular hospitalization or cardiovascular death Secondary: Cardiovascular death, all-cause mortality, MI, stroke, composite	Primary: The primary end point (cardiovascular hospitalization or cardiovascular death) occurred in 321 and 323 patients receiving rosiglitazone and active control, respectively (HR, 0.99; 95% CI, 0.85 to 1.16; P=0.93). Secondary: There was no significant difference between rosiglitazone and active controls for the following end points: cardiovascular death (HR, 0.84; 95%, CI 0.59 to 1.18; P=0.32), all-cause mortality (HR, 0.86; 95% CI, 0.68 to 1.08; P=0.19), MI (HR, 1.14; 95% CI, 0.80 to 1.63; P=0.47), stroke (HR, 0.72; 95% CI, 0.49 to 1.06; P=0.10), and the composite of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	control (HbA_{1c} 7.0 to 9.0%)		of cardiovascular death, MI, and stroke	cardiovascular death, MI, or stroke (HR, 0.93; 95% CI, 0.74 to 1.15; P=0.50). Heart failure occurred in 61 patients receiving rosiglitazone compared to 29 patients receiving active control (HR, 2.10; 95% CI, 1.35 to 3.27; P=0.0010). There were no serious adverse event reports of macular edema. The incidence of bone fractures was higher with rosiglitazone compared to active control (RR, 1.57; 95% CI, 1.26 to 1.97; P<0.0001). The risk was higher in women than in men (RR, 1.82; 95% CI, 1.37 to 2.41 vs RR, 1.23; 95% CI, 0.85 to 1.77; P=0.10). The excess of fractures in patients on rosiglitazone was primarily in the upper limb (RR, 1.57; 95% CI, 1.12 to 2.19; P=0.0095) and distal lower limb (RR, 2.60; 95% CI, 1.67 to 4.04; P<0.0001). Hip and femur fracture did not increase with rosiglitazone treatment. There was a nonsignificant increase in spinal fractures.
Mahaffey et al.[20] (2013) RECORD re-evaluation Rosiglitazone plus either metformin or a sulfonylurea vs metformin plus a sulfonylurea	RETRO Patients 40 to 75 years of age with type 2 diabetes and BMI ≥25 kg/m^2, on maximum tolerated doses of metformin or a sulfonylurea monotherapy, and inadequate glycemic control (HbA_{1c} 7.0 to 9.0%)	N=4,458 5.5 years (mean follow-up)	Primary: Time to first cardiovascular hospitalization or cardiovascular death Secondary: Cardiovascular death, all-cause mortality, MI, stroke, composite of cardiovascular death, MI, and stroke	Primary: For the primary end point (time to first occurrence of CV (or unknown cause) death, MI, or stroke) no statistically significant difference was observed between rosiglitazone and metformin/sulfonylurea using the original RECORD end point definitions (HR, 0.95; 95% CI, 0.78 to 1.17). For the primary end point, no meaningful difference between rosiglitazone and metformin/sulfonylurea was observed using the original RECORD end point definitions (HR, 0.95; 95% CI 0.78 to 1.17) or new FDA end point definitions (HR, 0.97; 95% CI, 0.79 to 1.18). Furthermore, these results are similar to results from the original RECORD study (HR, 0.93; 95% CI, 0.74 to 1.15). Secondary: The original RECORD study results and the Duke Clinical Research Institute clinical events classification results were also similar for the individual components of the composite end point. These findings and the additional sensitivity analyses performed support the original RECORD results and suggest that when using essentially the same data, the observations were not affected by different clinical events classification processes, physician adjudicators, or end point definitions.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Lincoff et al.[21] (2007) Pioglitazone monotherapy vs metformin, placebo, sulfonylureas or rosiglitazone or pioglitazone combination therapy with insulin, metformin, or sulfonylureas vs active comparator or placebo	DB, MA, RCT with placebo or active comparator Adult patients with type 2 diabetes and inadequate glycemic control	N=16,390 (19 trials) 4 months to 3.5 years	Primary: Composite of death from any cause, MI or stroke Secondary: Incidence of serious heart failure	Primary: Death, MI, or stroke occurred in 375 of 8,554 patients (4.4%) receiving pioglitazone and 450 of 7,836 patients (5.7%) receiving control therapy (HR, 0.82; 95% CI, 0.72 to 0.94; P=0.005). Individual components of the primary end point were reduced with pioglitazone treatment with varying degrees of statistical significance (death: HR, 0.92; P=0.38, MI: HR, 0.81; P=0.08, death and MI: HR, 0.85; P=0.04, and stroke: HR, 0.80; P=0.09). Progressive separation of time-to-event curves became apparent after approximately one year of therapy. Secondary: Serious heart failure was reported in 2.3% of the pioglitazone-treated patients and 1.8% of the control treated patients (HR, 1.41; 95% CI, 1.14 to 1.76; P=0.002). The composite of serious heart failure and death was not significantly increased among patients receiving pioglitazone (HR, 1.11; 95% CI, 0.96 to 1.29; P=0.17).
Richter et al.[22] (2006) Pioglitazone monotherapy vs acarbose, metformin, placebo, repaglinide, rosiglitazone,	MA of DB (15) or OL (4) RCTs (last search conducted in August 2006, included PROactive Study), PG Adults with type 2 diabetes, trial duration of at least 24 weeks	22 trials N=6,200 randomized to pioglitazone treatment (total N not reported) 24 weeks to 34.5 months	Primary: Patient-oriented outcomes including mortality, morbidity and adverse effects Secondary: Health-related quality of life and HbA_{1c}	Primary: Only one trial (PROactive Study) evaluated mortality and morbidity as an end point. The primary composite end point (time from randomization to all-cause mortality, nonfatal MI, stroke, acute coronary syndrome, endovascular or surgical intervention on the coronary or leg arteries, or amputation above the ankle) did not show statistically significant differences between the pioglitazone and placebo group (HR, 0.90; 95% CI, 0.80 to 1.02; P=0.095). Time to the first event of the composite end point of death from any cause, MI and stroke indicated a statistically significant difference between pioglitazone and placebo (HR, 0.84; 95% CI, 0.72 to 0.98; P=0.027). The individual components of the primary composite end point did not disclose

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
sulfonylurea or pioglitazone combination therapy vs combination therapy not containing pioglitazone				statistically significant differences between the intervention and control groups. Significantly more patients developed heart failure requiring hospitalization following administration of pioglitazone (6 vs 4% on placebo; P=0.007). The percentage of overall and serious adverse events was comparable between the intervention and control groups. Six trials reported a more pronounced (sometimes dose-related) decrease of hemoglobin after pioglitazone intake in comparison to other active compounds or placebo; hemoglobin reductions ranged between -0.50 and- 0.75 g/dL. Fifteen trials evaluated body weight and observed an increase up to 3.9 kg after pioglitazone treatment; seven trials described a rise in BMI up to 1.5 kg/m^2. Eleven of the 22 included trials showed data on hypoglycemic episodes: compared to the active monotherapy control, pioglitazone treatment resulted in somewhat lower rates of hypoglycemia (P value not reported). The RR for development of edema with pioglitazone compared to the control was 2.86 (95% CI, 2.14 to 3.18; P<0.00001) when results from 18 trials were pooled. Secondary: No study investigated health-related quality of life. Active glucose-lowering compounds like metformin, glibenclamide‡, gliclazide* or glimepiride resulted in similar reductions of HbA_{1c} compared to pioglitazone treatment (P values not reported).
Mannucci et al.[23] (2008) Pioglitazone vs active comparators, placebo, no treatment	MA (94 trials) Patients treated with pioglitazone (with or without type 2 diabetes)	N=21,180 Variable duration	Primary: All-cause mortality, non-fatal coronary event (defined as MI, unstable angina or coronary revascularization), non-fatal chronic heart failure requiring hospitalization	Primary: In PROactive, pioglitazone treatment was not associated with a significant reduction in all-cause mortality (P value not reported). In non-diabetic patients, only one death was observed occurring among pioglitazone-treated patients. In type 2 diabetic patients (excluding PROactive), the total number of deaths reported was 17 and 39 in the pioglitazone and comparator groups, respectively (RR, 0.41; 95% CI, 0.23 to 0.72).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Secondary: Not reported	When analyzing all trials, no significant reduction of mortality was observed with pioglitazone. Comparing different agents, pioglitazone was associated with a lower mortality rate compared to sulfonylureas. There was no significant difference in all-cause mortality with metformin, rosiglitazone, glitazars, or placebo. When trials with zero events were included in the analysis, no significant difference was observed with sulfonylureas (RR, 0.22; 95% CI, 0.05 to 1.03), metformin (RR, 0.66; 95% CI 0.19 to 2.34), rosiglitazone (RR, 0.49; 95% CI, 0.04 to 5.36), glitazars (RR, 0.42; 95% CI, 0.11 to 1.61), or placebo (RR, 0.16; 95% CI, 0.02 to 1.45). In PROactive, pioglitazone significantly reduced the incidence of non-fatal coronary events (P value not reported). In non-diabetic subjects, only two non-fatal coronary events occurred and one case of heart failure in pioglitazone group were reported. In type 2 diabetes, 44 and 50 non-fatal coronary events were observed in pioglitazone and comparator groups, respectively (RR, 0.82; 95% CI, 0.55 to 1.23). Combining trials with at least one event, the difference between pioglitazone and comparators was not statistically significant. In PROactive, pioglitazone was associated with an increased risk for chronic heart failure. In the other 40 trials reporting data on non-fatal heart failure requiring hospitalization, 58 cases were reported in pioglitazone-treated subjects and 39 in controls (RR ,1.32; 95% CI, 0.88 to 1.98). Combining the results of all trials with at least one event except PROactive, the overall difference between pioglitazone and comparators was not significant (P value not reported). When adding PROactive or excluding trials vs dual PPARα/γ agonists pioglitazone was associated with a significant increase of risk for chronic heart failure.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				In comparison with different agents, pioglitazone was associated with an increased risk of chronic heart failure in PC trials, while differences with sulfonylureas or glitazars did not reach significance. Secondary: Not reported
Nagajothi et al.[24] (2008) Pioglitazone vs active comparators (metformin and/or sulfonylurea) or placebo	MA (5 trials) Patients treated with pioglitazone	N=not reported Duration varied	Primary: MI Secondary: Stroke, revascularization, total mortality, cardiovascular mortality	Primary: The RR for MI was 0.86 (95% CI, 0.69 to 1.07; P=0.17). Secondary: The RR for stroke was 0.79 (95% CI, 0.61 to 1.02; P=0.07). The RR for total mortality was 0.94 (95% CI, 0.78 to 1.15; P=0.56). The RR for coronary revascularization was 0.40 (95% CI, 0.13 to 1.23; P=0.11. The RR for cardiovascular mortality was 0.92 (95% CI, 0.73 to 1.16; P=0.47).
Vaccaro et al.[25] (2017) TOSCA.IT Pioglitazone (15 to 45 mg) vs sulfonylurea (5 to 15 mg glibenclamide, 2 to 6 mg glimepiride, or 30 to 120 mg gliclazide)	MC, OL, RCT Patients 50 to 75 years of age with type 2 diabetes inadequately controlled with metformin monotherapy (2 to 3 g per day)	N=3,028 Median follow-up of 57.3 months	Primary: Composite of first occurrence of all-cause death, non-fatal MI, non-fatal stroke, or urgent coronary revascularization, assessed in the modified intention-to-treat population (all randomly assigned participants with baseline data available and without any protocol violations	Primary: The primary cardiovascular composite outcome occurred in 105 patients (7%; 1.5 per 100 person-years) who were given pioglitazone and 108 patients (7%; 1.5 per 100 person-years) who were given sulfonylureas. There were no significant between-group differences in the composite primary outcome (HR, 0.96; 95% CI, 0.74 to 1.26; P=0.79) or in its components. On the basis of a futility analysis, the study was stopped when the median follow-up was 57.3 months. Secondary: The key secondary outcome occurred in 74 patients (5%; 1.1 per 100 person-years) in the pioglitazone group and in 83 patients (6%; 1.2 per 100 person-years) in the sulfonylureas group (HR, 0.88; 0.65 to 1.21; P=0.44).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			in relation to inclusion or exclusion criteria) Secondary: Composite of ischemic cardiovascular disease, which included first occurrence of sudden death, fatal and non-fatal MI (including silent MI), fatal and non-fatal stroke, leg amputation above the ankle, and any revascularization of the coronary, leg, or carotid arteries	
Nissen et al.[26] (2007) Rosiglitazone monotherapy or combination therapy vs monotherapy or combination therapy with gliclazide*, glimepiride, glipizide, glyburide, insulin,	MA of RCTs of more than 24 weeks that had outcome data for MI and death from cardiovascular causes (included ADOPT and DREAM trials) Mean age of participants was 56 years, mean baseline HbA_{1c} 8.2%	42 trials n=15,560 for rosiglitazone; n=12,283 for comparator 24 to 208 weeks	Primary: MI and death from cardiovascular causes Secondary: Not reported	Primary: Rosiglitazone was associated with a significant increase in the risk of MI compared to the control agent (OR, 1.43; 95% CI, 1.03 to 1.98; P=0.03). Compared to the control agent, rosiglitazone was associated with a trend toward increased cardiovascular death (OR, 1.64; 95% CI, 0.98 to 2.74; P=0.06). Although not a prespecified end point, the OR for death from any cause with rosiglitazone was 1.18 (95% CI, 0.89 to 1.55; P=0.24). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
metformin, placebo				
Singh et al.[27] (2007) Rosiglitazone vs placebo or other non-TZD oral hypoglycemic agent (including glyburide or metformin)	MA of RCTs (available up to May 2007 and included ADOPT, DREAM and RECORD trials) of rosiglitazone of at least 12 months duration Study participants with impaired glucose tolerance or type 2 diabetes, studies monitored cardiovascular adverse events and provided numerical data on all adverse events	4 trials N=14,291 (n=6,421 rosiglitazone; n=7,870 control) 1 to 4 years	Primary: RR of MI, heart failure, and cardiovascular mortality Secondary: Not reported	Primary: Rosiglitazone significantly increased the risk of MI (94 vs 83; RR, 1.42; 95% CI, 1.06 to 1.91; P=0.02) and heart failure (102 vs 62; RR, 2.09; 95% CI, 1.52 to 2.88; P<0.001) compared to the control. There was no significant difference in the risk of cardiovascular mortality between the rosiglitazone and control group (59 vs 72; RR, 0.90; 95% CI, 0.63 to 1.26; P=0.53). Rosiglitazone had no effect on all-cause mortality (146 vs 180; RR, 0.99; 95% CI, 0.80 to 1.23; P=0.92). Secondary: Not reported
Richter et al.[28] (2007) Rosiglitazone monotherapy vs glyburide, metformin, pioglitazone, placebo, repaglinide or	MA of DB (11) or OL (5) RCTs (last search conducted in April 2007, included the ADOPT trial), PG Adults with type 2 diabetes, trial duration of at least 24 weeks	18 trials N=3,888 randomized to rosiglitazone treatment (total N not reported) 24 weeks to 4 years (median 26 weeks)	Primary: Patient-oriented outcomes including mortality, morbidity and adverse effects Secondary: Health-related quality of life and metabolic control (HbA_{1c})	Primary: No study included mortality as a primary or secondary end point. While not an initial primary or secondary study end point, the ADOPT trial reported that the all-cause mortality was 2.3% in the rosiglitazone group, 2.1% in the metformin group and 2.2% in the glyburide group (P values not reported in this reference). The ADOPT trial also reported comparable hospitalization rates for any cause between rosiglitazone (11.6%), metformin (11.8%), and glyburide (10.4%) groups (P values were not reported in this reference). Cardiovascular disease was increased in the rosiglitazone group compared to the glyburide group but not the metformin group with serious/total events reported in 3.4/4.3% and 1.8/2.8% of patients receiving rosiglitazone and glyburide, respectively (events were 3.2/4.0% with metformin; P values were not reported in this reference). Congestive heart

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
rosiglitazone combination therapy vs combination therapy not containing rosiglitazone				failure was observed more frequently in patients receiving rosiglitazone (1.5%) than patients receiving glyburide (0.6%) but not metformin (1.3%; P values were not reported in this reference). The percentage of overall adverse events was comparable between the intervention and control groups (which included placebo arms); serious adverse events appeared to happen more often after rosiglitazone treatment (median of 6 vs 4% in the control groups; P value not reported). Median discontinuation rate following rosiglitazone administration was also higher than after control therapy (median of 7 vs 4%; P value not reported). Three studies reported a more pronounced (apparently dose-related) decrease of hemoglobin after rosiglitazone intake in comparison to other active compounds or placebo; hemoglobin reductions ranged between 0.5 and 1.0 g/dL. Eleven studies evaluated body weight and observed an increase up to 5.0 kg after rosiglitazone treatment; four studies described a rise in BMI up to 1.5 kg/m^2. Seven of the 18 included studies showed data on hypoglycemic episodes: compared to active monotherapy control, rosiglitazone treatment resulted in somewhat lower rates of hypoglycemia, especially when compared to sulfonylureas. Occurrence of edema was significantly raised when results of nine studies were pooled (OR, 2.27; 95% CI, 1.83 to 2.81; P<0.00001). The ADOPT trial reported a higher incidence of fractures in women receiving rosiglitazone (9.30%) than metformin (5.08%; P<0.01) or glyburide (3.47%; P<0.01). Secondary: No study investigated health-related quality of life. Active glucose-lowering compounds like metformin, glibenclamide‡ or glimepiride resulted in similar reductions of HbA_{1c} compared to rosiglitazone treatment.
Lago et al.[29] (2007) Pioglitazone 15 to 45 mg per day or rosiglitazone 4 to 8 mg per day	MA of DB, RCTs of TZDs that reported risk estimates or frequency data for congestive heart	7 trials N=20,191 29.7 months (range, 12 to 48 months)	Primary: Development of congestive heart failure, risk of cardiovascular death	Primary: Three hundred and sixty of 20,191 patients who had either prediabetes or type 2 diabetes had congestive heart failure events (214 with TZDs and 146 with comparators). The overall event rate for congestive heart failure was 2.3% for patients receiving TZDs and 1.4% in the comparator group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo, glibenclamide‡, glimepiride, metformin, metformin plus sulfonylurea	failure and cardiovascular death Patients with prediabetes or type 2 diabetes (with and without cardiovascular disease), mean age 59.2 years, mean BMI 31 kg/m^2, mean baseline HbA_{1c} 7.72%		Secondary: Not reported	Patients given pioglitazone (RR, 1.32; 95% CI, 1.04 to 1.68; P=0.02) or rosiglitazone (RR, 2.18; 95% CI, 1.44 to 3.32; P=0.0003) had increased risk for development of congestive heart failure across a wide background of cardiac risk compared to the control agent (combined RR, 1.72; 95% CI, 1.21 to 2.42; P=0.002). The risk for congestive heart failure did not differ for rosiglitazone and pioglitazone (RR, 1.74; 95% CI, 0.97 to 3.14; P=0.07). The overall event rate for cardiovascular death was 0.7% in both groups. The risk of cardiovascular death was not increased with pioglitazone (RR, 1.01; 95% CI, 0.51 to 2.01; P=0.98), rosiglitazone (RR, 0.91; 95% CI, 0.63 to 1.32; P=0.63) or both TZDs (combined RR, 0.93; 95% CI, 0.67 to 1.29; P=0.68). The risk of cardiovascular death did not differ between both drug groups (RR, 1.01; 95% CI, 0.73 to 1.40; P=0.96). Secondary: Not reported
Karter et al.[30] (2005) Patients initiated pioglitazone (15.2%), sulfonylureas (25.3%), metformin (50.9%), and insulin (8.6%) alone, or in addition to pre-existing therapies	Cohort study of all patients in the Kaiser Permanente Medical Care Program with type 2 diabetes (Kaiser Permanente Northern California Diabetes Registry) who initiated any new diabetes pharmacotherapy between October 1999 and November 2001	N=23,440 10.2 months (mean)	Primary: Time-to-incident admission to hospital for congestive heart failure Secondary: Not reported	Primary: Three hundred and twenty admissions for congestive heart failure were observed during the follow-up (mean, 10.2 months) after drug initiation. Relative to patients initiating sulfonylureas, there were no significant increases in the incidence of hospitalization for congestive heart failure in those initiating pioglitazone (HR, 1.28; 95% CI, 0.85 to 1.92). There was a significantly higher incidence among those initiating insulin (HR, 1.56; 95% CI, 1.00 to 2.45) and lower incidence among those initiating metformin (HR, 0.70; 95% CI, 0.49 to 0.99). Secondary: Not reported
Gerrits et al.[31] (2007) Pioglitazone	RETRO cohort study Patients median age 56 years who were	N=29,911 (n=14,807 pioglitazone; n=15,104 rosiglitazone)	Primary: Risk of hospitalization for acute MI	Primary: Among the patients that initiated pioglitazone, 1.1% of patients were hospitalized for acute MI during follow-up compared to 1.4% for rosiglitazone (no P value reported). The unadjusted HR for hospitalization for acute MI associated with pioglitazone relative to rosiglitazone was

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs rosiglitazone	initiated treatment with pioglitazone or rosiglitazone between 2003 and 2006	1.2 to 1.3 years	Secondary: Risk of composite of acute MI or coronary revascularization	0.82 (95% CI, 0.67 to 1.01; P value not reported). After readjustment for baseline covariants (e.g., medical conditions, procedures and dispensed drugs), the HR was 0.78 (95% CI, 0.63 to 0.96; P value not reported). Secondary: There were 2.6 and 3.1% of patients in the pioglitazone and rosiglitazone groups, respectively, with a first event in the composite end point of acute MI or coronary revascularization. The adjusted HR for the composite of acute MI or coronary revascularization was 0.85 (95% CI, 0.75 to 0.98; P value not reported).
Lipscombe et al.[32] (2007) Pioglitazone or rosiglitazone vs other oral hypoglycemic agents	Nested case-control analysis of a RETRO cohort study using health care databases in Ontario, Canada Diabetes patients 66 years of age or older treated with at least 1 oral hypoglycemic agent between 2002 and 2005, follow-up until March 31, 2006	N=159,026 Median follow-up 3.8 years	Primary: Emergency department visit or hospitalization for congestive heart failure Secondary: Emergency department visit or hospitalization for acute MI, all-cause mortality	Primary: Current treatment with TZD monotherapy was associated with a significantly increased risk of congestive heart failure (78 cases; adjusted RR, 1.60; 95% CI, 1.21 to 2.10; P<0.001) compared to other oral hypoglycemic agent combination therapies (3,478 congestive heart failure cases). The increased risk of congestive heart failure associated with TZD use appeared limited to rosiglitazone. Secondary: Current treatment with TZD monotherapy was associated with a significantly increased risk of acute MI (65 vs 3,695 cases; RR, 1.40; 95% CI, 1.05 to 1.86; P=0.02) and death (102 vs 5,529 cases; RR, 1.29; 95% CI, 1.02 to 1.62; P=0.03) compared to other oral hypoglycemic agent combination therapies.
Saenz et al.[33] (2005) Metformin monotherapy vs placebo, sulfonylureas, TZDs, meglitinides,	MA (29 RCTs) Adult patients with type 2 diabetes	N=5,259 ≥3 months	Primary: Incidence of any diabetes-related outcomes (sudden death, death from hyperglycemia or hypoglycemia, fatal or nonfatal MI, angina, heart failure, stroke, renal failure,	Primary: Obese patients receiving metformin showed a greater benefit than chlorpropamide, glibenclamide*, or insulin for any diabetes-related outcomes (P=0.009) and for all-cause mortality (P=0.03). Obese patients receiving metformin showed a greater benefit than overweight patients on conventional treatment (diet) for any diabetes-related outcomes (P=0.004), diabetes-related death (P=0.03), all cause mortality (P=0.01), and MI (P=0.02). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
α-glucosidase inhibitors, diet, any other oral antidiabetic intervention, insulin			amputation [of at least one digit], vitreous hemorrhage, retinopathy requiring photocoagulation, blindness in one eye, or cataract extraction); diabetes-related death (death from MI, stroke, peripheral vascular disease, renal disease, hypo-glycemia or hyperglycemia, and sudden death); all-cause mortality Secondary: Changes in HbA_{1c}, FPG, quality of life, weight, BMI, lipids, insulin, C-peptide, BP, micro-albuminuria, glomerular filtration rate, renal plasma flow	Patients receiving metformin monotherapy showed a significant benefit for glycemic control, weight, dyslipidemia, and DBP. Metformin presents a strong benefit for HbA_{1c} when compared to diet and placebo. Additionally, metformin showed a moderate benefit for glycemic control, LDL-C, and BMI or weight when compared to sulfonylureas.
Type 2 Diabetes – Monotherapy				
Khan et al.[34] (2002) Pioglitazone 15 to 45 mg QD	OL, PRO, RCT Patients previously stabilized on troglitazone* with	N=186 4 months	Primary: Change in body weight, HbA_{1c}, and lipoproteins	Primary: Both groups experienced equal and significant weight gain of ~2 kg from baseline ($P<0.01$).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs rosiglitazone 2 to 4 mg QD or 4 mg BID	stable liver function, baseline HbA_{1c} 7.9% for pioglitazone and 8.0% for rosiglitazone		Secondary: Not reported	No significant change in HbA_{1c} from baseline or difference between groups was observed after four months. Pioglitazone had significant reductions in TC (~ -20 mg/dL†) compared to rosiglitazone (~5 mg/dL†; P<0.01). Pioglitazone had significant reductions in LDL-C (~ -16 mg/dL†) compared to rosiglitazone (~2 mg/dL†; P<0.01). Secondary: Not reported
Goldberg et al.[35] (2005) Pioglitazone 30 mg QD, titrated to 45 mg QD after 12 weeks vs rosiglitazone 4 mg QD, titrated to 4 mg BID after 12 weeks	DB, MC, PG, PRO, RCT Patients >35 years of age with type 2 diabetes with HbA_{1c} >7.0%, TG ≥150 mg/dL, LDL-C ≤130 mg/dL and C-peptide ≥1 ng/mL; baseline HbA_{1c} 7.6% for pioglitazone and 7.5% for rosiglitazone; patients were excluded if they had NYHA class III-IV heart failure, MI or stroke in past 6 months; liver disease; serum creatinine >2 mg/dL; receiving renal dialysis or having renal	N=802 24 weeks	Primary: Change in TG, lipoproteins, and HbA_{1c}; safety Secondary: Not reported	Primary: TG levels significantly decreased (-51.9 mg/dL) with pioglitazone while TG levels increased with rosiglitazone (13.1 mg/dL; P<0.001). Pioglitazone significantly increased HDL-C (5.2 mg/dL) compared to rosiglitazone (2.4 mg/dL; P<0.001). Non-HDL-C was significantly higher with rosiglitazone (25.7 mg/dL) compared to pioglitazone (3.6 mg/dL; P<0.001). Both treatment groups increased LDL-C, however, smaller increases were observed with pioglitazone (12.3 vs 21.3 mg/dL; P<0.001). LDL particle concentration was reduced with pioglitazone and increased with rosiglitazone (P<0.001). LDL particle size increased more with pioglitazone (P=0.005). Similar reductions in HbA_{1c} were observed with pioglitazone (-0.7%) and rosiglitazone (-0.6%; P=0.129). No difference between agents was observed in adverse events including edema, heart failure, liver function tests, BP, and hypoglycemic episodes. Similar weight gain was observed with pioglitazone (2.0 kg) and rosiglitazone (1.6 kg; P=0.164).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	transplant; current glucocorticoid use; receiving any lipid-lowering medication, insulin, combination oral antidiabetic therapy or weight loss agent; pregnant or breast feeding; receiving therapy for malignancy; or drug or alcohol abuse			Secondary: Not reported
Tran et al.[36] (2006) Pioglitazone 45 mg daily vs rosiglitazone 8 mg daily	RETRO Chart review of type 2 diabetic patients who received a TZD for >4 months after inadequate glycemic control on maximally tolerated doses of metformin and a sulfonylurea, baseline HbA_{1c} 9.5% for pioglitazone and 9.3% for rosiglitazone	N=104 1 year	Primary: Proportion of patients with $HbA_{1c} \leq 7.5\%$ at four and 12 months Secondary: Not specified	Primary: After four months, 62% of patients on pioglitazone (35 total) and 65% of patients on rosiglitazone (31 total) achieved an $HbA_{1c} \leq 7.5\%$ (P value not reported). Mean HbA_{1c} levels were 7.4% for pioglitazone and 7.5% for rosiglitazone. Of the original population with an $HbA_{1c} \leq 7.5\%$ at four months, 63% of patients on pioglitazone (22 total) and 61% of patients on rosiglitazone (19 total) maintained an $HbA_{1c} \leq 7.5\%$ after one year (P value not reported). Secondary: Not specified
Derosa et al.[37] (2004) Pioglitazone 15 mg once daily vs	DB, MC, PG, RCT Patients $\geq$18 years of age with type 2 diabetes and metabolic syndrome, poor	N=87 12 months	Primary: Change in baseline BMI, HbA_{1c}, FPG, PPG, fasting plasma insulin, postprandial plasma insulin,	Primary: Patients in the pioglitazone and rosiglitazone groups experienced a significant increase in mean BMI at 12 months compared to baseline (4.92 and 6.17%, respectively; both $P<0.05$). At 12 months, there was a 1.3% improvement from baseline in mean values for HbA_{1c} ($P<0.01$), 19.3% in FPG ($P<0.01$), 16.3% in PPG

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
rosiglitazone 4 mg once daily	glycemic control (HbA_{1c} >7.5%) or experienced adverse effects with diet and oral hypoglycemic agents, such as sulfonylureas or metformin, administered up to maximum tolerated dose		HOMA index, lipid profile, and lipoprotein variables; safety Secondary: Not reported	(P<0.01), 42.4% in fasting plasma insulin (P<0.05), and 23.3% in postprandial plasma insulin (P<0.05); no significant differences were found between treatment groups. Significant improvements in mean HOMA index were also observed in both groups compared to baseline (both P<0.01). Patients receiving pioglitazone experienced a significant improvement at 12 months in almost all variables of lipid metabolism from baseline including TC (-11%), LDL-C (-12%), HDL-C (15%), and Apo B (-10.6%; all P<0.05). Patients receiving rosiglitazone experienced a significant increase in TC (14.9%), LDL-C (16.5%), TG (17.9%), and Apo B (10.3%; all P<0.05). Of the 87 patients who completed the study, three out of 45 patients in the pioglitazone group and five out of 42 patients in the rosiglitazone group had transient, mild-to-moderate adverse events that did not cause withdrawal from the trial. Secondary: Not reported
Derosa et al.[38] (2006) Pioglitazone 15 mg QD vs rosiglitazone 4 mg QD	DB, MC, PG, RCT Patients ≥18 years of age with type 2 diabetes and metabolic syndrome, poor glycemic control (HbA_{1c} >7.5%) or experienced adverse effects with diet and metformin, administered up to maximum tolerated dose	N=96 12 months	Primary: Change in baseline BMI, HbA_{1c}, lipid profile, lipoprotein (a), and homocysteine Secondary: Change in baseline FPG, PPG, and HOMA index	Primary: No BMI change was observed at three, six, nine and 12 months in either group. There was no difference in BMI value between pioglitazone and rosiglitazone (P value not reported). Significant HbA_{1c} decreases were observed at nine (both P<0.05 vs baseline) and 12 months (both P<0.01 vs baseline) in both groups. Significant TC, LDL-C, HDL-C, and TG improvement was present in the pioglitazone group at 12 months compared to the baseline values, and these variations were significantly different than rosiglitazone (P<0.05). No TC, LDL-C, HDL-C, or TG improvement was present in the rosiglitazone group after 12 months. Significant lipoprotein (a) and homocysteine improvement was present in the pioglitazone group at 12 months compared to the baseline values (both P<0.05), and lipoprotein (a) change was significant compared to the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				rosiglitazone group (P<0.05). A significant homocysteine decrease was observed in the rosiglitazone group at the end of the study (P<0.05). Secondary: After nine and 12 months, mean FPG and PPG levels decreased in both groups compared to baseline (both P<0.05 and P<0.01, respectively). HOMA index improved in both groups at 12 months (P<0.05).
Berneis et al.[39] (2008) Pioglitazone 30 mg QD for 4 weeks, then 45 mg QD for 8 weeks vs rosiglitazone 4 mg QD for 4 weeks, then 4 mg BID for 8 weeks All lipid-lowering medications were discontinued 4 weeks prior to the study.	RCT, XO Patients with type 2 diabetes for ≥6 months with a stable HbA_{1c} (6.5 to 9.0%) and on a maximum of 2 oral antidiabetic drugs	N=9 24 weeks of active treatment (plus an additional 8 week wash-out period)	Primary: Change in HbA_{1c}, insulin sensitivity, lipid parameters Secondary: Not reported	Primary: The mean change in HbA_{1c} from baseline to week 12 was -0.54% with pioglitazone and -0.59% with rosiglitazone (P=0.55). Insulin resistance decreased 14% with pioglitazone and 10% with rosiglitazone (P=0.51). There were no significant differences among the treatment groups in the following fasting lipid parameters: HDL-C (P=0.26), LDL-C (P=0.31), LDL size (P=0.51). TC increased more after rosiglitazone compared to pioglitazone (9 vs 3%; P=0.04). TG decreased after treatment with pioglitazone and increased after treatment with rosiglitazone (-21 vs 19%; P=0.004). The only postprandial lipid parameters that demonstrated a significant effect of pioglitazone compared to rosiglitazone was an increased LDL-IIB (5 vs -4%; P=□0.01) and decreased LDL-IVB (-15 vs 10%; P=□0.05) after three hours. After six hours, there were no significant changes found. Secondary: Not reported
Chappuis et al.[40] (2007) Pioglitazone 30 mg QD for 4 weeks, then 45 mg QD for 8 weeks	RCT, XO Patients with type 2 diabetes for ≥6 months with a stable HbA_{1c} (6.5 to 9.0%) and on a maximum	N=17 24 weeks of active treatment (plus an additional 8 week wash-out period)	Primary: Change in HbA_{1c}, FPG, insulin, insulin sensitivity, non-esterified fatty acids, lipid parameters	Primary: Treatment with pioglitazone and rosiglitazone resulted in similar changes in HbA_{1c} (-0.3 and -0.5%, respectively; P=0.43), FPG (-1.4 and -1.6 mmol/L, respectively; P=0.68), fasting insulin concentrations (-3.9 and -8.2 mU/L, respectively; P=0.33), insulin sensitivity (-2.4 and -4.7 mmol/L × mU/L, respectively; P=0.33), and fasting non-esterified fatty acids concentrations (0.2 and -0.5 mmol/L; P=0.25).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs rosiglitazone 4 mg QD for 4 weeks, then 4 mg BID for 8 weeks All lipid-lowering medications were discontinued 4 weeks prior to the study.	of 2 oral antidiabetic drugs		Secondary: Not reported	Pioglitazone led to a reduction in fasting TG compared to an increase with rosiglitazone (−0.35 and 0.44 mmol/L, respectively; P=0.037). Pioglitazone did not change the fasting TC concentration, whereas there was an increase with rosiglitazone (0.06 and 0.59 mmol/L, respectively; P=0.031). Pioglitazone did not change the fasting VLDL-protein concentrations within the VLDL fractions, whereas rosiglitazone increased the protein content of VLDL-2 (−2.6 and 17.7 mg/dL, respectively; P=0.035). There were no significant differences on apoB and apoA-I between the groups. Pioglitazone led to a reduction in apoC-II concentrations compared to an increase with rosiglitazone (−0.1 and 1.0 mg/dL, respectively; P=0.022). There was no significant difference in apoC-III (P=0.094) or the apoC-II/apoC-III ratio among the groups. There was no difference in lipoprotein and hepatic lipase activity among patients receiving pioglitazone and rosiglitazone. Cholesterol ester transfer protein activity decreased after treatment with rosiglitazone and increased following treatment with pioglitazone (−6.2 and 4.6 pmol/mL/min, respectively; P<0.001). There was no difference in PPG and post-prandial insulin concentrations between the treatment groups (P=0.944 and P=0.703, respectively). AUC of TG concentrations showed a significant difference between rosiglitazone and pioglitazone (P=0.017). AUC of non-esterified fatty acids concentrations was not significantly different among the treatment groups (P=0.610). The VLDL composition after three and six hours was significantly different following treatment with pioglitazone compared to rosiglitazone, favor of pioglitazone. Secondary: Not reported
Kikuchi et al.[41]	DB, PG, RCT	N=372	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2012) Pioglitazone 15 to 45 mg/day vs rosiglitazone 4 to 8 mg/day vs placebo	Drug-naïve Japanese type 2 diabetes patients aged 20 to 75 years with an HbA_{1c} ≥7.4%	28 weeks	Superiority of each active treatment compared to placebo in HbA_{1c} at week 16, and non-inferiority between active agents in HbA_{1c} at week 28, based on a −0.45% margin Secondary: Change in FPG from baseline to week 16, the proportions of HbA_{1c} responders (≥0.7% reduction from baseline in HbA_{1c} or an HbA_{1c} <6.5%) and FPG responders (≥30 mg/dL reduction from baseline in FPG or an FPG <126 mg/dL) at week 28, and changes in fasting HOMA-IR and HOMA-β at week 28	Both active treatments were significantly more effective than placebo. The placebo-subtracted HbA_{1c} treatment differences for rosiglitazone and pioglitazone from baseline to week 16 were -0.96% (95% CI, -1.22 to -0.69) and -1.26% (95% CI, -1.56 to -0.97), respectively. In the efficacy evaluable set at week 28, rosiglitazone and pioglitazone had mean changes in HbA_{1c} from baseline of -0.94% and -1.35%, respectively. By the criteria predefined in the study design, non-inferiority of rosiglitazone to pioglitazone was not demonstrated (treatment difference mean -0.41%; 95% CI, -0.64 to -0.18). Secondary: Similar reductions in FPG were seen at week 16 and week 28 with the active agents. The proportion of patients with a ≥0.7% reduction from baseline HbA_{1c} was 56.0% with rosiglitazone and 72.7% with pioglitazone, and the proportion with HbA_{1c} <6.5% was 6.0% and 20.1%, respectively. The proportion of patients with ≥30 mg/dL reduction from baseline FPG was 49.3% with rosiglitazone and 55.4% with pioglitazone and the proportion with FPG <126 mg/dL was 20.0% and 33.1%, respectively. At week 28 in the full analysis set, mean (±SD) HOMA-IR decreased from baseline in both the rosiglitazone (-0.8±4.0) and pioglitazone groups (-1.5±3.7), and HOMA-β increased in both groups (8.6±23.4 and 5.7±19.1, respectively).
Pavo et al.[42] (2003) Pioglitazone 30 to 45 mg daily	DB, MC, RCT Recently diagnosed (<12 months) type 2 diabetic patients ≥40 years old,	N=205 32 weeks	Primary: Change in HbA_{1c} from baseline Secondary:	Primary: Each treatment group had a significant reduction in HbA_{1c} from baseline (P<0.0001 for each group). The difference between pioglitazone and metformin was not significant (P=0.280). Secondary:

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vs metformin 850 to 2,550 mg daily	HbA_{1c} 7.5 to 11.0%, and naïve to oral antihyperglycemic medications		Changes in FPG, fasting serum insulin, and insulin sensitivity	Each treatment group had a significant reduction in FPG (P<0.0001 for each group). The difference between pioglitazone and metformin was not significant (P=0.620). Pioglitazone reduced fasting serum insulin significantly (P<0.0001). The change in fasting serum insulin was not significant for metformin (P=0.803). Pioglitazone was significantly more effective than metformin in improving indicators of insulin sensitivity, as determined by reduction of fasting serum insulin (P=0.003) and by analysis of HOMA-S (P=0.002).
Giles et al.[43] (2008) Pioglitazone 30 to 45 mg QD vs glyburide 10 to 15 mg daily Insulin was the only rescue medication allowed.	DB, MC, RCT Patients ≥18 years of age with type 2 diabetes, HbA_{1c} ≥7.0%, BMI ≤48 kg/m^2, NYHA functional Class II/III heart failure, left ventricular systolic dysfunction (≤40%), and receiving sulfonylurea therapy (+/- insulin) for ≥30 days before screening or discontinued metformin therapy within 30 days of screening	N=518 6 months	Primary: Heart failure progression (defined as the composite of cardiovascular mortality and hospitalization or emergency room visit for heart failure) and metabolic parameters. Secondary: Not reported	Primary: Pioglitazone was associated with a higher incidence rate of the composite end point compared with glyburide (13.4 vs 8.2%, respectively; P=0.024). Death from cardiovascular cause was similar between the treatment groups (1.9 and 2.3% for pioglitazone and glyburide, respectively). Overnight hospitalization for heart failure was higher in the pioglitazone group (9.9%) compared to glyburide group (4.7%). Emergency room visits for heart failure occurred in 1.5% of pioglitazone patients compared to 1.2% of glyburide patients. Echocardiographic data demonstrated preserved cardiac function with similar changes in the left ventricular mass index (P=0.959) and left ventricular ejection fraction (P=0.413) among the treatment groups. Cardiac index was significantly increased with pioglitazone compared with glyburide (P=0.012). FPG was significantly decreased with glyburide relative to pioglitazone during the first 4 weeks of treatment. By week 16, a significant difference in mean FPG was observed favoring pioglitazone. At week 24, pioglitazone decreased the HbA_{1c} by -0.98% compared to -0.73% with glyburide (P=0.007). At week 24, significant differences were seen between pioglitazone and glyburide in TGs (-36.8 vs +7.6 mg/dL, respectively; P<0.001), HDL-C

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				(+4.8 vs -0.8 mg/dL, respectively; P<.001), and LDL-C (+6.9 vs -2.4 mg/dL, respectively; P<0.016). Rates of adverse events and serious adverse events were similar between treatment groups. Hypoglycemia was more common with glyburide and edema was more common with pioglitazone. Weight gain was reported as an adverse event more frequently with pioglitazone than glyburide. (6.1 vs 2.7%, respectively). Mean weight gain was greater (2.10 vs 1.23 kg, respectively; P=0.012) with pioglitazone than with glyburide. Secondary: Not reported
Kahn et al.[44] (2006) Rosiglitazone 4 mg QD to 4 mg BID vs glyburide 2.5 mg QD to 7.5 mg BID vs metformin 500 mg QD to 1 g BID	DB, MC, RCT (ADOPT) Patients 30 to 75 years of age recently diagnosed with type 2 diabetes with a FPG 126 to 180 mg/dL	N=4,360 4 years	Primary: Time to monotherapy failure (defined as FPG >180 mg/dL after an overnight fast on consecutive testing after at least six weeks of treatment at the maximum-dictated or tolerated dose of study drug) Secondary: Effect on FPG, HbA_{1c}, weight, insulin sensitivity, β-cell function, adverse events	Primary: The cumulative incidence of monotherapy failure at five years was 15% for rosiglitazone, 34% for glyburide and 21% with metformin. This represents a risk reduction of 63% for rosiglitazone as compared with glyburide, and 32% for rosiglitazone as compared with metformin (P<0.001 for both comparisons). Secondary: The rate of progression to a confirmed FPG >140 mg/dL was significantly lower with rosiglitazone than glyburide (RR, 62%; 95% CI, 51 to 72; P<0.001) or metformin (RR, 36%; 95% CI, 15 to 52; P=0.002). At the four-year evaluation, 40% of the patients in the rosiglitazone group had an HbA_{1c} <7.0%, as compared with 26% for glyburide (P<0.001) and 36% for metformin (P=0.03). Rosiglitazone was associated with more weight gain and edema than either metformin or glyburide but with fewer gastrointestinal events than metformin and with less hypoglycemia than glyburide (P<0.001 for all comparisons). During the first six months, insulin sensitivity increased more in the rosiglitazone group than in the metformin group. Thereafter, insulin sensitivity improved at similar rates in the two groups, with a significant

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				difference between the two groups noted at four years (P<0.001). Insulin sensitivity did not change significantly in the glyburide group. During the first six months, levels of β-cell function increased more with glyburide than rosiglitazone or metformin. Thereafter, levels of β-cell function declined in all three groups. The annual rate of decline after six months was 6.1% for glyburide (P<0.001), 3.1% for metformin (P=0.02) and 2.0% for rosiglitazone. The number of deaths from all causes was similar in the three groups; however, adverse events differed among the groups. Glyburide was associated with a lower risk of cardiovascular events (MI, CHF and stroke) than was rosiglitazone (P<0.05), and the risk associated with metformin was similar to that with rosiglitazone. There was no significant difference in the risk for CHF with rosiglitazone compared to metformin (HR, 1.22; 95% CI, 0.66 to 2.26; P=0.52), but the risk was significantly higher with rosiglitazone than glyburide (HR, 2.20; 95% CI, 1.01 to 4.79; P=0.05). While there was no significant difference noted in men, significantly more women who received rosiglitazone (9.30%) than glyburide (3.47%) or metformin (5.08%) experienced fractures (both P<0.01).
Russell-Jones et al.[45] (2012) DRUATION-4 Exenatide ER 2 mg SC once weekly vs metformin 2,000 mg/day vs	DB, DD, MC, PG, RCT Drug-naïve (patients excluded if treated with any antihyperglycemic drug for >7 days within 3 months of screening) adult type 2 diabetics with HbA_{1c} 7.1 to 11.0%, BMI 23 to	N=820 26 weeks	Primary: Change in baseline HbA_{1c} Secondary: Proportion of patients achieving HbA_{1c} <7.0 and ≤6.5%, fasting serum glucose, seven-point self-monitored glucose concentrations, weight, lipid	Primary: Decreases in HbA_{1c} were -1.53±0.07, -1.48±0.07, -1.63±0.08, and -1.15±0.08% with exenatide ER, metformin (P=0.620 vs exenatide ER), pioglitazone (P=0.328 vs exenatide ER), and sitagliptin (P<0.001 vs exenatide ER). The HbA_{1c} at trial end was 6.94±0.07, 6.99±0.07, 6.84±0.08, and 7.32±0.08% with exenatide ER, metformin, pioglitazone, and sitagliptin, respectively. Secondary: Similar proportions of patients receiving exenatide ER and metformin achieved HbA_{1c} <7.0% (63 vs 55%; P value not reported). A significantly greater proportion of patients receiving exenatide ER achieved HbA_{1c} <7.0% compared to patients receiving sitagliptin (63 vs 43%; P<0.001),

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pioglitazone 45 mg/day vs sitagliptin 100 mg/day	45 kg/m^2, and stable weight		profile, insulin profile, safety and tolerability, patient-reported quality of life	and ≤6.5% compared to patients receiving metformin (49 vs 36%; P=0.004) and sitagliptin, respectively (49 vs 26%; P<0.001). Decreases in fasting serum glucose at weeks 16 and 26 were significantly greater with exenatide ER compared to sitagliptin (P<0.001 for both). There were no differences observed with exenatide ER compared to metformin (P=0.155 at week 26) and pioglitazone (P=0.153 at week 26). Seven-point self-monitored glucose concentrations demonstrated similar decreases with exenatide ER, metformin, and pioglitazone. Exenatide ER demonstrated greater decreases at all time points compared to sitagliptin. Mean decreases in post-meal excursions after 26 weeks were similar among all treatments. Decreases in weight were significantly greater with exenatide ER compared to pioglitazone and sitagliptin by weeks four and eight, and the effect was sustained through 26 weeks (P≤0.003 for all). There was no difference between exenatide ER and metformin after 26 weeks (-2.0 vs -2.0 kg; P=0.892). No clinically significant changes in serum lipids were observed with any treatment. Mean HOMA-B was significantly improved with exenatide ER compared to metformin, pioglitazone, and sitagliptin (P<0.001 for all). HOMA-S significantly improved with metformin and pioglitazone compared to exenatide ER (P<0.001 for both), and the change with exenatide ER was similar to sitagliptin (P=0.329). Serious adverse events were reported in 1.6, 5.3, 5.5, and 1.8% of patients receiving exenatide ER, metformin, pioglitazone, and sitagliptin, respectively. No serious adverse event was reported by more than one patient. Treatment-emergent adverse events reported by at least five percent of patients in any group included headache (highest with metformin), diarrhea (highest with metformin), injection site nodule (highest with exenatide ER), nasopharyngitis (highest with sitagliptin), nausea (highest with exenatide ER), dyspepsia (highest with exenatide

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				ER), constipation (highest with exenatide ER), back pain (highest with metformin), arthralgia (highest with exenatide ER), hypertension (highest with pioglitazone), and peripheral edema (highest with pioglitazone). No major hypoglycemia was reported. One patient receiving sitagliptin with elevated lipase at screening experienced moderate chronic pancreatitis after eight days and discontinued from study treatment. All treatments resulted in improvements in perceived treatment satisfaction, weight-related quality of life, and binge eating behavior. All treatments, except pioglitazone, resulted in significant improvements in health status. Significant improvements in weight-related quality of life, binge eating behavior, and health status were reported with exenatide ER compared to pioglitazone (P values not reported).
Nichols et al.[46] (2007) Metformin vs sulfonylurea vs insulin vs TZDs	MC, OS, RETRO Patients who initiated metformin, sulfonylurea, insulin or TZDs between 1996 and 2002 and continued use of that drug for at least 12 months without adding other therapies	N=9,546 ≥12 months	Primary: Weight changes Secondary: Not reported	Primary: Patients treated with metformin lost an average of 2.4 kg, sulfonylurea-treated patients gained 1.8 kg, insulin-treated patients gained 3.3 kg, and thiazolidinedione-treated patients gained 5.0 kg. All comparisons with metformin were statistically significant. Secondary: Not reported
Norris et al.[47] (2007) Pioglitazone vs rosiglitazone	MA (112 trials) Patients with metabolic syndrome, pre-diabetes, and type 2 diabetes receiving treatment with	N=14,290 Duration varied	Primary: HbA_{1c}, lipids, weight, adverse events Secondary: Not reported	Primary: For pioglitazone, the between-group change in HbA_{1c} was -0.99% (95% CI, -1.18 to -0.81) and for rosiglitazone was -0.92% (95% CI, -1.2 to -0.64). Indirect comparison of pioglitazone and rosiglitazone found no significant difference in HbA_{1c} (between-group difference, -0.07%; 95% CI, -0.41 to 0.27).

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	pioglitazone or rosiglitazone			Rosiglitazone increased TC (13.70 mg/dL; 95% CI, 1.06 to 26.35) and pioglitazone decreased TG levels (-1.08 mg/dL; 95% CI, -2.08 to -0.09). Using indirect comparisons, rosiglitazone increased TC compared to pioglitazone (net between-drug effect, 13.91 mg/dL; 95% CI, 1.20 to 26.62). Data were insufficient to assess comparative effects of pioglitazone and rosiglitazone on microvascular and macrovascular events. Few data were available on the comparative effect of pioglitazone and rosiglitazone on cardiovascular risk factors among persons with pre-diabetes or the metabolic syndrome. There were insufficient data to determine whether pioglitazone and rosiglitazone have different effects on the incidence of diabetes among persons with either pre-diabetes or the metabolic syndrome. There was limited reporting of adverse events in the available head-to-head trials. Among 719 patients with type 2 diabetes and dyslipidemia, there were no differences between pioglitazone and rosiglitazone at 24-weeks follow-up for weight change (pioglitazone, 2.0 kg and rosiglitazone, 1.6 kg; P=0.164), liver function tests, creatinine phosphokinase, BP, heart rate, hematocrit, hypoglycemic episodes, edema, or congestive heart failure. There were generally no differences in rates of adverse events between the active-treatment and placebo groups. The most frequently reported adverse events were edema, hypoglycemia, and weight gain. Both drugs increased weight compared to placebo: pioglitazone, 2.96 kg (95% CI, 0.73 to 5.20) and rosiglitazone, 2.12 kg (95% CI, 0.89 to 3.36), with no significant difference between the two drugs (95% CI, -1.71 to 3.39). Secondary: Not reported
Singh et al.[48] (2011) TZDs (pioglitazone, rosiglitazone)	MA, SR (13 RCTs) Type 2 diabetics	N=17,627 1 to 5.5 years (follow-up)	Primary: Any pneumonia or lower respiratory tract infection reported as an	Primary: TZDs are associated with a significantly increased risk for any pneumonia or lower respiratory tract infection compared to control (130/8,163 vs 100/9,464; RR, 1.40; 95% CI, 1.08 to 1.82; P=0.01). In addition TZDs were associated with a significantly increased risk of serious pneumonia or

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vs placebo, sulfonylurea, or metformin			adverse event, pneumonia or lower respiratory tract infection reported as a serious adverse event Secondary: Not reported	lower respiratory tract infection compared to control (111/7,391 vs 87/8,692; RR, 1.39; 95% CI, 1.05 to 1.83; P=0.02). Secondary: Not reported
Loke et al.[49] (2009) TZDs (rosiglitazone, pioglitazone, troglitazone*) vs no TZDs	MA (2 OS, 10 RCTs) Type 2 diabetics with impaired glucose	N=45,394 ≥1 years	Primary: Incidence of fracture, change in baseline BMD Secondary: Not reported	Primary: Rosiglitazone and pioglitazone were associated with a significantly increased risk of fractures overall in the 10 RCTs (OR, 1.45; 95% CI, 1.18 to 1.79; *P*<0.001). Five of these RCTs demonstrated a significantly increased risk of fractures among women (OR, 2.23; 95% CI, 1.65 to 3.01; *P*<0.001), but not among men (OR, 1.00; 95% CI, 0.73 to 1.39; *P*=0.98). The two OS demonstrated an increased risk of fractures with rosiglitazone and pioglitazone. BMD at the lumbar spine (WMD, -1.11%; 95% CI, -2.08 to -0.14; *P*=0.02) and hip (WMD, -1.24%; 95% CI, -2.34 to -0.67; *P*<0.001) significantly decreased in women receiving TZDs within two RCTs. Results from one OS supported these findings (WMD, -1.36%; 95% CI, -2.05 to -0.67; *P*=0.001 and WMD, -1.24%; 95% CI, -1.78 to -0.70; *P*<0.001). Secondary: Not reported
Louisa et al.[50] (2011) TZDs (pioglitazone, rosiglitazone) vs	MA (37 RCTs) Type 2 diabetics	N=3,000 >3 months	Primary: Glycemic outcomes Secondary: Change in baseline BMI, lipid profile, BP, high-sensitivity CRP,	Primary: Both pioglitazone (WMD, -0.12%; 95% CI, -0.38 to -0.16) and rosiglitazone (WMD, -0.47%; 95% CI, -0.62 to -0.33) significantly decreased HbA_{1c}. Pioglitazone only demonstrated a significant decrease compared to placebo, while rosiglitazone significantly decreased HbA_{1c} compared to placebo and a sulfonylurea. Both pioglitazone (WMD, -9.16 mg/dL; 95% CI, -15.60 to -2.72) and rosiglitazone (WMD, -16.10 mg/dL; 95% CI, -22.20 to -10.01)

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placebo or other hypoglycemic agents			and insulin sensitizing effect; cardiovascular and clinical endpoints	significantly decreased FPG compared to control. Pioglitazone demonstrated a significant decrease compared to placebo, metformin, and voglibose*, while rosiglitazone significantly decreased FPG compared to placebo, metformin, and a sulfonylurea. Secondary: Pioglitazone and rosiglitazone had similar effects on BMI (pioglitazone: WMD, 0.57; 95% CI, 0.34 to 0.80 and rosiglitazone: WMD, 0.72; 95% CI, 0.29 to 1.14). Pioglitazone demonstrated a neutral effect of LDL-C (WMD, 3.89 mg/dL; 95% CI, -0.04 to 7.83) and TC (WMD, 2.30 mg/dL; 95% CI, -3.81 to 8.41). Rosiglitazone significantly increased LDL-C (WMD, 11.30 mg/dL; 95% CI, 7.80 to 14.79) and TC (WMD, 7.34 mg/dL; 95% CI, 2.34 to 12.31). Both agents had favorable effects on HDL-C and TGs. Pioglitazone produced a small decrease in DBP and SBP, while rosiglitazone demonstrated a neutral effect. In 13 trials, pioglitazone demonstrated a neutral effect on high sensitivity CRP, while rosiglitazone demonstrated a small improvement in hsCRP. Consistent increase in adiponectin and improvement in HOMA-IR were observed with both pioglitazone and rosiglitazone. Four trials evaluated cardiovascular events as secondary endpoints. There were significant decreases in major cardiac events with both pioglitazone vs control (RR, 0.24; 95% CI, 0.09 to 0.63) and rosiglitazone vs control (RR, 0.41; 95% CI, 0.19 to 0.87).
Xu et al.[51] (2015) CONFIDENCE Exenatide twice daily	MC, PG, RCT Treatment-naïve patients, 30 to 70 years of age, with	N=416 48 weeks	Primary: Change in baseline HbA_{1c} Secondary:	Primary: At week 48, mean HbA_{1c} changes from baseline were −1.8% (95% CI, −1.55 to −2.05%) with exenatide, −1.7% (95% CI, −1.52 to −1.96%) with insulin and −1.5% (95% CI, −1.23 to −1.71%) with pioglitazone. Treatment differences were −0.20% (95% CI, −0.46 to 0.06%) for

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vs insulin (75% insulin lispro protamine suspension and 25% insulin lispro injection) twice daily vs pioglitazone once daily	newly diagnosed type 2 diabetes		Effects on weight, blood pressure, lipid profiles and β-cell function	exenatide vs insulin (P=0.185), and −0.37% (95% CI, −0.63 to −0.12%) for exenatide vs pioglitazone (P=0.002). Secondary: Mean weight change was significantly different between the exenatide group and the insulin and pioglitazone groups from weeks four and eight until the end of the study, with weight decreasing in the exenatide group. Decreases in mean systolic and diastolic blood pressures at 48 weeks were not statistically different between groups, although significant decreases in systolic and diastolic blood pressures were observed with exenatide (P<0.05 vs baseline), and a significant decrease in diastolic blood pressure alone was found with pioglitazone (P<0.001). Exenatide treatment resulted in improvements in overall lipid profiles, with significant decreases in TG, total cholesterol and LDL cholesterol levels, and an increase in HDL cholesterol (P<0.05 vs baseline for all variables). HDL cholesterol increased with pioglitazone (P<0.001), and LDL cholesterol decreased with insulin (P<0.05). At week 48, HOMA-B (which, together with fasting proinsulin-to-insulin ratio (PI/I), provides an indication of β-cell function during the fasting state) increased in patients treated with insulin (P<0.001 vs baseline). Improvements from baseline were similar in all treatment groups with regard to PI/I, as well as acute insulin response (AIR, which represents β-cell function during the stimulated state after intravenous glucose injection). Disposition index (DI), which provides a measure of β-cell function during the stimulated state under near-physiological conditions of food intake via the gastrointestinal system, increased significantly in all treatment groups (P<0.001 vs baseline for exenatide; P<0.05 vs baseline for insulin and pioglitazone). The greatest mean improvements from baseline in DI and AIR were observed in the exenatide treatment group.
Bolen et al.[52] (2007) Biguanides vs	MA (Analysis of 216 controlled trials and cohort studies, and 2 SRs)	N=136 (articles on intermediate outcomes) N=167 (articles on	Primary: Intermediate outcomes: HbA_{1c}, body weight, BP, lipid panels, all-cause mortality, cardiovascular	Primary: Results from clinical trials showed that most oral agents including TZDs, metformin, and repaglinide improved glycemic control to the same degree as sulfonylureas (absolute decrease in HbA_{1c} level of about 1%). Nateglinide and α-glucosidase inhibitors have slightly weaker effects, on the basis of indirect comparisons of placebo-controlled trials.

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meglitinides vs TZDs vs α-glucosidase inhibitors vs second-generation sulfonylureas	Patients with type 2 diabetes	adverse events) N=68 (articles on microvascular outcomes and mortality) Duration varied	morbidity and mortality, microvascular outcomes Secondary: Adverse events: hypoglycemia, gastrointestinal problems, congestive heart failure, edema or hypervolemia, lactic acidosis, elevated liver enzymes, allergic reactions requiring hospitalization, other serious adverse events	TZDs were the only class with beneficial effect on HDL-C (mean relative increase, 3 to 5 mg/dL) but a harmful effect on LDL-C (mean relative increase, 10 mg/dL) compared to other oral agents. Metformin decreased LDL-C levels by about 10 mg/dL, whereas other oral agents had no effects on LDL-C. TZDs, second-generation sulfonylureas, and metformin had similarly minimal effects on SBP. Most agents except metformin increased body weight by 1 to 5 kg. In the ADOPT (A Diabetes Outcome Progression Trial), the incidence of cardiovascular events was lower with glyburide compared to rosiglitazone or metformin (1.8, 3.4, and 3.2%, respectively; P<0.05). In the RECORD study (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of glycemia in Diabetes), rosiglitazone plus metformin or a sulfonylurea compared to metformin plus a sulfonylurea had a HR of 1.08 (95% CI, 0.89 to 1.31) for the primary end point of hospitalization or death from cardiovascular disease. The HR was driven by more congestive heart failure in the rosiglitazone plus metformin group compared to the control group of metformin plus sulfonylurea (absolute risk, 1.7 vs 0.8%, respectively). Too few comparisons were made to draw firm comparative conclusions on microvascular outcomes. Secondary: According to several RCTs and some OS trials, sulfonylureas and repaglinide were associated with greater risk for hypoglycemia. In many RCTs, TZDs were associated with a higher risk for edema than sulfonylureas or metformin (absolute risk difference, 2 to 21%). In cohort studies, TZDs were associated with higher risk for congestive heart failure although absolute risks were small (1 to 3%) and higher risk for mild anemia yet produced similarly low rates of elevated aminotransferase levels (<1%) compared to sulfonylureas and metformin.

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				In many trials and a few OS trials, metformin was associated with greater risk for gastrointestinal problems compared to other oral diabetes agents. According to a SR of 176 comparative trials, lactic acidosis events were similar between metformin and other oral diabetes agents.
Monami et al.[53] (2008) Metformin vs sulfonylureas, α-glucosidase inhibitors, TZDs, glinides, GLP-1 agonists	MA Patients with type 2 diabetes mellitus	N=7,890 (27 RCT) Variable duration	Primary: Reduction in HbA_{1c} at 16 to 36 months Secondary: Not reported	Primary: Combining the results of different placebo-controlled trials, sulfonylurea, α-glucosidase inhibitors, and TZDs led to a reduction in HbA_{1c} by -0.85% (95% CI, 0.78 to 0.94], -0.61% (95% CI, 0.55 to 0.67), and -0.42% (95% CI, 0.40 to 0.44), respectively when combined with metformin. In direct comparisons, sulfonylureas led to a greater reduction in HbA_{1c} (0.17%; 95% CI, 0.16 to 0.18; P<0.05) than TZDs. Differences between sulfonylureas and α-glucosidase inhibitors, and between α-glucosidase inhibitors and TZDs, were not statistically significant. Secondary: Not reported
Shyangdan et al.[54] (2011) GLP-1 receptor agonist based therapies (albiglutide, exenatide ER, liraglutide, lixisenatide*, semaglutide*, and taspoglutide*) vs non-GLP-1 receptor based therapies (placebo, TZDs,	MA (RCTs) Type 2 diabetics ≥18 years of age	N=not reported 8 to 26 weeks	Primary: Change in baseline HbA_{1c}, incidence of hypoglycemia, weight change Secondary: Health-related quality of life, safety, mortality, morbidity, BP, FPG, PPG, lipid profile, β cell function	Primary: Change in baseline HbA_{1c} Exenatide ER significantly decreased HbA_{1c} compared to TZDs (-1.5 vs -1.2%; P=0.02), DPP-4 inhibitors (-1.5 vs -0.9%; P<0.0001), and insulin glargine (-1.5 vs -1.3%; treatment difference, -0.2%; 95% CI, -0.35 to -0.05; P=0.03). There was no difference in the proportion of patients achieving an HbA_{1c} <7.0% between exenatide ER and TZDs (60 vs 52%; P=0.15). A significantly greater proportion of patients receiving exenatide ER achieved an HbA_{1c} <7.0% compared to patients receiving DPP-4 inhibitors (60 vs 35%; P<0.0001) and patients receiving insulin glargine (60 vs 48%; P=0.03). Compared to placebo, treatment with liraglutide 1.2 mg significantly decreased HbA_{1c} (-1.15%; 95% CI, -1.33 to -0.96; P<0.00001). Patients receiving liraglutide 1.2 mg were more likely to achieve an HbA_{1c} <7.0% compared to patients receiving placebo (OR, 2.91; 95% CI, 1.74 to 4.87; P<0.05). Liraglutide 1.2 mg decreased HbA_{1c} to a greater extent compared to TZDs (-0.64%; 95% CI -0.83 to -0.45; P value not reported). The

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DPP-4 inhibitors, insulin glargine, and sulfonylureas)				likelihood of achieving an HbA_{1c} <7.0% was greater with liraglutide 1.2 mg compared to TZDs (OR, 1.60; 95% CI, 1.18 to 2.15; P value not reported). Liraglutide 1.2 mg decreased HbA_{1c} to a greater extent compared to DPP-4 inhibitors (-0.34%; 95% CI, -0.53 to -0.15; P value not reported). The likelihood of achieving an HbA_{1c} <7.0% was greater with liraglutide 1.2 mg compared to DPP-4 inhibitors (OR, 2.56; 95% CI, 1.94 to 3.37; P value not reported). Liraglutide 1.2 mg was not associated with a decrease in HbA_{1c} compared to sulfonylureas (-0.01%; 95% CI -0.27 to 0.29; P value not reported). The likelihood of achieving an HbA_{1c} <7.0% was not greater with liraglutide 1.2 mg compared to sulfonylureas (OR, 0.98; 95% CI, 0.84 to 1.14; P=0.78). Compared to placebo, liraglutide 1.8 mg significantly decreased an HbA_{1c} (-1.15%; 95% CI, -1.31 to -0.99; P<0.05). Patients receiving liraglutide 1.8 mg were more likely to achieve HbA_{1c} <7.0% compared to patients receiving placebo (OR, 3.25; 95% CI, 1.97 to 5.36; P<0.05). Liraglutide 1.8 mg decreased HbA_{1c} to a greater extent compared to TZDs (-0.69%; 95% CI -0.88 to -0.50%; P value not reported). The likelihood of achieving an HbA_{1c} <7.0% was greater with liraglutide 1.8 mg compared to TZDs (OR, 1.91; 95% CI, 1.43 to 2.53; P value not reported). Liraglutide 1.8 mg decreased HbA_{1c} to a greater extent compared to DPP-4 inhibitors (-0.60%; 95% CI -0.78 to -0.42; P value not reported). The likelihood of achieving HbA_{1c} <7.0% was greater with liraglutide 1.8 compared to DPP-4 inhibitors (OR, 1.99; 95% CI, 1.48 to 2.66; P value not reported). Liraglutide 1.8 mg was not associated with a reduction in HbA_{1c} compared to sulfonylureas (-0.02%; 95% CI -0.30 to 0.26; P value not reported). The likelihood of achieving an HbA_{1c} <7.0% was not greater with liraglutide 1.8 mg compared to sulfonylureas (OR, 1.09; 95% CI, 0.94 to 1.26; P=0.27). Liraglutide decreased HbA_{1c} to a greater extent compared to insulin glargine (-0.24%; 95% CI, -0.49 to 0.01; P value not reported). The likelihood of achieving an HbA_{1c} <7.0% was not different between insulin glargine and liraglutide (OR, 1.16; 95% CI, 0.96 to 1.40; P value not reported).

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				Liraglutide 1.2 mg was associated with a non-significant increase in HbA_{1c} compared to 1.8 mg (0.10%; 95% CI, -0.03 to 0.23; P=0.13). Patients receiving liraglutide 1.2 mg were not more likely to achieve an HbA_{1c} <7.0% compared to the 1.8 mg dose (P=0.92). Incidence of hypoglycemia The incidence of minor hypoglycemia was similar between exenatide ER and TZDs. The incidence of minor hypoglycemia was higher with DPP-4 inhibitors (five vs two patients) and insulin glargine (26 vs 8%) compared to exenatide ER. The incidence of major hypoglycemia was higher with insulin glargine compared to exenatide ER (two vs one patients). Overall, there was no difference in the incidence of minor hypoglycemia between liraglutide 1.2 mg and placebo (P=0.42), and there was significantly more hypoglycemia with liraglutide 1.8 mg (OR, 1.66; 95% CI, 1.15 to 2.40; P=0.007). The incidence of minor hypoglycemia was higher with insulin glargine compared to liraglutide (29 vs 27%). Liraglutide was associated with a significantly higher rate of minor hypoglycemia compared to TZDs (P=0.048), and similar rates compared to DPP-4 inhibitors (P values not reported). Liraglutide was associated with a significantly lower incidence of hypoglycemia compared to sulfonylureas (P<0.00001). Weight loss Exenatide ER significantly decreased weight compared to TZDs (-2.3 vs 2.8 kg; P<0.00001), DPP-4 inhibitors (-2.3 vs -0.8 kg; P=0.0009), and insulin glargine (-2.6 vs 1.4 kg; P<0.00001). Patients receiving liraglutide 1.2 mg experienced an average weight loss of -0.75 kg (95% CI, -1.95 to 0.45; P=0.22). Liraglutide 1.2 mg was associated with a greater decrease in weight compared to insulin glargine (-3.40 kg; 95% CI, -4.31 to -2.49; P value not reported), TZDs (-3.40 kg; 95% CI, -4.31 to -2.49; P value not reported), DPP-4 inhibitors (-1.90 kg; 95% CI, -2.65 to -1.15; P value not reported), and sulfonylureas (-3.60 kg; 95% CI, -4.15 to -3.05; P value not reported).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Patients receiving liraglutide 1.8 mg experienced a significant weight loss compared to placebo (-1.33 kg; 95% CI, -2.38 to 0.27; P=0.0014). Liraglutide 1.8 mg was associated with a greater decrease in weight compared to TZDs (-2.30 kg; 95% CI, -2.85 to -1.75; P value not reported), DPP-4 inhibitors (-2.42 kg; 95% CI, -3.17 to -1.67; P value not reported), and sulfonylureas (-3.80 kg; 95% CI, -4.35 to -3.25; P value not reported). Patients were more likely to experience weight gain with liraglutide 1.2 compared to 1.8 mg (0.48 kg; 95% CI, 0.16 to 0.80; P value not reported). Secondary: Data on mortality and morbidity were not reported for any treatment. Quality of life Exenatide ER significantly improved weight-related quality of life and IWQOL total scores compared to TZDs (IWQOL treatment difference, 3.94; 95% CI, 1.28 to 6.61; P=0.0038). Both exenatide ER (IWQOL total score, 5.15; 95% CI, 3.11 to 7.19) and DPP-4 inhibitors (4.56; 95% CI, 2.56 to 6.57) resulted in significant improvements in weight-related quality of life and IWQOL total scores. Treatment satisfaction was significantly greater with exenatide ER compared to DPP-4 inhibitors (treatment difference, 1.61; 95% CI, 0.07 to 3.16; P=0.0406). Exenatide ER significantly improved the self-esteem IWQOL domain and one EQ-5D dimensions compared to insulin glargine. Data for liraglutide were not reported. Safety Withdrawals due to adverse events were greater with exenatide ER compared to TZDs (6.9 vs 3.6%), DPP-4 inhibitors (6.9 vs 3.0%), and insulin glargine (4.7 vs 0.9%). More serious adverse events occurred with TZDs (6 vs 3%) compared to exenatide ER. The incidence of serious adverse events was similar between exenatide ER and DPP-4 inhibitors (3 vs 3%) and insulin glargine (5 vs 4%).

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				Compared to placebo, withdrawals due to adverse events were between 5 and 10% with liraglutide 1.2 mg and between 4 and 15% with liraglutide 1.8 mg. Withdrawals were also higher with liraglutide compared to sulfonylureas (9.4 to 12.9 vs 1.3 to 3.0%). Liraglutide was associated with more gastrointestinal adverse events (nausea, vomiting, and diarrhea) compared to insulin glargine, TZDs, DPP-4 inhibitors, and sulfonylureas. BP There was no difference in the decreases in SBP and DBP between exenatide ER and TZDs. Exenatide ER significantly decreased SBP compared to DPP-4 inhibitors (treatment difference, -4 mm Hg; 95% CI, -6 to -1; P=0.0055). There was no difference in the decrease in DBP between treatments. Data comparing exenatide ER and insulin glargine were not reported. Liraglutide 1.2 mg did not significantly decrease SBP (P=0.15) compared to placebo (P=0.15) and DPP-4 inhibitors (P=0.76). Liraglutide 1.8 mg significantly decreased SBP (P=0.05) compared to placebo, but not DPP-4 inhibitors (P=0.86). Liraglutide also significantly decreased SBP compared to insulin glargine (P=0.0001) and sulfonylureas (P value not reported). No difference in SBP was observed between liraglutide and DPP-4 inhibitors. There was no difference between liraglutide in the decrease in DBP compared to placebo, insulin glargine, or sulfonylureas. DPP-4 inhibitors significantly decreased DBP compared to liraglutide 1.8 mg (P value not reported). Data comparing liraglutide and TZDs were not reported. FPG There was no difference in the decrease in FPG between exenatide ER and TZDs (-1.8 vs -1.5 mmol/L; P=0.33). Exenatide ER significantly decreased FPG compared to DPP-4 inhibitors (-0.90 mmol/L; 95% CI, -1.50 to -0.30; P=0.0038), and insulin glargine significantly decreased FPG compared to exenatide ER (-0.70 mmol/L; 95% CI, 0.14 to 1.26; P=0.01). Liraglutide significantly decreased FPG compared to placebo (1.2 mg; P<0.0001 and 1.8 mg; P<0.00001), TZDs (P≤0.006), and DPP-4 inhibitors

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				(P<0.00001). There was no difference between liraglutide and insulin glargine or sulfonylureas in decreases in FPG (P value not reported). PPG There was no difference in the decrease in PPG between exenatide ER and TZDs. Exenatide ER significantly decreased PPG at all measurements on a six-point self-monitored glucose concentrations profile compared to DPP-4 inhibitors (P<0.05). Both exenatide ER and insulin glargine decreased PPG at all eight time points, with significant difference in favor of exenatide ER after dinner (P=0.004) and insulin glargine at 03000 hour (P=0.022) and before breakfast (P<0.0001). Liraglutide significantly decreased PPG compared to placebo (P value not reported), TZDs (P<0.05), and sulfonylureas (liraglutide 1.8 mg; P<0.0001). There was no difference between liraglutide and insulin glargine in decreases in PPG (P value not reported). It was reported that PPG recorded in trials comparing liraglutide and DPP-4 inhibitors was highly variable. Lipid profile TZDs significantly decreased TG compared to exenatide ER. Exenatide ER decreased TC and LDL-C, while TZDs and DPP-4 inhibitors increased these measures. All treatments increased HDL-C. Data comparing exenatide ER and insulin glargine were not reported. Compared to placebo, liraglutide 1.2 decreased TG (P<0.05) and LDL-C (P<0.05), and no difference was observed with liraglutide 1.8 mg. Data comparing liraglutide to insulin glargine, TZDs, DPP-4 inhibitors, and sulfonylureas were not reported. β cell function Data for exenatide ER are not reported. Liraglutide significantly improved HOMA-B compared to placebo (P value not reported), TZDs (P<0.05), and DPP-4 inhibitors (P value not reported); and proinsulin:insulin ratio compared to placebo (P value not reported), insulin glargine (P=0.0019), and TZDs (P≤0.02). There was no difference between liraglutide and

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				sulfonylureas in the improvements in HOMA-B and proinsulin:insulin ratio.
Type 2 Diabetes – Combination Therapy				
Chogtu et al.[55] (2009) Pioglitazone (variable doses) and glimepiride 2 mg daily vs rosiglitazone (variable doses) and glimepiride 2 mg daily	OL, RCT Patients 30 to 70 years of age with type 2 diabetes who received glimepiride and required a TZD due to a lack of glycemic control, normotensive, and not on antilipemic therapy	N=63 12 weeks	Primary: Blood glucose levels, plasma lipids, BP Secondary: Not reported	Primary: The mean change in the FPG and PPG from baseline to week 12 was significant in both groups (P<0.05). There was no significant difference between the groups with regard to the change in FPG (P=0.10) and PPG (P=0.95). HbA_{1c} levels also decreased from baseline to week 12. There was no significant difference between the treatment groups (P>0.05). At week 12, 37.9% of patients in the pioglitazone group and 17.8% of patients in the rosiglitazone group had HbA_{1c} <7.0% (P value not reported). TC decreased in both treatment groups; however, to a greater extent with pioglitazone compared to rosiglitazone (P=0.004). TG in the pioglitazone group (P=0.0006) decreased significantly in comparison to the rosiglitazone group (P=0.255) at 12 weeks (P=0.002 pioglitazone vs rosiglitazone). LDL-C decreased significantly (P=0.005) in the pioglitazone group compared to the rosiglitazone group. There was no significant difference in HDL-C among the treatment groups (P>0.05). There was no change in SBP with pioglitazone or rosiglitazone from baseline to week 12. There was also no significant difference in SBP between the treatment groups (P=0.45). There was an increase in the weight following treatment with pioglitazone and rosiglitazone; however, there was no difference between the groups (P=0.10). Secondary: Not reported
Brackenridge et al.[56] (2009)	DB, PC, RCT	N=24 3 months	Primary: Change in baseline lipid profile	Primary: Of the various lipid concentrations, pioglitazone only significantly decreased non-esterified fatty acid (0.66±0.08 to 0.48±0.04 mmol/L;

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Pioglitazone 30 mg/day vs rosiglitazone 8 mg/day vs placebo All patients also received metformin.	Type 2 diabetics for ≥6 months currently managed on metformin and diet and exercise		Secondary: Change in baseline glycemic outcomes	P=0.02) and VLDL-TG:apoB (31.00±3.91 to 25.30±3.71; P=0.04) compared to baseline. Rosiglitazone also only significantly decreased non-esterified fatty acid (0.68±0.09 to 0.49±0.10; P=0.003) and VLDL-TG:apoB (25.50±2.70 to 20.60±2.47; P=0.01). Placebo significantly increased LDL-C compared to baseline (2.10±0.10 to 2.50±0.19; P=0.03). No significant differences were observed between any of the treatments. Of the various LDL subfraction concentrations, pioglitazone significantly increased LDL3-C compared to placebo (1.25±0.15 to 1.53±0.23 mmol/L; P=0.05). Rosiglitazone significantly increased LDL2-C (1.02±0.14 to 1.39±0.20 mmol/L; P=0.02) and LDL2 apoB (0.25±0.03 to 0.34±0.05 mmol/L; P=0.02), and significantly decreased LDL3-C (1.33±0.12 to 0.96±0.14 mmol/L; P=0.02). Decreases in LDL3-C (P=0.03) and LDL3 apoB (P=0.03) with rosiglitazone were significantly greater compared to pioglitazone. Of the various lipoprotein metabolism variables, rosiglitazone only decreased VLDL absolute secretion rate compared to baseline (7.24 to 5.83 mg/kg/day; P=0.01). No significant differences were observed between any of the treatments. Secondary: Of the glycemic outcomes evaluated, pioglitazone significantly decreased HbA_{1c} (7.50±0.21 to 6.80±0.18; P=0.01) and significantly increased body weight (96.40±3.62 to 98.30±3.96; P=0.04) and BMI (30.80±1.26 to 31.50±1.45; P=0.04) compared to baseline. Rosiglitazone significantly decreased HbA_{1c} compared to baseline (6.90±0.30 to 6.50±0.19; P=0.04). No significant differences were observed between any of the treatments.
Rosenstock et al.[57] (2010) Alogliptin 25 mg QD vs	DB, PG, RCT Treatment naïve patients 18 to 80 years of age with type 2 diabetes, an HbA_{1c} value 7.0 to 11.0%, a BMI 23 to 45 kg/m^2, who	N=655 26 weeks	Primary: Mean change from baseline in HbA_{1c} at week 26 Secondary: HbA_{1c} and FPG changes from baseline at each	Primary: Coadministration of the 25 mg dose with pioglitazone compared to 25 mg alone and to pioglitazone 30 mg alone resulted in statistically significant improvements from baseline in HbA_{1c} (-1.7 vs -1.0 and -1.2%, respectively; P<0.01 for both comparisons). Similar reductions were observed with the combination therapy arm involving the 12.5 mg strength. Secondary:

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alogliptin 12.5 mg QD and pioglitazone 30 mg QD vs alogliptin 25 mg QD and pioglitazone 30 mg QD vs pioglitazone 30 mg QD	failed diet and exercise interventions for ≥2 months		study visit, percentage of patients achieving specific HbA_{1c} goals, frequency of glycemic rescue and safety evaluations	Coadministration of the 25 mg dose with pioglitazone compared to 25 mg alone and to pioglitazone 30 mg alone resulted in statistically significant improvements from baseline in FPG (-50 vs -26 and -37 mg/dL, respectively; P<0.01 for both comparisons). In addition, each treatment resulted in prompt and progressive reductions in HbA_{1c} and FPG that were sustained throughout the 26 weeks. In addition, both combination therapy groups were associated with significantly greater percentage of patients meeting glycemic goals compared to monotherapy. Fewer patients in the combination therapy groups required hyperglycemic rescue (3.7 and 2.4% with combination alogliptin 12.5 and 25 mg groups, respectively) than with either pioglitazone (6.1%) or alogliptin monotherapy (11.0%). The safety profile of combination therapy was consistent with that of the individual components. The most frequently reported adverse events included headache, back pain, urinary tract infection and peripheral edema.
DeFronzo et al.[58] (2012) Alogliptin 12.5 mg QD vs alogliptin 25 mg QD vs pioglitazone 15 mg QD vs pioglitazone 30 mg QD	DB, MC, PC, PG, RCT Patients 18 to 80 years of age with type 2 diabetes, an HbA_{1c} value 7.5% to 10.0%, FPG <16.7 mmol/L, BMI 23 to 45 kg/m^2, blood pressure ≤160/110 mm Hg, HGB ≥12 g/dL (men) or ≥10 g/dL (women), ALT ≤2.5 X ULN, TSH ≤ULN, SCR <133 µmol/L (men) or <124 µmol/L	N=1,554 26 weeks	Primary: Mean change from baseline in HbA_{1c} at week 26 Secondary: HbA_{1c} and FPG changes from baseline at each study visit, hyperglycemic rescue, C-peptide, proinsulin, insulin and proinsulin/ insulin ratio, HOMA-B, achievement of glycemic goals, changes in body	Primary: Coadministration of alogliptin and pioglitazone provided significant improvements in HbA_{1c} and FPG compared to placebo, or either treatment as a single agent added to metformin therapy (P<0.01 for all comparisons). Secondary: More patients in the placebo group (41 of 129; 31.8%) required hyperglycemic rescue than in any active treatment group. The alogliptin and pioglitazone therapy groups had a higher percentage of patients requiring hyperglycemic rescue (8.5 to 14.7%) than any combination therapy (1.5 to 4.6%). Measures of β-cell function found a greater decrease in alogliptin 25 mg/pioglitazone compared to pioglitazone alone. However, the decrease in the alogliptin 12.5 mg/pioglitazone arms were similar to the pioglitazone arms alone. Body weight decreased slightly in patients receiving placebo (-0.7 kg) or alogliptin (-0.02 and -0.7 kg for the 12.5 and 25 mg groups, respectively),

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vs pioglitazone 45 mg QD vs alogliptin 12.5 mg QD and pioglitazone 15 mg QD vs alogliptin 12.5 mg QD and pioglitazone 30 mg QD vs alogliptin 12.5 mg QD and pioglitazone 45 mg QD vs alogliptin 25 mg QD and pioglitazone 15 mg QD vs alogliptin 25 mg QD and pioglitazone 30 mg QD vs	(women), and C-peptide concentration ≥0.26 nmol/L who were inadequately controlled on metformin at a dose of ≥1,500 mg/day for ≥2 months		weight and safety evaluations	whereas there were modest but significant increases in body weight in all groups receiving pioglitazone (P values not reported). In general, the combination of alogliptin and pioglitazone was well tolerated. In addition, the incidence of adverse events was similar across treatment groups.

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alogliptin 25 mg QD and pioglitazone 45 mg QD vs placebo Patients received metformin at a dose of 1,500 mg/day.				
Bosi et al.[59] (2011) Alogliptin 25 mg QD and pioglitazone 30 mg QD vs pioglitazone 45 mg QD All members received metformin at a dose ≥1,500 mg throughout the study.	AC, DB, MC, PG, RCT Patients 18 to 80 years of age with type 2 diabetes, an HbA_{1c} value 7.0 to 10%, FPG <15.3 mmol/L, BMI 23 to 45 kg/m^2, blood pressure ≤160/110 mm Hg, and C-peptide concentration ≥0.26 nmol/L who were inadequately controlled on metformin at a dose of ≥1,500 mg/day and pioglitazone 30 mg daily for ≥2 months	N=803 52 weeks	Primary: Mean change from baseline in HbA_{1c} at weeks 26 and 52 Secondary: Mean change from baseline in HbA_{1c} and FPG at all other visits, proportions of patients achieving glycemic goals, proinsulin: insulin ratio, C-peptide, HOMA-B, HOMA insulin resistance, body weight, serum triglycerides, cholesterol, and safety endpoints	Primary: In combination with pioglitazone and metformin, alogliptin was associated with a significantly greater decrease compared to the titration of pioglitazone in HbA_{1c} (-0.7 vs -0.3%, respectively; P=0.025) and FPG (-15 vs -4 mg/L, respectively; P<0.001) at 52 weeks. Similar, the decrease was greater with the alogliptin group at 26 weeks (P<0.001). Secondary: In combination with pioglitazone and metformin, alogliptin was associated with a significantly greater decrease compared to the titration of pioglitazone in FPG (-15 vs -4 mg/L, respectively; P<0.001) at 52 weeks. Decreases favored alogliptin for HbA_{1c} and FPG at 26 weeks and other time points. At week 52, the proportions of patients achieving HbA_{1c} levels ≤7.0 (33.2 vs 21.3%, respectively) and ≤6.5% (8.7 vs 4.3%, respectively) were significantly higher in the alogliptin group than in the pioglitazone titration group (P<0.001 for all comparisons). Proinsulin: insulin ratio (-0.048 vs -0.007, respectively) and HOMA β-cell function (15.02 vs 2.06, respectively) were significantly improved in the alogliptin group compared to the pioglitazone titration group at 52 weeks (P< 0.001 for all comparisons). However, no statistically significant differences in mean change from baseline in C-peptide, HOMA insulin, in body weight, total cholesterol, HDL cholesterol, LDL-C, triglycerides or

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				free fatty acids resistance were observed between the treatment groups at week 52 (P>0.05 for all comparisons). No meaningful differences in incidences of individual adverse events were observed between treatments.
Einhorn et al.[60] (2000) Pioglitazone 30 to 45 mg and metformin (existing therapy) vs metformin (existing therapy)	DB, PC, RCT Patients with poorly controlled type 2 diabetes (HbA_{1c} ≥8.0%) with metformin monotherapy	N=328 16 weeks	Primary: Change in HbA_{1c}, FPG, insulin, lipoproteins, and C-peptide Secondary: Not reported	Primary: Reductions in HbA_{1c} with pioglitazone add-on therapy were significantly lower compared to placebo (-0.83% difference between treatment groups; P≤0.05). Reductions in FPG with pioglitazone add-on therapy were significantly lower compared to placebo (-37.7 mg/dL difference between treatment groups; P≤0.05). Pioglitazone reduced fasting C-peptide levels (-0.1 ng/mL) while placebo increased levels (0.1 ng/mL; P≤0.05). Pioglitazone reduced fasting C-insulin levels (-2.1 ng/mL) while placebo increased levels (0.4 ng/mL; P<0.05). Pioglitazone add-on therapy significantly reduced TG (-9.7 vs 8.5 mg/dL; P≤0.05) and increased HDL-C (10.2 vs 1.5 mg/dL; P≤0.05) compared to placebo. Both treatment groups increased LDL-C (7.7 vs 11.9 mg/dL; P value not significant). No significant difference between treatment groups in number of adverse events was observed. Higher rate of edema was reported with pioglitazone (5.9 vs 2.5%). Weight loss was observed with placebo (-1.36 kg) while patients receiving pioglitazone had weight gain (0.95 kg; P value not reported). Secondary: Not reported
Kaku et al.[61]	DB, PC, PG, RCT	N=169	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2009) Pioglitazone 15 to 30 mg QD and metformin 500 to 750 mg daily vs metformin 500 to 750 mg daily	Patients 20 to 65 years of age with type 2 diabetes, HbA_{1c} 6.5 to 10.0%, who were drug naïve or on metformin monotherapy	28 weeks	HbA_{1c}, FPG, fasting insulin, insulin resistance, lipid parameters Secondary: Not reported	At week 28, mean change in HbA_{1c} from baseline was -0.67% with pioglitazone compared to 0.25% with placebo (P<0.0001). More patients receiving pioglitazone achieved an HbA_{1c} <6.5% compared to placebo (38.6 vs 8.1%, respectively; P<0.0001). At week 28, mean change in FPG from baseline was -20.5 mg/dL with pioglitazone compared to 1.9 mg/dL with placebo (P<0.0001). Mean fasting insulin concentrations were reduced to a greater extent with pioglitazone (-2.15 mU/mL) compared to placebo (-0.38 mU/mL; P=0.021). Insulin resistance was reduced more by pioglitazone compared to placebo (-1.34 vs -0.15; P=0.0025). The main differences in lipids between pioglitazone compared to placebo were significant increases in TC (P=0.0057) and HDL-C (P<0.0001). Adiponectin levels were significantly increased by pioglitazone compared to placebo (P=0.0001). Secondary: Not reported
Perez et al.[62] (2009) Pioglitazone/ metformin fixed dose combination 15/850 mg BID vs pioglitazone 15 mg BID vs	DB, PG, RCT Patients ≥18 years of age with type 2 diabetes, HbA_{1c} 7.5 to 10.0%, BMI ≤45 kg/m^2, who were drug naïve	N=600 24 weeks	Primary: Change in baseline HbA_{1c} Secondary: HbA_{1c} responder rate, changes in baseline FPG, fasting insulin, insulin resistance	Primary: At week 24, mean change in HbA_{1c} from baseline was -1.83% with pioglitazone/metformin compared to -0.96% pioglitazone and -0.99% with metformin (P<0.0001 for combination therapy vs either monotherapy). Secondary: In the pioglitazone/metformin group, 63.8% achieved HbA_{1c} <7.0% compared to 46.9% with pioglitazone and 38.9% with metformin (P value not reported). Pioglitazone/metformin led to the greatest reduction in FPG from baseline to final visit (-39.9 mg/dL) compared to -22.2 mg/dL with pioglitazone and -24.8 mg/dL with metformin (P<0.01 for combination therapy vs either monotherapy).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
metformin 850 mg BID				Pioglitazone/metformin led to the greatest reduction in fasting insulin from baseline to final visit (-3.91 µIU/mL), followed by pioglitazone (-3.18 µIU/mL). Both reductions were significantly greater compared to metformin (-0.98 µIU/mL; P<0.05). At week 24, the greatest decrease in insulin resistance was seen with pioglitazone/metformin and pioglitazone compared to metformin; however, the difference was significant only with pioglitazone/metformin (P<0.01).
Kipnes et al.[63] (2001) Pioglitazone 15 to 30 mg vs placebo All patients received existing sulfonylurea regimens.	DB, MC, PC, RCT Patients on a stable regimen of a sulfonylurea for ≥30 days with an HbA_{1c} ≥8.0%, fasting C-peptide >1 ng/mL, BMI 25 to 45 kg/m^2	N=560 16 weeks	Primary: Change in baseline HbA_{1c}, FPG, TG, and lipoproteins Secondary: Not reported	Primary: Patients receiving pioglitazone and a sulfonylurea had significant decreases (P<0.05) from baseline in HbA_{1c} and FPG levels compared to patients in the placebo and sulfonylurea group. Both pioglitazone and sulfonylurea groups had significant (P<0.05) mean percent decreases in TG levels (-17%; 95% CI, -6 to -27 for 15 mg and -26%; 95% CI, -16 to -36 for 30 mg) and increases in HDL-C levels (6%; 95% CI, 1 to 11 for 15 mg and 13%; 95% CI, 8 to 18 for 30 mg) compared to the placebo and sulfonylurea group. There were small but statistically significant (P≤0.05) mean percent increases in LDL-C levels in all groups. The adverse event rates were similar in all groups. Secondary: Not reported
Matthews et al.[64] (2005) Pioglitazone 15 to 45 mg QD and metformin (existing therapy) vs	DB, RCT Patients with type 2 diabetes that was poorly controlled (HbA_{1c} 7.5 to 11.0%) with metformin monotherapy	N=630 12 months	Primary: Effect on HbA_{1c} Secondary: Effect on FPG, insulin, lipoproteins, and C-peptide	Primary: Similar reductions in HbA_{1c} were observed in pioglitazone- (–0.99%) and gliclazide-treated groups (–1.01%; P=0.837). Secondary: Similar reductions in FPG were observed in pioglitazone- (–2.1 mmol/L) and gliclazide- (–1.6 mmol/L) treated groups (P=0.506).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
gliclazide* 80 to 320 mg QD and metformin (existing therapy)				Gliclazide significantly reduced LDL-C compared to pioglitazone (–4.2 vs +10.4 mg/dL; P=0.001). Pioglitazone significantly reduced TG (–53.1 vs –19.5 mg/dL; P<0.001) and increased HDL cholesterol (6.9 mg/dL vs no change; P<0.001) compared to gliclazide.
Charbonnel et al.[65] (2005) Pioglitazone 15 to 45 mg QD and metformin (existing therapy) vs gliclazide* 80 to 320 mg QD and metformin (existing therapy)	DB, RCT Patients with type 2 diabetes that was poorly controlled (HbA_{1c} 7.5 to 11.0%) with metformin monotherapy	N=630 24 months	Primary: Effect on HbA_{1c} Secondary: Effect on FPG, insulin, lipoproteins, and C-peptide	Primary: Similar reductions in HbA_{1c} were observed with pioglitazone add-on therapy (–0.89%) and with gliclazide add-on therapy (–0.77%; P=0.200) after two years. Secondary: Significant reductions in FPG were observed with pioglitazone add-on therapy (–1.8 mmol/L) compared to gliclazide add-on therapy (–1.1 mmol/L; P<0.001) after two years. Gliclazide add-on therapy had significantly reduced LDL-C compared to pioglitazone add-on therapy (–6 vs +2 mg/dL; P<0.001). Pioglitazone add-on therapy significantly reduced TG (–23 vs –7 mg/dL; P<0.001) and increased HDL-C (22 vs 7 mg/dL; P<0.001) compared to gliclazide add-on therapy. No significant difference between treatment groups in number of adverse events or discontinuation due to adverse events was reported. Less weight gain was observed with gliclazide add-on therapy to metformin (1.2 kg) compared to pioglitazone add-on therapy (2.5 kg).
Hanefeld et al.[66] (2004) Pioglitazone 15 to 45 mg QD and sulfonylurea (existing therapy) vs	DB, MC, PG, RCT Patients with type 2 diabetes inadequately controlled on sulfonylurea monotherapy	N=639 12 months	Primary: Change in HbA_{1c} Secondary: FPG, fasting plasma insulin, lipids, urinary albumin and creatinine (to	Primary: HbA_{1c} was reduced by 1.20 and 1.36% in the pioglitazone and metformin groups, respectively (P=0.065 for differences between treatments). Secondary: FPG (P=0.528) and fasting plasma insulin (P=0.199) were also reduced but the between-treatment differences were not statistically significant. Pioglitazone addition to sulfonylurea significantly reduced TG (–16 vs

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
metformin 850 to 2,250 mg daily and sulfonylurea (existing therapy)			determine albumin-to-creatinine ratio)	–9%; P=0.008) and increased HDL-C (14 vs 8%; P<0.001) compared with metformin addition. LDL-C was increased 2% by the addition of pioglitazone and decreased 5% by the addition of metformin to sulfonylurea monotherapy (P<0.001). Urinary albumin-to-creatinine ratio was reduced by 15% in the pioglitazone group and increased 2% in the metformin group (P=0.017). Both combinations were well tolerated with no evidence of hepatic or cardiac toxicity in either group.
Comaschi et al.[67] (2008) Pioglitazone 15 to 30 mg QD as add-on to existing oral hypoglycemic therapy (either metformin or sulfonylurea) vs metformin/ glibenclamide‡ fixed dose combination 400/2.5 mg 1 to 3 tablets daily	MC, OL, PG, RCT Patients ≥35 years of age with type 2 diabetes who had received treatment with a stable dose of either metformin or a sulfonylurea as monotherapy for at least 3 months before study entry, HbA_{1c} 7.5 to 11.0%, and fasting C-peptide >0.33 nmol/L	N=250 6 months	Primary: Change in HbA_{1c} from baseline to six months Secondary: Change in lipid profiles after six months of treatment	Primary: Pioglitazone-based and fixed-dose metformin/glibenclamide resulted in similar reductions in HbA_{1c} (-1.11 vs -1.29%, respectively; P=0.192) and FPG (-2.13 vs -1.81 mmol/L, respectively; P=0.370). Secondary: No changes in TC were observed with pioglitazone-based therapy (-0.017 mmol/L) compared to the fixed-dose combination of metformin/glibenclamide (-0.099 mmol/L; P=0.479). The addition of pioglitazone to metformin or a sulfonylurea led to a slight increase in HDL-C (+0.04 mmol/L) compared to a reduction in HDL-C with metformin/glibenclamide (-0.09 mmol/L; P<0.001). There was no significant change in non-HDL-C in patients treated with pioglitazone-based therapy (-0.06 mmol/L) or the fixed-dose combination of metformin/glibenclamide (-0.01 mmol/L; P=0.677). There was no significant change in LDL-C in patients treated with pioglitazone-based therapy (+0.06 mmol/L) or the fixed-dose combination of metformin/glibenclamide (-0.03 mmol/L; P=0.425) There was a significant reduction in TGs with pioglitazone-based therapy (-0.25 mmol/L) compared to no change with the fixed-dose combination of metformin/glibenclamide (0.03 mmol/L; P=0.045).
Seufert et al.[68] (2008)	2 MC, RCT	N=1,269	Primary:	Primary: <u>Study 1</u>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<u>Study 1</u> Pioglitazone 15 to 45 mg QD and metformin (existing therapy) vs gliclazide* 80 to 320 mg daily and metformin (existing therapy) <u>Study 2</u> Pioglitazone 15 to 45 mg QD and sulfonylurea (existing therapy) vs metformin 850 to 2,550 mg daily and sulfonylurea (existing therapy)	Patients 35 to 75 years of age with type 2 diabetes who were inadequately controlled on either metformin or sulfonylurea monotherapy (HbA_{1c} 7.5 to 11.0%), and fasting C-peptide >1.5 ng/ml)	104 weeks	Change in HbA_{1c} from baseline, FPG, glucose excursions using Three hour oral glucose tolerance test, and insulin sensitivity Secondary: Not reported	The mean change in HbA_{1c} from baseline to week 104 was -0.89% with pioglitazone and metformin compared to -0.77% with gliclazide and metformin (P=0.20). The mean change in FPG from baseline to week 104 was -1.8 mmol/l with pioglitazone and metformin compared to -1.1 mmol/l with gliclazide and metformin (P<0.001). Pioglitazone therapy in patients failing metformin therapy achieved decreases in glucose excursions at the end of the two-year treatment period. This effect was not seen in the patients receiving gliclazide for two years as add-on therapy to failing metformin. Insulin sensitivity increased when pioglitazone was added to metformin therapy (+13.8%) compared with a decrease when gliclazide was added to metformin (-7.2%; P<0.0001). <u>Study 2</u> The mean change in HbA_{1c} from baseline to week 104 was -1.03% for patients receiving pioglitazone and sulfonylurea compared to -1.16% for patients receiving metformin and sulfonylurea (P=0.173). The mean change in FPG from baseline to week 104 was -2.0 mmol/L with pioglitazone and sulfonylurea compared to -1.9 mmol/L with metformin and sulfonylurea (P=0.506). The addition of pioglitazone to failing sulfonylurea therapy for two years resulted in a decrease of post-load glucose excursions which was not seen when metformin was added to sulfonylurea treatment. Insulin sensitivity increased when pioglitazone was added to sulfonylurea, (+5.8%) compared to an increase of +3.9% when metformin was added to sulfonylurea (P=0.581 between treatments). Secondary: Not reported
Home et al.[69]	DB, MC, PG, RCT	N=685	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2015) HARMONY 5 Albiglutide (30 mg/week) vs pioglitazone (30 mg/day) vs placebo current dose of metformin (>1500 mg/day) was maintained throughout and blinded uptitration of study drug was allowed	Patients ≥18 years of age with a historical diagnosis of type 2 diabetes and inadequate glycemic control on their current regimen of metformin and a sulfonylurea	156 weeks	Change in HbA_{1c} from baseline to 52 weeks Secondary: HbA_{1c} change over time, FPG, HbA_{1c} responders, body weight change, adverse events	The week 52 model-adjusted difference in change in HbA_{1c} for albiglutide versus placebo was -0.87 (95% CI, –1.07 to –0.68)%-units (P<0.001), and for albiglutide versus pioglitazone it was 0.25 (95% CI, 0.10 to 0.40)%-units; therefore, not non-inferior. Secondary: In the albiglutide group only, fasting plasma glucose reduced rapidly in the first two weeks. Confirmed hypoglycemia occurred in 14% of participants on albiglutide, 25% on pioglitazone and 14% on placebo. The mean (± standard error) weight change was −0.42 (±0.2) kg with albiglutide, 4.4 (±0.2) kg (P<0.001) with pioglitazone, and −0.40 (±0.4) kg with placebo and serious adverse events occurred in 6.3, 9.0 and 6.1% of participants in the respective groups. Injection site reactions occurred in 13% of participants on albiglutide and resulted in treatment discontinuation for four participants (1.4%).
Bergenstal et al.[70] (2010) DURATION-2 Exenatide ER 2 mg SC once weekly vs sitagliptin 100 mg QD vs	DB, DD, MC, PG, RCT Type 2 diabetics ≥18 years of age, receiving a stable metformin therapy for ≥2 months, HbA_{1c} 7.1 to 11.0%, and BMI 25 to 45 kg/m^2	N=514 26 weeks	Primary: Change in baseline HbA_{1c} Secondary: Proportion of patients achieving an HbA_{1c} ≤6.5 or ≤7.0%, FPG, six-point self-monitored glucose concentrations, body weight, fasting lipid	Primary: Exenatide ER (-1.5%; 95% CI, -1.7 to -1.4) significantly decreased HbA_{1c} compared to sitagliptin (-0.9% [95% CI, -1.1 to -0.7]; treatment difference, -0.6% [95% CI, -0.9 to -0.4]; P<0.0001) and pioglitazone (-1.2% [95% CI, -1.4 to -1.0]; treatment difference, -0.3% [95% CI, -0.6 to -0.1]; P=0.0165). Secondary: A significantly greater proportion of patients receiving exenatide achieved HbA_{1c} targets of ≤6.5 (P<0.0001 and P=0.0120) or ≤7.0% (P<0.0001 and P=0.0015) compared to patients receiving sitagliptin or pioglitazone. Exenatide ER (-1.8 mmol/L; 95% CI, -2.2 to -1.3) achieved significantly greater decreases in FPG compared to sitagliptin (-0.9 mmol/L [95% CI, -

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
pioglitazone 45 mg QD All patients received existing metformin therapy.			profile, fasting insulin profile, BP, cardiovascular risk markers, patient-reported quality of life, safety	1.3 to -0.5]; treatment difference, -0.9 mmol/L [95% CI, -0.3 to -1.4]; P=0.0038), but not pioglitazone (-1.5 mmol/L [95% CI, -1.9 to -1.1]; treatment difference, -0.2 mmol/L [95% CI, -0.8 to 0.3]; P=0.3729). A significantly greater proportion of patients receiving exenatide ER (60%) achieved the FPG goal of ≤7 mmol/L compared to patients receiving sitagliptin (35%; P<0.0001), but no difference was observed between patients receiving pioglitazone (52%; P=0.1024). In all measurements of the six-point self-monitored glucose concentrations profile, decreases at week 26 were significantly greater with exenatide ER compared to sitagliptin, but not pioglitazone (P values not reported). Weight loss with exenatide ER (-2.3 kg; 95% CI, -2.9 to -1.7) was significantly greater compared to sitagliptin (difference, -1.5 kg; 95% CI, -2.4 to -0.7; P=0.0002) and pioglitazone (difference, -5.1 kg; 95% CI, -5.9 to -4.3; P<0.0001). Pioglitazone was the only treatment to achieve significant decreases in TG (-16%; 95% CI, -21 to -11) and increases in TC (0.16 mmol/L; 95% CI, 0.04 to 0.28), the former of which was significantly different compared to exenatide ER (-5%; 95% CI, -11 to 0). Fasting insulin was significantly increased after 26 weeks with exenatide ER (3.6 µIU/mL; 95% CI, 1.6 to 5.6) compared to sitagliptin (0.4 µIU/mL [95% CI, -1.6 to 2.3]; treatment difference, 3.2 µIU/mL [95% CI, 0.6 to 5.8]; P=0.0161) and pioglitazone (-3.9 µIU/mL [95% CI, -5.9 to -2.0]; treatment difference, 7.5 µIU/mL [95% CI, 4.9 to 10.1]; P<0.0001). Decreases in SBP with exenatide ER were significantly greater compared to sitagliptin (treatment difference, -4 mm Hg; 95% CI, -6 to -1), but not pioglitazone (data reported in graphical form only). All treatments achieved significant improvements in high-sensitivity CRP and adiponectin. Exenatide ER was the only treatment to achieve a significant improvement in BNP and albumin:creatinine ratio, with the changes in BNP being significantly greater compared to sitagliptin and pioglitazone (P values not reported).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				All five domains of weight-related quality of life and IWQOL total score were significantly improved with exenatide ER (IWQOL total score, 5.15; 95% CI, 3.11 to 7.19) and sitagliptin (4.56; 95% CI, 2.56 to 6.57), but not pioglitazone (1.20; 95% CI, -0.87 to 3.28), which improved only on self-esteem. Improvements in IWQOL with exenatide ER were significantly greater compared to sitagliptin (treatment difference, 3.94; 95% CI, 1.28 to 6.61; P=0.0038). All treatments achieved improvements in all domains of the PGWB and DTSQ total score, with greater improvement in overall satisfaction recorded with exenatide ER (3.96; 95% CI, 2.78 to 5.15) compared to sitagliptin (2.35 [95% CI, 1.19 to 3.51]; treatment difference, 1.61 [95% CI, 0.07 to 3.16]; P=0.0406). The most commonly reported adverse events with exenatide ER and sitagliptin were nausea (24 vs 10%, respectively) and diarrhea (18 vs 10%, respectively). Upper respiratory tract infection (10%) and peripheral edema (8%) were the most commonly reported adverse events with pioglitazone. No episodes of major hypoglycemia were reported.
Aljabri et al.[71] (2004) Pioglitazone 30 to 45 mg QD vs NPH insulin 0.3 unit/kg QD All patients were receiving existing sulfonylurea or metformin therapy.	OL, RCT Patients with poorly controlled type 2 diabetes (HbA_{1c} >8.0%) with insulin secretagogues and metformin monotherapy	N=62 16 weeks	Primary: Effect on HbA_{1c}, FPG, incidence of hypoglycemia (<68 mg/dL), effect on lipoproteins, quality of life (assessed using the DTSQ) Secondary: Not reported	Primary: Similar reductions in HbA_{1c} were observed in pioglitazone-treated (–1.9%) and NPH insulin-treated patients (–2.3%; P=0.32). Nonsignificant differences in reduction in FPG were observed with NPH insulin (–77 mg/dL) and pioglitazone (–52 mg/dL; P=0.07). Significantly more patients reported hypoglycemia with NPH insulin (19) than with pioglitazone (11; P=0.02). Significant increases in HDL-C were observed with pioglitazone (4 mg/dL) compared to NPH insulin (0 mg/dL; P=0.02). No significant differences in TC, LDL-C and TG were reported between the two treatment groups. No significant differences were noted for the DTSQ scores between the two treatment groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Dorkhan et al.[72] (2008) Pioglitazone 30 to 45 mg QD and existing oral hypoglycemic therapy vs insulin glargine 6 to 10 IU/day administered in the morning (titrated as necessary) and existing oral hypoglycemic therapy	RCT, OL Patients with type 2 diabetes and inadequate glycemic control (defined as treatment with metformin and sulfonylurea/ meglitinide in doses ≥50% of maximum recommended doses and HbA_{1c} >6.2%	N=36 26 weeks	Primary: Change in HbA_{1c}, β-cell function, insulin sensitivity, degree of patient satisfaction Secondary: Not reported	Primary: After 26 weeks, the change in HbA_{1c} from baseline was -1.3% (P<0.01) for pioglitazone and -2.2% (P<0.01) for insulin glargine. There was no significant difference between the treatment groups (P=0.050). There was no difference in insulin, β-cell function, or insulin sensitivity among the two treatment groups (P=NS). Insulin glargine resulted in a greater reduction in proinsulin concentrations than pioglitazone (-55% vs -25%; P<0.01). Pioglitazone increased HDL-C (0.14 mmol/L) compared to a slight decrease in the insulin glargine group (-0.04 mmol/L; P<0.01 between groups). There were no significant differences between the treatment groups with regards to other lipid parameters (P=NS). The degree of satisfaction with treatment was similar in the pioglitazone and insulin glargine treatment groups. There was a doubling of serum adiponectin levels in the pioglitazone group (7.5 to 15; P<0.01) compared to a significant decrease in the insulin glargine group (8.7 to 7.6; P=0.04; P<0.01 between groups). Secondary: Not reported
Ligvay et al.[73] (2009) Pioglitazone 15 to 45 mg QD plus glyburide 1.25 mg BID vs	RCT, OL Patients 21 to 70 years of age with type 2 diabetes who were treatment naïve	N=58 36 months	Primary: HbA_{1c}, rate of treatment failures (defined as HbA_{1c} >8.0%), hypoglycemia, weight gain, compliance, QoL, and patient satisfaction	Primary: After 36 months, HbA_{1c} was 6.1 % in the insulin-treated group compared to 6.0% in the triple oral group (P=0.26). The percentage of patients achieving HbA_{1c} <7.0% was 100% in both groups at baseline; 92% of patients in the insulin group and 76% of patients in the triple oral group met the HbA_{1c} goal at the end of 36 months. Three patients in each group reached the “treatment failure” end point.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
insulin aspart protamine and insulin aspart (NovoLog Mix 70/30) 0.2 units/kg divided twice daily All patients were receiving metformin 1,000 mg BID Doses of medications could be titrated at the investigator's discretion.			Secondary: Not reported	The insulin group had 0.51 mild hypoglycemia events/person month and the triple oral group had 0.68 event/person-month (P=0.18). The insulin group averaged 0.04 severe hypoglycemic event/person-year, and the triple oral group averaged 0.09 event/ person-year (P=0.53). In the completer analysis, the triple oral group experienced more weight gain than the insulin group: 10.10 kg (95% CI, 4.46 to 15.74) vs 3.36 kg (-0.47 to 7.20; P=0.04). Compliance was high throughout the trial: 93% in the insulin-treated group and 90% in the triple oral group. There were differences between the groups for any of the 12 QoL domains evaluated. All patients receiving insulin reported satisfaction with insulin treatment and willingness to continue insulin at 18 months after randomization. Secondary: Not reported
Meneghini et al (abstract).[74] (2010) Insulin glargine vs pioglitazone	MC, OL, PG Adults with poorly controlled type 2 diabetes (HbA_{1c} 8.0 to 12.0%), despite ≥3 months of sulfonylurea or metformin monotherapy	N=389 48 weeks	Primary: Change in baseline HbA_{1c} Secondary: Change in baseline FPG, BMI, body weight, safety	Primary: At trial end, insulin glargine resulted in a significantly greater reduction in HbA_{1c} compared to pioglitazone (-2.48 vs -1.86%; 95% CI, -0.93 to -0.31; *P*=0.001). Secondary: Insulin glargine resulted in significantly greater reductions in FPG at all time points (trial end difference, -34.9 mg/dL; 95% CI, -47.6 to -22.2; *P*<0.0001). Changes in weight and BMI were similar between the two treatments. Compared to pioglitazone, insulin glargine resulted in a lower overall incidence of possibly treatment-emergent adverse events (12.0 vs 20.7%) and fewer study discontinuations (2.2 vs 9.1%), but a higher rate (per patient-year) of confirmed clinically relevant hypoglycemic episodes (4.97 vs 1.04; *P*<0.0001) and severe hypoglycemia (0.07 vs 0.01; *P*=0.0309).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Perez-Monteverde et al.[75] (2011) Sitagliptin/ metformin vs pioglitazone 30 to 45 mg QD In Phase 1, patients were randomized to either sitagliptin 100 mg QD or pioglitazone 30 mg QD. In Phase 2, patients randomized to sitagliptin in Phase 1 were switched to sitagliptin/ metformin, and patients randomized to pioglitazone in Phase 1 were up titrated to 45 mg/day	DB, RCT Patients with type 2 diabetes and HbA_{1c} 7.5 to 12.0%	N=492 (Phase 1) 12 weeks (Phase 1) plus 28 weeks (Phase 2)	Primary: Change in baseline HbA_{1c} Secondary: Change in baseline FPG and two-hour PPG, proportion of patients achieving HbA_{1c} <7.0%, safety, body weight	Primary: At the end of Phase 1 (12 weeks), mean changes from baseline in HbA_{1c} were -1.0 and -0.9% with sitagliptin and pioglitazone. At the end of Phase 2 (40 weeks), improvements in HbA_{1c} were greater with combination therapy compared to pioglitazone (-1.7 vs -1.4%; P=0.002). Secondary: At the end of Phase 1 (12 weeks), mean changes from baseline were -26.6 and -28.0 mg/dL for FPG and -52.8 and -50.1 mg/dL for two-hour PPG. At the end of Phase 2 (40 weeks), improvements in FPG and two-hour PPG were greater with combination therapy compared to pioglitazone (-45.8 vs -37.6 mg/dL; P=0.03 and -90.3 vs -69.1 mg/dL; P=0.001). Significantly more patients receiving combination therapy achieved an HbA_{1c} <7.0% (55.0 vs 40.5%; P=0.004). A numerically higher incidence of gastrointestinal adverse events and a significantly lower incidence of edema were observed with combination therapy compared to pioglitazone. The incidence of hypoglycemia was similarly low with both treatments. Body weight decreased with combination therapy and increased with pioglitazone (-1.1 vs 3.4 kg; P<0.001).
Wainstein et al.[76] (2012) Sitagliptin/ metformin 50/500 mg BID, titrated up to 50/1,000 mg BID vs	DB, RCT Treatment-naïve patients with type 2 diabetes HbA_{1c} 7.5 to 12.0%	N=517 32 weeks	Primary: Change from baseline HbA_{1c}, proportion of patients who achieved HbA_{1c} <7.0% Secondary:	Primary: The least squares mean changes in HbA_{1c} at week 32 were -1.9 and -1.4% with combination therapy compared to pioglitazone, respectively (between-group differences, -0.5%; P<0.001). A greater proportion of patients achieved an HbA_{1c} <7.0% at week 32 with combination therapy compared to pioglitazone (57 vs 43%; P<0.001). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
pioglitazone 30 mg/day, titrated up to 45 mg/day			Change from baseline FPG	Compared to pioglitazone, combination therapy resulted in a greater least squares mean reductions in FPG (-56.0 vs -44.0 mg/dL; P<0.001) and 2-hour PPG (-102.2 vs -82.0 mg/dL; P<0.001) at week 32. A substantially greater reduction in FPG (-40.5 vs -13.0 mg/dL; P<0.001) was observed at week 1 with combination therapy compared to pioglitazone. A greater reduction in the fasting proinsulin:insulin and a greater increased in HOMA-B were observed with combination therapy compared to pioglitazone, while greater decreases in fasting insulin and HOMA-IR, and a greater increase in quantitative insulin sensitivity check index were observed with pioglitazone compared to combination therapy. Combination therapy resulted in a decrease in body weight (-1.4 kg) and pioglitazone resulted in an increase in body weight (3.0 kg; P<0.001). Higher incidences of diarrhea (15.3 vs 4.3%; P<0.001), nausea (4.6 vs 1.2%; P=0.02), and vomiting (1.9 vs 0.0%; P=0.026), and a lower incidence of edema (1.1 vs 7.0%; P<0.001) were observed with combination therapy compared to pioglitazone. There was no difference between the two treatments in the incidence of hypoglycemia (8.4 vs 8.3%; P=0.055).
Takihata et al.[77] (2013) Sitagliptin 50 mg/day vs pioglitazone 15 mg/day (both groups could have doses titrated up at 16 weeks if HbA_{1c} ≥6.5%)	MC, OL, RCT Japanese type 2 diabetic men and women between the ages of 20 and 75 years whose diabetes had been inadequately controlled (HbA_{1c}, 6.9 to 9.5%) with metformin and/or sulfonylurea.	N=130 Up to 24 weeks	Primary: Difference in the mean changes in the HbA_{1c} level from baseline at 24 weeks Secondary: Levels of FPG, fasting insulin, inflammation mediators, N-terminal pro-B-type natriuretic peptide, and	Primary: Difference in HbA_{1c} in the sitagliptin group was -0.86 and in the pioglitazone group was -0.58 (P=0.024). Secondary: Difference in FPG and fasting insulin did not differ significantly between groups. Body weight decreased by 0.29 kg in the sitagliptin group and increased by 1.70 kg in the pioglitazone group (P<0.001). The levels of LDL-C and HDL-C were significantly decreased in the sitagliptin group. The triglyceride level was not altered. The Estimated glomerular filtration rate and creatinine level were significantly exacerbated in both groups, and the uric acid level was also exacerbated in the sitagliptin group. Hypoglycemia (3.4 vs 3.5%), gastrointestinal symptoms (5.2 vs 1.8%) and pedal edema (0 vs 68.4%, P<0.001) were observed for 24 weeks in the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			markers of lipids, uric acid, liver function, and renal function	sitagliptin and pioglitazone groups, respectively. No severe cases of hypoglycemia, rash, or bone fracture were observed in either group during the trial.
Borges et al.[78] (2011) Rosiglitazone/ metformin vs metformin	DB, MC, RCT Drug naïve patients with type 2 diabetes	N=688 18 months	Primary: Change in baseline HbA_{1c}, FPG Secondary: Bone mineral density	Primary: Combination therapy was more efficacious in achieving significant reductions in HbA_{1c} (P<0.0001) and FPG (P<0.001) compared to metformin. In addition, more patients achieved HbA_{1c} and FPG goals with combination therapy compared to metformin. Secondary: In a bone substudy, at week 80 combination therapy was associated with significantly lower BMD compared to metformin in the lumbar spine (P<0.0012) and total hip (P=0.0005, respectively). There was no difference between treatments for distal one-third of radius, femoral neck, and total bone mineral densities (P values not reported).
Fonseca et al.[79] (2000) Rosiglitazone 4 mg and metformin 2,500 mg daily vs rosiglitazone 8 mg and metformin 2,500 mg daily vs metformin 2,500 mg daily	DB, PC, RCT Patients with poorly controlled type 2 diabetes (mean FPG 140 to 300 mg/dL) with metformin; baseline HbA_{1c} 8.6% in the metformin treatment group, 8.9% in the rosiglitazone/ metformin 4/2,500 mg treatment group and 8.9% in the rosiglitazone/ metformin 8/2,500 mg treatment group; patients were excluded if they had NYHA class III-IV	N=348 26 weeks	Primary: Change in baseline HbA_{1c}, FPG, fructosamine, C-peptide, FFA, lipids, lactate, and estimates of insulin sensitivity (HOMA-S) and β-cell function (HOMA-B) Secondary: Not reported	Primary: Addition of rosiglitazone significantly reduced HbA_{1c} in a dose-related fashion from baseline compared to metformin monotherapy. Mean difference from the metformin control group was -1.0% (P<0.001) with rosiglitazone/metformin 4/2,500 mg and -1.2% with rosiglitazone/metformin 8/2,500 mg (P<0.001). Mean FPG concentrations were reduced significantly with rosiglitazone/metformin 4/2,500 mg (-33 mg/dL; P<0.0001) and with rosiglitazone/metformin 8/2,500 mg (-48.4 mg/dL; P<0.0001). No significant change in FPG was observed with metformin monotherapy. Fructosamine levels were reduced with both rosiglitazone/metformin 4/2,500 mg (-27.9 µmol/L; P value not reported) and rosiglitazone/metformin 8/2,500 mg (-36.8 µmol/L; P value not reported). Fructosamine levels increased with metformin monotherapy (12.3 µmol/L; P value not reported). C-peptide values were reduced significantly in all treatment groups compared to baseline (P<0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	heart failure, angina, renal or liver disease, symptomatic neuropathy, or prior use of rosiglitazone or insulin			FFA levels were significantly less in both rosiglitazone/metformin groups compared to metformin monotherapy group (P<0.05). Significant increases in TC, HDL-C and LDL-C were observed with both rosiglitazone groups when compared to metformin monotherapy group (P<0.05). Mean fasting lactate levels were significantly less in both rosiglitazone/metformin groups compared to metformin monotherapy group (P<0.05). Both insulin sensitivity (as measured by HOMA-S) and β-cell function (as measured by HOMA-B) were increased in a dose-dependent fashion with rosiglitazone/metformin compared to metformin monotherapy (P value not reported). Secondary: Not reported
Weissman et al.[80] (2005) Rosiglitazone 8 mg QD and metformin 1,000 mg/day (RSG + MET) vs metformin 1,500 mg/day (MET)	DB, MC, PG, RCT Patients 18 to 75 years of age diagnosed with type 2 diabetes (defined as HbA_{1c} 6.5 to 8.5% for patients receiving combination therapy with metformin and sulfonylurea or HbA_{1c} 7.0 to 10.0% for drug-naïve or patients receiving monotherapy), FPG of 126 to 270 mg/dL and BMI ≥27kg/m^2; any	N=766 2-week wash out period followed by 4 to 7 weeks of run-in period and 24 weeks of treatment	Primary: Change in baseline HbA_{1c} Secondary: Change in baseline FPG at week 24, proportion of patients responding to treatment (reduction ≥0.7% for HbA_{1c} and ≥30 mg/dL for FPG at week 24), clinical safety, adverse events, tolerability, clinical laboratory tests	Primary: After 24 weeks, RSG+MET and MET were both effective in improving HbA_{1c} with mean reductions of -0.93% (95% CI, -1.06 to -0.80) and -0.71% (95% CI, -0.83 to -0.60), respectively, with a mean treatment difference of -0.20% (95% CI, -0.36 to -0.04). Secondary: Significant reductions in FPG from baseline were seen in patients receiving RSG+MET (-2.29 mmol/L; 95% CI, -2.59 to -1.99) compared to patients receiving MET (-1.12 mmol/L; 95% CI, -1.43 to -0.82), with a treatment difference of -0.85 mmol/L (95% CI, -1.23 to -0.47). The proportion of patients who responded to treatment (reduction in HbA_{1c} ≥0.7%) was greater in the RSG+MET group than the MET group (59.5 and 49.5%, respectively) with the treatment difference of 10% (95% CI, 1.9 to 18.1).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	subjects previously receiving metformin or metformin and sulfonylurea must have received ≤metformin 1,000 mg/day for at least 3 months prior to study entry and patients must have stopped previous treatment with TZD at least 3 months prior to screening			The proportion of FPG responders (reduction in FPG ≥30 mg/dL) was also greater in the RSG+MET group than in the MET group (55.0 vs 32.5%, respectively). The percentage of patients experiencing a gastrointestinal effect was greater in the MET group compared to the RSG+MET group (38.7 and 27.9%). The odds of experiencing a gastrointestinal side effect were 63% greater for patients receiving MET compared to patients receiving RSG+MET (OR, 1.63; 95% CI, 1.19 to 2.24). RSG+MET resulted in a mean weight gain of 1.79 kg (P<0.0001) compared to a mean weight loss of -1.78 kg (P<0.001) with MET. There were three deaths during the course of the study with two prior to DB study medication, and one while on RSG+MET; the cause of which was unknown, although it was not considered to be treatment related.
TODAY Study Group.[81] (2012) TODAY Metformin vs rosiglitazone 4 mg BID plus metformin vs metformin plus lifestyle intervention (focusing on weight loss through eating and activity behaviors)	MC, RCT Patients 10 to 17 years of age, with type 2 diabetes	N=699 3.86 years (average follow-up)	Primary: Loss of glycemic control (HbA_{1c} ≥8.0% for six months or sustained metabolic decompensation requiring insulin) Secondary: Body weight, metabolic outcomes, safety	Primary: Overall, a total of 319 (45.6%) patients reached the primary outcome, with a median time to treatment failure of 11.5 months (range, <1 to 66). Rates of failure were 51.7 (95% CI, 45.3 to 58.2), 38.6 (95% CI, 32.4 to 44.9), and 46.6% (95% CI, 40.2 to 53.0) of patients on metformin, rosiglitazone plus metformin, and metformin plus lifestyle intervention, respectively. Rosiglitazone plus metformin was more efficacious to metformin; combination therapy was associated with a 25.3% decrease in the occurrence of the primary outcome compared to metformin (P=0.006). The outcome with metformin plus lifestyle intervention was intermediate, but not significantly different from metformin or rosiglitazone plus metformin (P value not reported). The reasons for treatment failure did not differ significantly across treatments. Prespecified analyses according to sex and race or ethnic group showed differences in sustained effectiveness, with metformin least effective in non-Hispanic black patients and rosiglitazone plus metformin most effective in female patients. Secondary:

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Patients were treated during a run-in period of 2 to 6 months with metformin 1,000 mg BID to attain an HbA_{1c} <8.0% prior to randomization.				BMI over time (up to 60 months) differed significantly according to the study treatment (P<0.001 for the overall comparison), and the results of all three pairwise comparisons between treatment groups were also significant. Patients treated with rosiglitazone plus metformin had the greatest increase in BMI and patients receiving metformin plus lifestyle intervention had the least. The change in fat mass from baseline differed significantly across the treatment groups (P<0.05) because of a significant difference between rosiglitazone plus metformin and metformin plus lifestyle interventions. There were no significant between-group differences in the change from baseline for any other outcome. Serious adverse events were reported in 19.2% of all patients, including 18.1, 14.6, and 24.8% with metformin, rosiglitazone plus metformin, and metformin plus lifestyle intervention (P=0.02). Hospitalizations accounted for more than 90% of serious adverse events. Severe hypoglycemia occurred in one, one, and two patients receiving metformin, rosiglitazone plus metformin, and metformin plus lifestyle intervention. No effects of rosiglitazone on bone mineral content or rate of fracture were noted.
Stewart et al.[82] (2006) Rosiglitazone 8 mg QD and metformin 2,000 mg/day (MET + RSG) vs metformin 3,000 mg/day (MET)	DB, MC, PG, RCT Type 2 diabetic patients 18 to 70 years of age, who were either antidiabetic-drug-naïve with FPG of 7.0 to 9.0 mmol/L and HbA_{1c} 7.0 to 9.0%, or previously treated with oral antidiabetic monotherapy with FPG 6.0 to 8.0 mmol/L and HbA_{1c} 6.5 to 8.0%	N=526 32 weeks	Primary: Proportion of patients achieving HbA_{1c} ≤6.5% at week 32, change in baseline HbA_{1c} Secondary: Proportion of patients achieving target HbA_{1c} and FPG levels, change in baseline FPG and fasting plasma insulin, change in insulin resistance, pancreatic β-cell	Primary: At week 32, there was a reduction from baseline in mean HbA_{1c} in the MET+RSG group from 7.2 to 6.7% compared to 7.2 to 6.8% in the MET group (P=0.0357). Secondary: The proportion of patients achieving HbA_{1c} ≤6.5% at week 32 was similar in the two groups (P=0.095). The proportion of patients achieving FPG <7.0 mmol/L at week 32 was 56% in the MET+RSG group compared to 38% in the MET group (OR, 2.33; P<0.0001). The reduction in fasting plasma insulin from baseline was greater in the MET+RSG group compared to the MET group (treatment difference, -12.2 pmol/L; P=0.00029).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			function, CRP, lipid parameters and 24-hour ambulatory BP, safety	HOMA-S, β-cell function, CRP, and SBP were greater in the MET+RSG group at week 32 compared to the MET group (P<0.05 for all). TC, HDL-C, and LDL-C increased, FFAs decreased, and TG did not change in the MET+RSG group, whereas in the MET group there were decreases in TC, LDL-C, and TG, and increases in HDL-C and FFAs. The difference between the treatments was significant for the above parameters (P<0.05). The proportion of patients with reductions in 24-hour mean SBP was greater in the MET+RSG group compared to the MET group (treatment difference, -3.6 mm Hg; P=0.0315). The overall incidences of gastrointestinal adverse events were comparable between groups, but there was a lower incidence of diarrhea in the MET+RSG group (8 vs 18%). Hypoglycemia was reported in 17 patients (7%) in the MET+RSG group compared to 10 patients (4%) in the MET group. There were greater reductions in mean hemoglobin and hematocrit over 32 weeks in the MET+RSG group compared to the MET group (P<0.0001).
Rosak et al.[83] (2005) Rosiglitazone 4 to 8 mg and metformin (existing therapy)	OS, PM Two studies in which type 2 diabetics on metformin therapy received rosiglitazone add-on therapy; baseline HbA_{1c} was 8.1% in both trials	N=11,014 6 months	Primary: Change in baseline HbA_{1c}, FPG, body weight, and BP Secondary: Not reported	Primary: Addition of rosiglitazone significantly reduced HbA_{1c} from baseline (-1.3%; P<0.0001). Addition of rosiglitazone significantly reduced FPG from baseline (-47.0 mg/dL; P<0.0001). Significant reduction in BP from baseline (-7/-3 mm Hg; P<0.0001) was observed with rosiglitazone add-on therapy. Significant reduction in weight (-1.7 kg; P<0.0001) was observed with rosiglitazone add-on therapy. Most commonly reported adverse events were weight gain (0.16%) and edema (0.15%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Bailey et al.[84] (2005) Rosiglitazone/ metformin fixed dose combination 4/1,000 mg to 8/2,000 mg daily vs metformin 2,500 to 3,000 mg daily	DB, MC, PG, RCT Patients with type 2 diabetes poorly controlled (FPG ≥126 to 216 mg/dL) with metformin alone or in combination with an insulin secretagogue or acarbose; baseline HbA_{1c} 7.4% for rosiglitazone add-on therapy and 7.5% for metformin; patients were excluded if they had been treated with a TZD or insulin, had unstable cardiovascular or cerebrovascular conditions, or had uncontrolled hypertension	N=568 24 weeks	Primary: Change in baseline HbA_{1c} Secondary: Change in baseline FPG and insulin, proportion of patients who achieved HbA_{1c} and FPG targets	Primary: Reductions in HbA_{1c} observed with rosiglitazone add-on therapy were significantly lower compared to metformin monotherapy (-0.22% difference between treatment groups; P=0.001). Secondary: Reductions in FPG observed with rosiglitazone add-on therapy were significantly lower compared to metformin monotherapy (-18.3 mg/dL difference between treatment groups; P<0.001). Significant reduction in fasting insulin was observed with rosiglitazone add-on therapy compared to metformin monotherapy (-12.4 pmol/L difference between treatment groups; P=0.001). Greater proportion of patients on rosiglitazone add-on therapy (54%) reached HbA_{1c} targets (<7.0%) compared to those treated with metformin monotherapy (36%; OR, 2.42; P<0.001). Greater proportion of patients on rosiglitazone add-on therapy (32%) reached FPG targets (<126 mg/dL) compared to those treated with metformin monotherapy (8%; OR, 5.71; P<0.001). Higher rate of withdrawal due to adverse events with metformin monotherapy (8 vs 4%; no P value reported) was noted. Gastrointestinal disorders were the most commonly reported event that caused withdrawal in the metformin monotherapy group.
Rosenstock et al.[85] (2006) Rosiglitazone/ metformin fixed dose combination 4/1,000 mg to 8/2,000 mg daily	DB, MC, RCT Type 2 diabetics with HbA_{1c} >7.5 to 11.0%, with FPG ≤270 mg/dL who were previously treated with diet and exercise or had not	N=468 32 weeks	Primary: Change in baseline HbA_{1c} Secondary: Proportion of patients achieving HbA_{1c} and FPG targets, change in	Primary: Patients receiving rosiglitazone/metformin showed significant improvements in HbA_{1c} with a reduction of -2.3% compared to baseline vs -1.8% with patients receiving metformin (P<0.0008) and -1.6% with patients receiving rosiglitazone (P<0.0001). Secondary: Target HbA_{1c} ≤6.5 and <7.0% were achieved in more patients in the rosiglitazone/metformin group (60 and 77%) than in the metformin (39

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs rosiglitazone 4 to 8 mg daily vs metformin 500 to 2,000 mg daily	been treated with a glucose-lowering agent for more than 15 days within 12 weeks prior to screening		baseline FPG, safety	and 57%) or rosiglitazone (35 and 58%) groups, respectively (P values not reported). The greatest mean decrease in FPG was seen with rosiglitazone/metformin (-74 mg/dL) and was significant compared to metformin (-50 mg/dL; P<0.0001) and rosiglitazone (-47 mg/dL; P<0.0001). Treatment was well tolerated with nausea, vomiting and diarrhea as the most commonly reported adverse events. Edema was comparable between rosiglitazone/metformin (6%) and rosiglitazone (7%) and lower with metformin.
Hamann et al.[86] (2008) Rosiglitazone/ metformin FDC 4 mg/2,000 mg daily (RSG+MET) vs glibenclamide‡ 5 mg and metformin 2,000 mg or gliclazide* 80 mg and metformin 2,000 mg daily (SU+MET)	DB, PG, RCT Overweight patients (BMI ≥25 kg/m^2) with type 2 diabetes, HbA_{1c} 7.0 to 10.0%, who received metformin ≥850 mg/day for at least 8 weeks	N=596 52 weeks	Primary: Change in HbA_{1c} from baseline to week 52 Secondary: Change in FPG, β-cell function, insulin resistance, hypoglycemia, BP	Primary: At week 52, mean change in HbA_{1c} from baseline was -0.78% for RSG+MET compared to -0.86% with SU+MET (95% CI, -0.08 to 0.25). Secondary: Reductions in FPG from baseline to week 52 was -2.29 mmol/L with RSG+MET compared to -2.25 mmol/L with SU+MET (P=0.8095). The degree of β-cell failure was significantly greater with SU+MET compared to RSG+MET as measured by the coefficient of failure (0.543 vs 0.055 HbA_{1c}%/year, respectively; P=0.0002). Insulin sensitivity increased 55% with RSG+MET compared to 12.3% with SU+MET (P<0.0001). Hypoglycemia occurred in 30% of patients receiving SU+MET compared to 6% of patients receiving RSG+MET (P<0.0001). After 52 weeks, 24-hour diastolic and systolic ambulatory BP were reduced with RSG+MET, but not with SU+MET. The difference between treatments was significant for diastolic ambulatory BP (-2.9 mm Hg; P=0.0013), but not for systolic ambulatory BP (-2.6 mm Hg; P=0.0549).
Marre et al.[87] (2009) LEAD-1	AC, DB, DD, MC, PG, RCT	N=1,041 26 weeks	Primary: Change in baseline HbA_{1c}	Primary: After 26 weeks, HbA_{1c} decreased by -1.1% with both liraglutide 1.2 and 1.8 mg, respectively, compared to placebo (0.2%) and rosiglitazone (-0.4%). Estimated treatment differences compared to placebo were:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Liraglutide 0.6, 1.2, and 1.8 mg SC QD plus glimepiride 2 to 4 mg/day and placebo vs placebo plus glimepiride 2 to 4 mg/day vs placebo plus glimepiride 2 to 4 mg/day and rosiglitazone 4 mg/day	Type 2 diabetic patients 18 to 80 years of age treated with an oral glucose-lowering agent for ≥3 months, HbA_{1c} 7.0 to 11.0% (previously on oral glucose lowering agent monotherapy) or 7.0 to 10.0% (previously on oral glucose lowering agent combination therapy), and BMI ≤45 kg/m^2		Secondary: Proportion of patients reaching HbA_{1c} (<7.0 and ≤6.5%), FPG (5.0 to ≤7.2 mmol/L), and PPG (10.0 mmol/L) targets; change in baseline body weight, FPG, mean PPG, β cell function, and BP	liraglutide 1.8 mg, -1.4% (95% CI, 1.6 to -1.1; P<0.0001); liraglutide 1.2 mg, -1.3% (95% CI, 1.5 to -1.1; P<0.0001); liraglutide 0.6 mg, -0.8% (95% CI, -1.1 to -0.6; P<0.0001); and rosiglitazone, -0.7% (95% CI, -0.9 to -0.4; P<0.0001). Additionally, the two higher doses of liraglutide (1.2 and 1.8 mg) were more efficacious compared to treatment with rosiglitazone (P<0.0001 for both measures). Decreases in HbA_{1c} were greater in patients previously on an oral glucose lowering agent monotherapy. Secondary: The proportion of patients reaching HbA_{1c} targets with liraglutide was dose-dependent. At week 26, 42, and 21% of patients receiving liraglutide 1.8 mg reached HbA_{1c} <7.0 and ≤6.5% compared to 8 and 4% of patients receiving placebo. Estimated proportions of patients receiving liraglutide 1.2 and 1.8 mg reaching HbA_{1c} targets were greater compared to patients receiving placebo (P<0.0001) and rosiglitazone (P<0.0003), respectively. More patients reached <7.0% with liraglutide 1.8 mg compared to 1.2 mg (P=0.018). The proportions of patients achieving FPG targets were significantly greater with liraglutide 0.6 mg (19%; P=0.002), 1.2 mg (37%; P<0.001), and 1.8 mg (38%; P=0.002) compared to placebo (7%). Compared to patients receiving rosiglitazone (26%), significantly more patients receiving liraglutide 1.2 and 1.8 mg achieved FPG targets (P=0.007 and P=0.01, respectively). The proportion of patients with one, two, or three PPG target measurements were significantly greater for all doses of liraglutide compared to placebo (P<0.05), but not rosiglitazone (P value not reported). Mean decreases in weight were -0.2 kg with liraglutide 1.8 mg and -0.1 kg with placebo. Mean increases in weight were 0.7 kg with liraglutide 0.6 mg, 0.3 kg with liraglutide 1.2 mg, and 2.1 kg with rosiglitazone. Differences between rosiglitazone and liraglutide were significant (P<0.0001), although there were no differences compared to placebo (P value not reported).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Decreases in the proinsulin:insulin ratio were significantly greater with liraglutide 1.2 and 1.8 mg compared to rosiglitazone and placebo (P≤0.02). HOMA-B increased with liraglutide 1.2 and 1.8 mg compared to rosiglitazone (P<0.05), and increases were only significant compared to placebo with liraglutide 1.2 mg (P=0.01). No differences between treatments were observed for changes in HOMA-IR. Decreases in SBP with liraglutide 1.2 and 1.8 mg (-2.6 to -2.8 mm Hg) were not different compared to placebo or rosiglitazone (-0.9 to -2.3 mm Hg; P values not reported).
Rosenstock et al.[88] (2006) Rosiglitazone/ metformin fixed dose combination 4/1,000 mg to 8/2,000 mg daily	MC, OL Type 2 diabetics with HbA_{1c} >11.0% or FPG >270 mg/dL who were previously treated with diet and exercise or had not been treated with a glucose-lowering agent for more than 15 days within 12 weeks prior to screening	N=190 24 weeks	Primary: Change in baseline HbA_{1c} Secondary: Proportion of patients achieving HbA_{1c} targets; change in baseline FPG, lipids, and insulin sensitivity (HOMA-S)	Primary: Clinically significant mean reductions in HbA_{1c} (11.8 to 7.8%; P<0.0001) were observed after initiation of rosiglitazone/metformin at week 24. Secondary: Treatment goals of HbA_{1c} ≤6.5% and <7.0% at week 24 were achieved in 33 and 44% of patients, respectively. Clinically significant mean reductions in FPG (304 to 166 mg/dL; P<0.0001) were observed after initiation of rosiglitazone/metformin at week 24. HDL-C increased 4.4% and TC (-3.7%), LDL-C (-0.7%) and TG (-13.4%) decreased compared to baseline (P values not reported). Rosiglitazone/metformin significantly increased HOMA estimates of insulin sensitivity by 68% (P<0.0001). Rosiglitazone/metformin was well tolerated. There was a 2% incidence of hypoglycemia, mean increase in weight of 2.6 kg from baseline and 2.6% of patients withdrew because of an adverse event.
Fonseca et al.[89] (2003) Rosiglitazone 8 mg QD and nateglinide	DB, MC, PC, RCT Patients ≥21 years of age with type 2 diabetes for ≥6	N=402 24 weeks	Primary: Change in baseline HbA_{1c} Secondary:	Primary: HbA_{1c} did not change significantly from baseline in the placebo group, but did change significantly in the nateglinide group. The change from baseline to end point was -0.8±0.1% (P<0.0001 vs baseline or placebo).

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120 mg before each meal vs rosiglitazone 8 mg QD and placebo	months previously and treated with rosiglitazone 8 mg/day, diet, and exercise for ≥3 months, had a BMI 22 to 40 kg/m^2, FPG 6.1 to 13.3 mmol/L, and HbA_{1c} 7.0 to 11.0%		FPG, two-hour postprandial insulin, TC, LDL-C, HDL-C, TG, body weight, four-hour AUC for glucose, insulin during meal challenges	Secondary: Change in FPG decreased significantly from a baseline of 9.8 to 9.0 mmol/L in the nateglinide group (P<0.001). FPG did not change significantly from the baseline (10 mmol/L) in patients receiving placebo. Two-hour postprandial insulin in the nateglinide group decreased from 14.0 to 11.4 mmol/L (P<0.0001). The group receiving placebo had an increase in 2-hour postprandial insulin from 14.4 to 14.8 mmol/L (P<0.0001 vs nateglinide). Total and incremental glucose $AUCs_{(0\text{-}4\ hours)}$ were significantly reduced in the nateglinide group (-8.6±0.8 and -6.2±0.5 mmol/L/hr, respectively; P<0.0001 vs baseline or placebo for both total and incremental AUCs). This represents a 16% reduction in the total and a 49% reduction in the incremental glucose AUC. Total and incremental insulin $AUCs_{(0\text{-}4\ hour)}$ were increased in the nateglinide group (425 and 395 pmol/L/hr, respectively; P<0.0001 vs baseline or placebo plus for both total and incremental AUCs). This represents a 46% increase in the total and 69% increase in the incremental insulin AUC. There were no significant changes in TC, LDL-C, or TG in either group. There was a small, but significant increase from baseline in HDL-C observed in patients receiving nateglinide (P<0.025) and in patients receiving placebo (P<0.005). Body weight increased in both groups. The mean change from baseline in patients receiving nateglinide (3.1±0.3 kg) was significantly greater compared to patients receiving placebo (1.1±0.3 kg; P<0.0001). Meal challenges were performed at week 0 and at end point. The glucose and insulin profiles were similar in the two groups at baseline, and PPG and insulin concentrations were unchanged at end point relative to baseline in patients receiving placebo.
Raskin et al.[90] (2004)	MC, OL, PG, RCT	N=252	Primary:	Primary: Mean change in HbA_{1c} from baseline with repaglinide was -0.17% and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Rosiglitazone 2 to 4 mg BID and repaglinide 0.5 to 4 mg TID before meals vs rosiglitazone 2 to 4 mg BID vs repaglinide 0.5 to 4 mg TID before meals	Patients ≥18 years old with type 2 diabetes for ≥12 months with an HbA_{1c} >7.0 to ≤12.0% during previous monotherapy with sulfonylurea or metformin for ≥3 months with a BMI ≤45 kg/m^2	24 weeks	Change in baseline HbA_{1c} Secondary: Change in baseline FPG	-0.56% with rosiglitazone. The mean change in HbA_{1c} from baseline with combination therapy was -1.43 (P≤0.001 vs either monotherapy). The reduction in HbA_{1c} from baseline was greater with combination therapy compared to the sum of the responses for monotherapy (P<0.01). Secondary: Mean FPG change from baseline with repaglinide was -3 mmol/L and -3.7 mmol/L with rosiglitazone. Mean FPG change from baseline with combination therapy was -5.2 mmol/L (P≤0.001 vs either monotherapy).
McCluskey et al.[91] (2004) Rosiglitazone (existing therapy) and glimepiride 2 to 8 mg QD vs rosiglitazone (existing therapy)	MC, PC, RCT Patients with type 2 diabetes poorly controlled (HbA_{1c} 7.5 to 9.5%) with rosiglitazone monotherapy	N=40 30 weeks	Primary: Effect on HbA_{1c} Secondary: Effect on FPG, body weight, lipoproteins, proportion of patients who achieved HbA_{1c} and FPG targets	Primary: Significant reductions in HbA_{1c} were observed with glimepiride (-1.2%) compared to placebo (-0.3%; P<0.001). Secondary: Significant reductions in FPG were observed with glimepiride (-24.41 mg/dL) compared to placebo (5.9 mg/dL; P<0.008). Significantly greater proportion of patients receiving glimepiride achieved the target HbA_{1c} ≤7.0% (60.0 vs 14.3%; P<0.008). There were no significant differences between treatment groups in TC, HDL-C, LDL-C, or TG at any time during study period.
Rosenstock et al.[92] (2008) <u>Study A</u> Rosiglitazone 4 mg QD and glimepiride	2 DB, PC, RCT Patients 40 to 80 years of age (Study A) or 18 to 75 years of age (Study B) with type 2	N=174 (Study A) N=391 (Study B) 26 weeks	Primary: Mean change in baseline HbA_{1c} Secondary: Proportion	<u>Study A</u> Primary: At week 26, the mean change in HbA_{1c} from baseline was -0.63% in the RSG 4 mg+GLIM (P=0.03 vs GLIM 3 mg), -1.17% in the RSG 8 mg+GLIM groups (P<0.0001 vs GLIM 3 mg), and -0.08% in the GLIM 3 mg group.

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3 mg QD (RSG 4 mg + GLIM) vs rosiglitazone 8 mg QD and glimepiride 3 mg QD (RSG 8 mg + GLIM) vs glimepiride 3 mg QD (GLIM alone) <u>Study B</u> Rosiglitazone 4 mg QD and glimepiride 2 to 4 mg QD (RSG add-on) vs glimepiride 4 to 8 mg QD and placebo (GLIM)	diabetes, HbA_{1c} ≥7.0% and FPG 126 to 270 mg/dL at baseline; in the 3 months prior to enrolment, eligible patients in Study A received monotherapy with an oral antidiabetic agent; eligible patients in Study B were treated with a non-TZD oral antidiabetic therapy for ≥3 months prior to screening, including metformin monotherapy, sulfonylurea monotherapy, or low-dose combination therapy with metformin and sulfonylurea	(Study A) 24 weeks (Study B)	of patients with HbA_{1c} <7.0% and/or HbA_{1c} reduction ≥0.7% at the end of the treatment period, mean change in baseline FPG	Secondary: The mean change in FPG from baseline was -21 mg/dL in the RSG 4 mg+GLIM (P=0.09 vs GLIM alone), -43 mg/dL in the RSG 8 mg+GLIM groups (P<0.0001 vs GLIM 3 mg), and -2 mg/dL for GLIM 3 mg. At week 26, 43% of patients achieved HbA_{1c} <7.0% in the RSG 4 mg+GLIM group (P=0.0129 vs GLIM alone) and 68% achieved the same HbA_{1c} goal in the RSG 8 mg+GLIM group (P=0.0001 vs GLIM 3 mg) compared to 32% in the GLIM 3 mg. <u>Study B</u> Primary: At week 24, the mean change in HbA_{1c} from baseline was -0.68% in the RSG add-on group compared to -0.08% in the GLIM 4 to 8 mg group (P<0.0001). Secondary: The mean change in FPG from baseline was -28 mg/dL in the RSG add-on group compared to -1 mg/dL in the GLIM 4 to 8 mg group (P<0.0001). At week 24, 39% of patients achieved HbA_{1c} <7.0% in the RSG add-on group compared to 15% in the GLIM 4 to 8 mg group (P<0.0001). Insulin sensitivity increased significantly in the RSG add-on group but was unchanged with GLIM 4 to 8 mg. β-cell function increased over 24 weeks in both treatment groups but with a significantly greater increase with RSG add-on group. RSG add-on significantly reduced fasting levels of C-peptide (P=0.025), proinsulin (P=0.0006), and insulin (P=0.013) and reduced the proinsulin: insulin ratio (P<0.0001). There were no significant changes in any of these parameters with GLIM 4 to 8 mg (C-peptide; P=0.075, proinsulin; P=0.42, insulin; P=0.10 and proinsulin:insulin ratio; P=0.34).
Chou et al.[93] (2008)	DB, MC, PG, RCT Type 2 diabetics, HbA_{1c} 7.5 to 12.0%,	N=901 28 weeks	Primary: Change in baseline HbA_{1c}	Primary: Both rosiglitazone/glimepiride regimens significantly reduced HbA_{1c} to a greater extent than glimepiride or rosiglitazone monotherapy regimens (P<0.0001).

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Rosiglitazone/ glimepiride fixed dose combination 4/1 mg titrated to 4/4 mg (regimen A) or titrated to 8/4 mg QD (regimen B) (RSG/GLIM) vs rosiglitazone 4 mg titrated to 8 mg QD (RSG) vs glimepiride 1mg titrated to 4 mg QD (GLIM)	fasting C-peptide ≥0.8 ng/mL, FPG ≥126 mg/dL, who had been treated with diet and/or exercise alone or who had not taken oral antidiabetic medication or insulin for >15 days in the preceding 4 months		Secondary: Change in baseline FPG, proportion of patients achieving HbA_{1c} and FPG targets, HOMA-S, HOMA-B, cardiovascular biomarkers, safety	Secondary: A significantly greater reduction in FPG levels was observed in the rosiglitazone/glimepiride group compared to the glimepiride or rosiglitazone monotherapy groups (P<0.0001). Significantly more patients achieved HbA_{1c} target levels ≤6.5 and <7.0% with either rosiglitazone/glimepiride regimen than patients with glimepiride or rosiglitazone monotherapy regimens (P<0.0001). Improvement in CRP was also observed in patients treated with rosiglitazone/glimepiride or rosiglitazone monotherapy compared to patients treated with glimepiride monotherapy (P<0.05). There were no new safety or tolerability issues identified from its monotherapy components and a similar adverse event profile was observed across the fixed-dose regimens. The most commonly reported adverse event was hypoglycemia and the incidence of confirmed symptomatic hypoglycemia (3.6 to 5.5%) was comparable among subjects treated with a fixed-dose regimen and glimepiride monotherapy.
Home et al.[94] (2007) Rosiglitazone plus either metformin or a sulfonylurea vs metformin plus a sulfonylurea	MC, OL, PG, RCT Patients 40 to 75 years of age with type 2 diabetes and BMI ≥25 kg/m^2, on maximum tolerated doses of metformin or a sulfonylurea monotherapy, and inadequate glycemic control (HbA_{1c} 7.0 to 9.0%)	N=1,122 18 months	Primary: Change in baseline HbA_{1c} Secondary: FPG, serum lipids, HOMA basal insulin sensitivity and islet β-cell function (HOMA %β), body weight, inflammatory/ thrombotic markers, CRP	Primary: At 18 months, HbA_{1c} reduction on background metformin was similar with rosiglitazone and sulfonylurea (difference, 0.07%; 95% CI, -0.09 to 0.23; P value not significant), as was the change when rosiglitazone or metformin was added to sulfonylurea (difference, 0.06%; 95% CI, -0.09 to 0.20; P value not significant). Secondary: Differences in FPG were not significant at 18 months (rosiglitazone vs sulfonylurea, -0.36 mmol/L; P=0.062 and rosiglitazone vs metformin, -0.34 mmol/L; P=0.089). Rosiglitazone increased TC (P≤0.001) and LDL-C (P=0.000) and reduced nonesterified fatty acids (P=0.000) at 18 months compared to the control. An increase in HDL-C and TG was observed with rosiglitazone compared to sulfonylurea (0.08 vs 0.02 mmol/L; P=0.001, 0.40 vs 0.15 mmol/L;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				P=0.016, respectively), but not with metformin (P value not significant for both). HOMA-estimated basal insulin sensitivity was substantially increased with rosiglitazone compared to the respective controls (P<0.001 for both). Both rosiglitazone and sulfonylurea when added to metformin increased HOMA %β, but this increase was greater with the sulfonylurea (P<0.001). Rosiglitazone or metformin added to background sulfonylurea also increased HOMA %β, to a similar extent (P value not significant). Rosiglitazone was associated with a significant increase in body weight compared to metformin (P<0.001) and a sulfonylurea (P=0.003). At 18 months, plasminogen activator inhibitor-1 antigen decreased from baseline with rosiglitazone, with a significant difference compared to sulfonylureas (-5.7 vs 7.0%; P=0.047); rosiglitazone and metformin did not differ (P value not significant). There was a significant reduction in CRP with rosiglitazone compared to a sulfonylurea (P<0.001) and metformin (P=0.001).
Komajda et al.[95] (2008) Rosiglitazone plus either metformin or a sulfonylurea vs metformin plus a sulfonylurea	MC, OL, RCT (RECORD) Patients 40 to 75 years of age with type 2 diabetes and BMI ≥25 kg/m^2, on maximum tolerated doses of metformin or a sulfonylurea monotherapy, and inadequate glycemic control (HbA_{1c} 7.0 to 9.0%)	N=668 12 months	Primary: Change from baseline in 24-hour ambulatory BP at six months and 12 months Secondary: Not reported	Primary: For patients receiving rosiglitazone and a sulfonylurea, the reduction in 24-hour SBP was greater at six months (-3.8 mm Hg) and 12 months (-3.8 mm Hg) than with metformin and sulfonylurea therapy (-1.2 mm Hg and -1.3 mm Hg, respectively; six months, P=0.015; 12 months, P=0.031). Reductions in 24-hour DBP were greater at six months and 12 months for patients receiving rosiglitazone and a sulfonylurea (-3.1 mm Hg and -3.7 mm Hg) compared to metformin and sulfonylurea (-0.4 mm Hg and -0.6 mm Hg; both P<0.001). At 12 months, the reduction in 24-hour SBP was greater for rosiglitazone and metformin (-4.9 mm Hg) than for metformin and sulfonylurea (-2.2 mm Hg; P=0.016).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				At 12 months, the reduction in DBP was greater for rosiglitazone and metformin (-3.8 mm Hg) than for metformin and sulfonylurea (-1.7 mm Hg; P=0.003). At six months, the reductions in SBP and DBP were not significantly different for rosiglitazone and metformin compared to metformin and sulfonylurea (SBP; P=NS, DBP; P=0.049). Secondary: Not reported
Scott et al.[96] (2008) Rosiglitazone 8 mg once daily and metformin (existing therapy) vs sitagliptin 100 mg once daily and metformin (existing therapy) vs metformin (existing therapy) and placebo	AC, DB, MC, PG, RCT Type 2 diabetics 18 to 75 years of age receiving stable metformin doses (≥1,500 mg/day for ≥10 weeks) and inadequate glycemic control (HbA_{1c} ≥7.0 and ≤11.0%)	N=273 18 weeks	Primary: Change in baseline HbA_{1c} Secondary: Change in baseline FPG, fasting serum insulin, fasting serum proinsulin, β cell function, insulin resistance, and lipid profile	Primary: Sitagliptin significantly decreased HbA_{1c} compared to placebo (treatment difference, -0.50%; 95% CI, -0.87 to -0.60; P≤0.001). Similar results were observed with rosiglitazone (treatment difference, -0.57%; 95% CI, -0.76 to -0.37; P value not reported). There was no difference between sitagliptin and rosiglitazone (treatment difference, -0.06%; 95% CI, -0.25 to 0.14). The proportion of patients achieving an HbA_{1c}<7.0% was significantly greater with sitagliptin (55%; P=0.006) and rosiglitazone (63%; P value not reported) compared to placebo (38%). There was no difference between sitagliptin and rosiglitazone (treatment difference, 8%; 95% CI, -6 to 22; P value not reported). Secondary: Sitagliptin (treatment difference, -17.8 mg/dL; 95% CI, -27.6 to -8.1; P≤0.001) and rosiglitazone (treatment difference, -30.6 mg/dL; 95% CI, -40.6 to -20.7; P value not reported) significantly decreased FPG compared to placebo. Rosiglitazone significantly decreased FPG compared to sitagliptin (treatment difference, -12.8 mg/dL; 95% CI, -22.6 to -3.0; P value not reported). Sitagliptin (treatment difference, 16.3; 95% CI, 2.3 to 30.3; P≤0.05) and rosiglitazone (treatment difference, 15.3; 95% CI, 1.0 to 29.6; P value not reported, respectively) had significant increases in HOMA-B compared to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				placebo. The increase in HOMA-B was not significantly different between sitagliptin and rosiglitazone (P value not reported). Rosiglitazone significantly decreased HOMA-IR compared to placebo (treatment difference, -2.4; 95% CI, -3.4 to -1.4; P value not reported) and sitagliptin (treatment difference, -1.6; 95% CI, -2.6 to -0.7; P value not reported). There decrease in HOMA-IR was similar between sitagliptin and placebo (treatment difference, -0.7; 95% CI, -1.7 to 0.2; P value not reported). Rosiglitazone significantly decreased fasting serum insulin compared to placebo (treatment difference, -3.4 µIU/mL; 95% CI, -5.5 to -1.4; P value not reported) and sitagliptin (treatment difference, -3.53 µIU/mL; 95% CI, -5.50 to -1.40; P value not reported). The proinsulin:insulin ratio was similar across all treatments. Compared to placebo, LDL-C decreased with sitagliptin (treatment difference, -5.3 mg/dL; 95% CI, -14.5 to 3.9; P value not reported) and increased with rosiglitazone (treatment difference, 9.5 mg/dL; 95% CI, 0.2 to 18.7; P value not reported). Compared to placebo, TC significantly decreased with sitagliptin (treatment difference, -6.3 mg/dL; 95% CI, -11.8 to -0.9; P≤0.05) and increased with rosiglitazone (treatment difference, 5.1 mg/dL; 95% CI, -0.3 to 10.6; P value not reported). Compared to placebo, TG significantly decreased with sitagliptin (treatment difference, -16.7 mg/dL; 95% CI, -27.9 to 5.5; P≤0.05) and increased with rosiglitazone (treatment difference, 1.2 mg/dL; 95% CI, -10.1 to 12.6; P value not reported). Compared to sitagliptin, lipid profiles measurements significantly increased with rosiglitazone (P values not reported).
Rigby et al.[97] (2010) Rosiglitazone 4 mg daily (QD or BID) and metformin (existing therapy)	OL Patients 18 to 80 years of age with type 2 diabetes mellitus who had inadequate glycemic	N=169 16 weeks	Primary: Change in HbA_{1c} from baseline to week 16 Secondary:	Primary: At week 16, HbA_{1c} was reduced from baseline in all treatment groups (least square mean change from baseline): colesevelam -0.3% (95% CI, -0.52 to -0.02; P=0.031); rosiglitazone -0.6% (95% CI, -0.83 to -0.32; P<0.001); sitagliptin -0.4% (95% CI, -0.64 to -0.13; P=0.009). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs sitagliptin 100 mg QD and metformin (existing therapy) vs colesevelam 3.75 g daily (QD or BID) and metformin (existing therapy)	control (HbA_{1c} 6.5 to 10.0% on a stable regimen of metformin (1,500-2,550 mg daily), with LDL-C ≥60 mg/dL and TG <500 mg/dL		Change in HbA_{1c} from baseline to week eight, change in fasting plasma glucose and fasting insulin from baseline to weeks eight and 16, change in two-hour PPG and postprandial insulin after a meal tolerance test, change in lipid parameters, percentage of participants who achieved an HbA_{1c} reduction >0.7% from baseline, percentage of participants who achieved HbA_{1c} <7.0%	At week eight, HbA_{1c} was reduced from baseline with colesevelam and sitagliptin (-0.3%; P=0.006 and -0.5%; P<0.001, respectively), but not with rosiglitazone (-0.2%; P=0.109). Fasting plasma glucose was significantly reduced from baseline at week eight and week 16 in all treatment groups. The two-hour PPG levels were significantly reduced from baseline at week 16 in all treatment groups. There was no significant change in fasting insulin or two-hour postprandial insulin from baseline to week 16 in any treatment group. Insulin resistance did not change with colesevelam or sitagliptin; however, there was a significant reduction with rosiglitazone from baseline to week 16 (P=0.008). LDL-C was significantly reduced from baseline with colesevelam (-11.6%; P=0.001), but was significantly increased with both rosiglitazone (7.8%; P=0.040) and sitagliptin (7.7%; P=0.011). TC levels were unchanged from baseline with colesevelam and sitagliptin; however, they were significantly increased with rosiglitazone from baseline to week 16 (P=0.006). Non-HDL-C levels were unchanged with colesevelam; however, they were significantly increased with rosiglitazone (P=0.001) and sitagliptin (P=0.029). Median TG levels increased significantly from baseline with colesevelam (P<0.00l) and rosiglitazone (P<0.00l); however, sitagliptin did not significantly affect triglyceride levels. HDL-C levels did not change significantly from baseline with any treatment. At week 16, 23.2% of patients in the colesevelam group, 48.l % of patients in the rosiglitazone group, and 34.5% of patients in the sitagliptin group achieved a reduction in HbA_{1c} 0.7% or greater from baseline. In addition, 10 patients in the colesevelam group, 19 in the rosiglitazone group, and 15 in the sitagliptin group achieved HbA_{1c} <7.0%.

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				The percentages of patients who had an adverse event were 61.4% in the colesevelam group, 46.4% in the rosiglitazone group, and 48.2% in the sitagliptin group. Most of the adverse events were mild to moderate in severity.
Hollander et al.[98] (2009) Thiazolidinedione (existing therapy) and saxagliptin 2.5 mg QD vs thiazolidinedione (existing therapy) and saxagliptin 5 mg QD vs thiazolidinedione (existing therapy) and placebo	DB, MC, RCT Type 2 diabetics 18 to 77 years of age with inadequate glycemic control (HbA_{1c} ≥7.0 to ≤10.5%) receiving stable doses of TZD (pioglitazone 30 or 45 mg/day or rosiglitazone 4 or 8 mg/day for ≥12 weeks), fasting C-peptide ≥0.3 nmol/L, and BMI ≤45 kg/m^2	N=565 24 weeks	Primary: Change in baseline HbA_{1c} Secondary: Change in baseline FPG and PPG AUC_{0-3hr}, proportion of patients achieving an HbA_{1c} <7.0%	Primary: Saxagliptin significantly decreased HbA_{1c} compared to placebo (saxagliptin 2.5 mg, -0.66%; treatment difference, -0.36%; P<0.0007 vs placebo and saxagliptin 5 mg, -0.94%; treatment difference, -0.63%; P<0.0001 vs placebo). Secondary: Saxagliptin significantly decreased FPG compared to placebo (saxagliptin 2.5 mg treatment difference, -0.8 mmol/L; P<0.0053 vs placebo and saxagliptin 5 mg treatment difference, -1.0 mmol/L; P=0.0005 vs placebo). A significantly greater proportion of patients receiving saxagliptin achieved an HbA_{1c} <7.0% compared to patients receiving placebo (42.2 [P=0.0010] and 41.8 [P=0.0013] vs 25.6%). Saxagliptin significantly decreased PPG AUC_{0-3hr} compared to placebo (P<0.0001 for both). Similar results were observed with PPG AUC_{0-2hr} (P<0.0001 for both). Overall, saxagliptin was well tolerated. The proportion of patients experiencing any adverse effect was 68.0 vs 66.8%, with the highest frequency with saxagliptin 5 mg. The frequency of hypoglycemic events was similar between the two treatments (3.4 vs 3.8%). The most commonly reported adverse events were upper respiratory tract infection, peripheral edema, and headache.
Pinelli et al.[99] (2008) Thiazolidinediones in combination with other antidiabetic agents	MA (22 RCTs) Patients with type 2 diabetes receiving combination therapy	N=9,325 ≥24 weeks	Primary: Mean change in baseline HbA_{1c} Secondary: Proportion of patients	Primary: There were small reductions in HbA_{1c} across the trials. The WMD were -0.80% (95% CI, -1.10 to -0.50) with TZD and -0.60% (95% CI, -1.04 to -0.16) with exenatide.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs exenatide in combination with other antidiabetic agents			reaching HbA_{1c} <7.0%, mean change from baseline in FPG and body weight, hypoglycemia, gastrointestinal adverse events	When only PC trials were analyzed, there were greater reductions in HbA_{1c} with both TZDs (WMD, -1.14%; 95% CI -1.30 to -0.98) and exenatide (WMD, -0.97%; 95% CI -1.11 to -0.83). When only TZD AC trials were analyzed, there was a significant difference in HbA_{1c} levels from baseline (WMD, -0.38%; 95% CI -0.75 to -0.01). There was no difference in HbA_{1c} reduction between exenatide and insulin comparators in OL, non-inferiority trials. Secondary: TZD and exenatide-based therapies were associated with OR of 2.27 (95% CI, 1.22 to 4.24) and 2.90 (95% CI, 1.28 to 6.55), respectively, for reaching HbA_{1c} <7.0%. FPG concentrations were reduced from baseline with TZD-based regimens (WMD, -29.58 mg/dL; 95% CI, -39.27 to -19.89), but did not reach significance with exenatide (WMD, -8.77 mg/dL; 95% CI, -28.85 to 11.31). Severe hypoglycemia was rare in the one exenatide and four TZD trials that identified a total of nine participants experiencing hypoglycemic episodes. In these five trials, participants reporting an event were also receiving an insulin secretagogue. The OR for developing nonsevere hypoglycemia with TZDs was not significantly different from other treatment arms (OR, 1.59; 95% CI, 0.76 to 3.32). In TZD trials, there was a nonsignificant difference in body weight from baseline compared to other treatment groups (WMD, 1.51 kg; 95% CI, -0.12 to 3.15). Mean change in body weight from baseline was reduced significantly with exenatide-based regimens (WMD, -2.74 kg; 95% CI, -4.85 to -0.64). The most commonly reported adverse effects were gastrointestinal disorders in the exenatide trials. ORs greater than one for nausea, vomiting, and diarrhea were observed with exenatide with pooled ORs of

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				9.02 (95% CI, 3.66 to 22.23), 4.56 (95% CI, 3.13 to 6.65), and 2.96 (95% CI, 2.05 to 4.26), respectively. Nausea occurred in 47% of patients receiving exenatide and 11% in the comparator arms. Vomiting occurred in 15% of patients receiving exenatide and 4% of patients receiving comparator. Diarrhea occurred in 12% of patients receiving exenatide and 4% in patients receiving comparator.
Clar et al.[100] (2009) Pioglitazone vs no additional treatment All patients were receiving insulin (with or without other oral hypoglycemic agents).	MA Patients with type 2 diabetes	N=3,092 (8 trials) ≥12 weeks	Primary: HbA_{1c}, frequency of hypoglycemia, total daily dose of insulin, weight changes, changes in cardiovascular risk factors, and adverse events Secondary: Not reported	Primary: HbA_{1c} values were significantly lower in the groups taking pioglitazone plus insulin than in the groups taking insulin without pioglitazone (weighted mean difference -0.58%, 95% CI: -0.70 to -0.46; P<0.00001). There were more patients with hypoglycemic episodes in the pioglitazone plus insulin groups than with insulin without pioglitazone; however, this difference was not statistically significant (relative risk 1.27, 95% CI: 0.99 to 1.63, P=0.06). Insulin dose ranged between 42 to 64 U/day or 0.5 to 1 U/kg/day in the pioglitazone groups and between 55 to 70 U/day and 0.7 to 1.2 U/kg/day in the groups taking no pioglitazone. Weight change ranged between +1.4 and +4.4 kg in the pioglitazone plus insulin groups and between -0.04 and +4.9 kg in the insulin only groups. Four studies reported results for serum TGs. Only two of the studies demonstrated a significant reduction in the pioglitazone groups (-0.44 to -0.70 mmol/L) compared to insulin only). None of the studies found a difference in TC between the pioglitazone plus insulin and the insulin without pioglitazone groups. Four studies reported on HDL-C and all found significantly increased values in the pioglitazone groups (+0.10 mmol/L to +0.18 mmol/L) compared to insulin only. None of the studies found a difference in LDL-C between the pioglitazone plus insulin and the insulin without pioglitazone groups. Besides weight gain and hypoglycemia, the only adverse event reported as occurring more frequently with pioglitazone was peripheral edema.
Abdul-Ghani et al.[101]	OL, RCT	N=221	Primary: HbA_{1c}	Primary:

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(2015) EDICT Metformin (escalating dose) vs Triple therapy (metformin/ pioglitazone/ exenatide)	Drug-naïve, recently diagnosed (<2 years) subjects 30 to 75 years of age with type 2 diabetes mellitus	2 years	Secondary: Percentage of participants achieving HbA_{1c} <6.5 and <7.0%; decrease in fasting and postprandial plasma glucose; change in body weight; and rate of hypoglycemic events	Baseline HbA_{1c} was identical in both groups (8.6%) and during the first six months decreased in both treatment arms. At six months, there was a small but significant HbA_{1c} difference (0.2%, P=0.03) between groups (triple therapy 6.0% vs metformin therapy 6.2%). After six months, HbA_{1c} gradually increased with metformin therapy to 6.5% at 24 months and remained stable at 5.95% with triple therapy; thus, the difference in HbA_{1c} between the two treatments progressively increased with time and was significantly different at two years (change in HbA_{1c}, 0.55%; P<0.0001). Secondary: More participants receiving metformin therapy failed to maintain the treatment goal (HbA_{1c} <6.5%) than did those receiving triple therapy (44 vs 17%; P=0.003). A total of 40 participants receiving metformin therapy failed to maintain HbA_{1c} at <6.5% at/after six months compared with only 13 participants receiving triple therapy (P<0.0001). More participants receiving triple therapy (61%) had HbA_{1c} reduced to the normal range (<6.0%) than those receiving metformin therapy (27%; P<0.0001). The median HbA_{1c} of participants receiving triple therapy was 5.9% compared with 6.4% for those receiving metformin therapy. More than 90% of participants receiving triple therapy maintained HbA_{1c} at <7.0% versus <75% of participants receiving metformin therapy. The most common adverse event was hypoglycemia, reported by 46 and 14% of participants receiving metformin and triple therapy, respectively. The overall frequency of hypoglycemic events was greater in participants receiving metformin therapy (2.2 vs 0.31 events/participant per year; P<0.0001).
Hollander et al.[102] (2015) Insulin glargine+ one oral antidiabetes drug (metformin or sulfonylurea) wherein previous TZD therapy was dropped and	MC, OL, RCT Type 2 diabetes patients 18 to 79 years of age with a HbA_{1c} of 7.5 to 12.0% despite ≥3 months of treatment with a TZD plus	N=337 48 weeks	Primary: Change in HbA_{1c} Secondary: Changes in FPG, weight, BMI, and serum lipid profile	Primary: Substitution of insulin glargine for a TZD and addition of a third OAD resulted in an adjusted mean change in HbA_{1c} from baseline of −1.66% and −1.86%, respectively (adjusted mean difference 0.20; 95% CI, −0.11 to 0.51). The upper limit of the 95% CI for the difference in the adjusted mean changes from baseline to endpoint for HbA_{1c} was 0.51%; therefore, the primary efficacy analysis did not demonstrate equivalent glycemic control during treatment with GLAR + 1 OAD and 3OAD as measured by HbA_{1c} levels. In patients originally taking sulfonylurea, there was a significantly greater reduction in HbA_{1c} in those adding metformin to TZD

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replaced with insulin glargine (GLAR +1 OAD) vs three oral antidiabetes drugs (3OAD) wherein patients receiving TZD and metformin received add-on sulfonylurea (glyburide) and patients receiving TZD and sulfonylurea received add-on metformin (3OAD)	metformin or a sulfonylurea			and sulfonylurea versus those switching the TZD for GLAR + SU at weeks 12, 24, and 48. Secondary: Adjusted mean FPG at baseline was similar between the two treatment arms (GLAR + 1 OAD 193.0 mg/dL vs 3OAD 199.5 mg/dL; P=0.4299). FPG reduced significantly from baseline to endpoint (P<0.0001 for both arms). Weight gain was observed in both treatment arms at each study visit and at endpoint. At each visit, patients in the GLAR + 1 OAD arm gained less weight than those in the 3OAD arm; this difference was significant at week 12 (P=0.0035). A similar pattern was observed for BMI. Overall, insulin glargine + metformin was as effective as 3OAD in achieving glycemic control but with greater improvements in lipid parameters, less weight gain, and lower hypoglycemia rates.
Schernthaner et al.[103] (2015) EUREXA TZD or glimepiride added to metformin plus exenatide twice daily vs exenatide twice daily added to metformin plus glimepiride	MC, OL, RCT Patients with type 2 diabetes with metformin failure (HbA_{1c} ≥6.5 to ≤9.0%), were 19 to 85 years of age, and had a BMI of ≥25 to ≤40 kg/m^2	N=310 Median duration of 2 years	Primary: Changes in HbA_{1c}, BMI, lipids, hypoglycemia, and vital signs Secondary: Not reported	Primary: Significant changes from baseline in HbA_{1c} were observed at 52, 78, 104 and 130 weeks with add-on TZD (all P<0.01), but only at 52 weeks with add-on glimepiride (P=0.001). Significant between-group differences favoring add-on TZD were observed at 78 (P=0.004) and 130 weeks (P=0.001). Among patients re-randomized to add-on glimepiride and add-on TZD, HbA_{1c} ≤7.0% was achieved by 26.0 and 30.7%, respectively, and HbA_{1c} ≤6.5% by 8.2 and 9.3%, respectively (no significant differences between the randomized groups). BMI significantly increased from baseline at 52, 78, 104 and 130 weeks with add-on TZD (all P≤0.01), but significantly increased at 52 and 78 weeks (both P<0.05) and decreased at 130 weeks with add-on glimepiride; the between-group difference was significant at 104 (P=0.022) and 130 weeks (P=0.008).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				HDL cholesterol significantly increased from baseline to 130 weeks in the TZD add-on group (P<0.001), but not in the add-on glimepiride group; the between-group difference significantly favored TZD (P<0.001). For total and LDL cholesterol, there were no significant within- or between-group changes from baseline to 130 weeks. Systolic blood pressure was significantly increased at 130 weeks with add-on TZD (P=0.043), but not with add-on glimepiride; the between-group difference significantly favored glimepiride (P=0.044). The incidence of any hypoglycemia and nocturnal, non-nocturnal and documented symptomatic hypoglycemia with blood glucose ≤70 mg/dl was significantly higher for glimepiride than TZD as add-on to exenatide plus metformin. Although the proportion of patients reporting documented symptomatic hypoglycemia with blood glucose <50 mg/dl was similar in the add-on glimepiride (1/74; 1.4%) or TZD (1/76; 1.3%) groups, the exposure-adjusted mean rate/year was higher in the glimepiride group (0.10 vs 0.01 events/year of patient exposure). Secondary: Not reported
Kheirbek et al.[104] (2013) Hypoglycemic medications (metformin, glyburide, glipizide, rosiglitazone, acarbose, chlorpropamide, glimepiride, pioglitazone, tolazamide, repaglinide, troglitazone,	OS, RETRO Veterans with diabetes cared for at a Veterans Administration Capital area medical center	N=17,773 Variable duration	Primary: All-cause mortality Secondary: Not reported	Primary: After adjustments were made for severity of illness and patient demographics, the remaining variance in mortality was explained by exposure to five medications, listed in order of impact on risk-adjusted mortality: glipizide (OR=1.566), glyburide (OR=1.804), rosiglitazone (OR=1.805), insulin (OR=2.382), and chlorpropamide (OR=3.026). None of the other medications (metformin, acarbose, glimepiride, pioglitazone, tolazamide, repaglinide, troglitazone, and DPP-4 inhibitors) were associated with excess mortality beyond what could be expected from the patients' severity of illness or demographic characteristics. Insulin, glyburide, glipizide, and rosiglitazone continued to be associated with statistically significant increased mortality after controlling for possible drug interactions. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
insulin, and DPP-4 inhibitors) *Defined as any use of the medication independent of dose or days of use				Not reported
Mearns et al.[105] (2015) Hypoglycemic medications (Alpha-glucosidase inhibitors, DPP-4 inhibitors, colesevelam, meglitinides, GLP-1 analogs, long-acting, once-daily basal insulin, SGLT2 inhibitors, sulfonylureas, TZDs, and combinations of the above agents)	Network MA (62 RCTs) Patients with inadequately controlled type 2 diabetes on metformin alone	N=32,185 3 to 12 months	Primary: Changes in HbA_{1c}, body weight, and SBP; risk of developing hypoglycemia and urinary and genital tract infection Secondary: Not reported	Primary: All agents significantly reduced HbA_{1c} vs placebo; although not to the same extent (range, 0.43% for miglitol to 1.29% for glibenclamide). Glargine, sulfonylureas, and nateglinide were associated with increased hypoglycemia risk vs placebo. SGLT2 inhibitors, GLP-1 analogs, miglitol, and empagliflozin/linagliptin significantly reduced body weight (range, 1.15 to 2.26 kg) whereas sulfonylureas, TZDs, glargine, and alogliptin/pioglitazone caused weight gain (range, 1.19 to 2.44 kg). SGLT2 inhibitors, empagliflozin/linagliptin, liraglutide, and sitagliptin decreased SBP (range, 1.88 to 5.43 mmHg). No therapy increased UTI risk vs placebo; however, SGLT2 inhibitors were associated with an increased risk of genital tract infection (RR range, 2.16 to 8.03). Secondary: Not reported
Diabetes Prevention Trials				
Zinman et al.[106] (2010) CANOE Rosiglitazone 2 mg/day plus metformin 500 mg BID vs	DB, RCT Patients with impaired glucose tolerance	N=207 3.9 years (median duration)	Primary: Time to development of diabetes Secondary: Insulin sensitivity, β cell function, safety	Primary: Incident diabetes occurred in significantly fewer patients receiving combination therapy compared to placebo (14 vs 39%; P<0.0001). The relative risk reduction was 66% (95% CI, 48 to 80) and the absolute risk reduction was 26% (95% CI, 14 to 37), yielding a number needed to treat of 4 (95% CI, 2.70 to 7.14). Seventy patients (80%) receiving combination therapy regressed to normal glucose tolerance compared to 52 patients (53%) receiving placebo (P=0.0002).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo				Secondary: Insulin sensitivity decreased by trial end in patients receiving placebo (median, -1.24) and remained unchanged in patients receiving combination therapy (median, -0.39; P=0.0006 vs placebo). Change in β cell function did not differ between the two treatments (P=0.28). Significantly more patients receiving combination therapy experienced diarrhea compared to placebo (P=0.0253).
Gerstein et al.[107] (2006) DREAM Rosiglitazone 4 mg once daily for 2 months, then 8 mg once daily vs placebo	MC, PRO, RCT Adults ≥30 years of age or more with impaired fasting glucose and/or impaired glucose tolerance and no previous cardiovascular disease; people with a history of diabetes (except gestational diabetes), cardiovascular disease or intolerance to either angiotensin-converting enzyme inhibitors or TZDs were excluded	N=5,269 Median 3 years (range, 2.5 to 4.7 years)	Primary: Composite of incident diabetes or death Secondary: Regression to normoglycemia, composite of cardiovascular events (e.g., MI, stroke, cardiovascular death, revascularization procedures and heart failure) and glucose concentrations	Primary: The composite primary outcome was observed in 11.6% of individuals given rosiglitazone and 26.0% of individuals given placebo (HR, 0.40; 95% CI, 0.35 to 0.46; P<0.0001). There was no difference in the number of deaths (HR, 0.91; 95% CI, 0.55 to 1.49; P=0.7). The frequency of diabetes was reported in significantly fewer patients receiving rosiglitazone than those receiving placebo (HR, 0.38; 95% CI, 0.33 to 0.44; P<0.0001). Secondary: Normoglycemia was reported in 1,330 (50.5%) individuals in the rosiglitazone group and 798 (30.3%) participants in the placebo group (HR, 1.71; 95% CI, 1.57 to 1.87; P<0001). The frequency of composite cardiovascular outcome was similar between rosiglitazone and placebo. The components of the composite were similar between the two groups with the exception of heart failure, which was reported in 14 (0.5%) participants in the rosiglitazone group and two (0.1%) participants in the placebo group (P=0.01). The median fasting plasma glucose concentration was 0.5 mmol/L lower in the rosiglitazone group than in the placebo group (P<0.0001); the two-hour plasma glucose concentration was 1.6 mmol/L lower with rosiglitazone than placebo (P<0.0001).
Dagenais et al.[108] (2008) DREAM	MC, PRO, RCT	N=5,269 3 years	Primary: Composite	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Rosiglitazone 4 mg once daily for 2 months, then 8 mg once daily vs placebo	Adults ≥30 years of age with impaired fasting glucose and/or impaired glucose tolerance and no previous cardiovascular disease		cardiovascular outcome, composite renal outcome Secondary: Not reported	During the three year follow-up, 836 patients had a first occurrence of the composite cardiorenal outcome (2.5% cardiovascular composite outcomes and 13.6% renal composite outcomes). The composite cardiorenal outcome occurred in 15.0% of patients receiving rosiglitazone and 16.8% of patients receiving placebo (HR, 0.87; 95% CI, 0.75 to 1.01; P=0.07). Rosiglitazone did not reduce the overall risk of cardiovascular events, but significantly increased the risk for heart failure (0.5%) compared to placebo (0.1%; 95% CI, 1.60 to 31.0). Rosiglitazone reduced the renal component of the composite outcome by 20% due to a reduction in progression of albuminuria compared to placebo (HR, 0.80; 95% CI, 0.68 to 0.93; P=0.031). The fall in estimated glomerular filtration rate by ≥30% was not significant (P=0.087). Secondary: Not reported

*Not available in the United States.
†Estimates approximate values since results were displayed in bar graph and precise values were not reported.
‡Synonym for glyburide.
Drug regimen abbreviations: BID=twice daily, ER=extended-release, QD=once daily, SC=subcutaneous, TID=three times daily
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, PM=post marketing, PRO=prospective, RCT=randomized-controlled trial, RETRO=retrospective, SR=systematic review, XO=cross-over
Miscellaneous abbreviations: ALT=alanine aminotransferase, apo=apolipoprotein, AUC=area under the curve, BMD=bone mineral density, BMI=body mass index, BNP=brain natriuretic peptide, BP=blood pressure, CI=confidence interval, CRP=C-reactive protein, DBP=diastolic blood pressure, DPP-4 inhibitor=dipeptidyl peptidase-4 inhibitor, DTSQ=Diabetes Treatment Satisfaction Questionnaire, EQ-5D=EuroQol Quality of Life, FFA=free fatty acid, FPG=fasting plasma glucose, GLP-1=glucagon-like peptide 1, HbA_{1c}=glycosylated hemoglobin, HDL-C=high density lipoprotein cholesterol, HOMA=homeostasis model assessment, HOMA-B=homeostasis model assessment-beta, HOMA-IR=homeostasis model assessment-insulin resistance, HOMA-S=homeostasis model assessment-insulin sensitivity, HR=hazard ratio, IWQOL=Impact of Weight on Quality of life Questionnaire, LDL-C=low density lipoprotein cholesterol, MACE=major adverse cardiovascular events, MI=myocardial infarction, NPH=neutral protamine Hagedorn, NYHA=New York Heart Association, OR=odds ratio, PGWB=psychological general well-being, PPAR=peroxisome proliferator-activated receptor, PPG=post-prandial glucose, QOL=quality of life, RR=relative risk, SBP=systolic blood pressure, TC=total cholesterol, TG=triglycerides, TZD=thiazolidinedione, VLDL=very low density lipoprotein cholesterol, WMD=weighted mean difference

Additional Evidence

Dose Simplification
Vanderpoel at al. investigated the adherence rates with the fixed-dose combination of rosiglitazone and metformin compared to monotherapy or concomitant administration of the individual components. Prescription claims for 16,929 type 2 diabetics were analyzed for a 12-month time period. Adherence pre- and post-index was measured by a medication possession ratio, a proxy measurement to determine adherence. Compared to the pre-index period for concomitant administration of the individual components, the fixed-dose combination product had a significant increase in the medication possession ratio (+4.8; P<0.005). There was no significant difference in pill burden, insulin use rate, or non-study oral hyperglycemic agents between the two groups.[109]

Stable Therapy
Berhanu et el. evaluated changes in lipid profiles in 305 patients with type 2 diabetes and dyslipidemia after treatment conversion from rosiglitazone to pioglitazone with continuation of statin and other lipid-lowering therapies. At 17 weeks after treatment conversion from rosiglitazone to pioglitazone, patients had significant reductions in triglycerides (–15.2%; P<0.0001), total cholesterol (–9.0%; P<0.0001), and low-density lipoprotein (LDL) particle concentration (–189 nmol/L; P<0.0001) without significant changes in HbA_{1c} (0.02%). LDL cholesterol (+2.2%), high-density lipoprotein cholesterol (+1.8%; P<0.05), and LDL particle diameter (+0.23 nm; P<0.0001) increased as well.[110]

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 15. Relative Cost of the Thiazolidinediones

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Single Entity Agents				
Pioglitazone	tablet	Actos®*	$$$$$	$
Combination Products				
Pioglitazone and glimepiride	tablet	Duetact®*	$$$$$	$$$$$
Pioglitazone and metformin	tablet	Actoplus Met®*	$$$$$	$

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

X. Conclusions

The thiazolidinediones are approved for use as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.[1-5] All agents are available in generic formulations. Metformin and glimepiride are also available generically in separate formulations.

The goal of treatment for type 2 diabetes is to control hyperglycemia and reduce the risk of long-term complications. A notable new theme in diabetes treatment guidelines is an emphasis on a complication-centric approach, beyond glucose levels, to frame decisions regarding first-line pharmacologic choices for the treatment of persons with diabetes. Pharmacologic therapy should be guided by person-centered treatment factors, including comorbidities and treatment goals. In adults with type 2 diabetes and established/high risk of atherosclerotic cardiovascular disease, heart failure, and/or chronic kidney disease, the treatment regimen should include agents that reduce cardiorenal risk. Pharmacologic approaches that provide adequate efficacy to achieve and maintain treatment goals should be considered, such as metformin or other agents, including combination therapy.[6-9] The thiazolidinediones are noted to be associated with weight gain, fluid retention, congestive heart failure, and fractures. [6-11]

A variety of clinical trials have been conducted with the thiazolidinediones.[12-108] Several studies evaluated the efficacy of thiazolidinediones in dual therapy regimens compared to monotherapy regimens. In these studies, the more aggressive treatment regimens improved glycemic parameters to a greater extent than the less-intensive treatment regimens.[60-63,80-82,89-92,98] However, in studies that directly compared various dual therapy regimens, there were no differences in efficacy noted.[64-73,86,94,96] The thiazolidinedione fixed-dose combination products have been shown to be improve glycemic control in patients with type 2 diabetes.[62,84-86,88,93]

Thiazolidinediones may cause weight gain and fluid retention, as well as increase the risk for congestive heart failure and fractures.[1-5] A variety of meta-analyses have been conducted by independent investigators to assess the link between the use of thiazolidinediones and cardiovascular events.[21-24,26-29] In December 2016, the FDA concluded that use of pioglitazone may be linked to an increased risk of bladder cancer. The labels of pioglitazone-containing medicines already contained warnings about this risk, and have now been updated to describe the additional studies reviewed.[3-5]

There is insufficient evidence to support that one brand thiazolidinedione 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 products 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 thiazolidinedione 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 Antidiabetic Agents, Miscellaneous
AHFS Class 682092
November 8, 2023

I. Overview

Mifepristone (Korlym®) is classified as an antidiabetic agent, miscellaneous by the American Hospital Formulary Service. Mifepristone is a cortisol receptor blocker Food and Drug Administration (FDA)-approved to control hyperglycemia secondary to hypercortisolism in adult patients with endogenous Cushing's syndrome who have type 2 diabetes or glucose intolerance and have failed surgery or are not candidates for surgery.[1,2] When administered in high doses, mifepristone is a selective antagonist of the GR-II glucocorticoid receptor and blocks the effects of cortisol. Mifepristone and the three active metabolites have a greater affinity for the glucocorticoid receptor compared to dexamethasone and cortisol, and have little to no affinity for estrogen, muscarinic, histaminic, or monoamine receptors. Of note, mifepristone does not reduce cortisol levels.[1-3]

Excess cortisol production, the biochemical hallmark of endogenous Cushing's syndrome, may be caused by either excess adrenocorticotropic hormone secretion (from a pituitary or other ectopic tumor) or independent adrenal overproduction of cortisol. Clinical features of Cushing's syndrome typically reflect prolonged and inappropriately high exposure to glucocorticoids, including weight gain, severe fatigue and muscle weakness, high blood pressure, depression, cognitive impairment, purplish skin striae, easy bruising, loss of libido, diabetes, hirsutism, acne, and mental disorders.[4-5] Medical therapies may have a primary or adjunctive role in some patients. In patients in whom surgery has failed to control the disease, medical management is essential to reduce or normalize hypercortisolemia, and should be utilized prior to considering bilateral adrenalectomy. Medical therapies consist of adrenolytic agents (ketoconazole, metyrapone, aminoglutethimide [not available in the United States], mitotane, and etomidate) and neuromodulatory agents (somatostatin analogs, dopamine agonists, peroxisome proliferator-activated receptor-γ agonists, retinoic acid, and glucocorticoid receptor antagonists).[4-6] Adrenolytic agents typically work to decrease cortisol levels and are the most widely used agents. In particular, among patients with hypercortisolism in whom medical therapy is indicated, ketoconazole is considered first-line therapy.[6] The safety and efficacy of neuromodulatory therapies in endogenous Cushing's syndrome are still being evaluated.[5]

At lower doses mifepristone is a selective antagonist of the progesterone receptor.[1] The agent is also available as the branded agent Mifeprex®, which is FDA-approved for the medical termination of intrauterine pregnancy through 70 days gestation.[7]

Tzield® (teplizumab-mzwv) is a CD3-directed antibody indicated to delay the onset of Stage 3 type 1 diabetes (T1DM) in adults and pediatric patients aged eight years and older with Stage 2 T1DM. Teplizumab-mzwv binds to CD3, a cell surface antigen present on T lymphocytes, the mechanism is thought to involve partial agonistic signaling and deactivation of pancreatic beta cell autoreactive T lymphocytes. Teplizumab-mzwv may deactivate the immune cells that attack insulin-producing cells, while increasing the proportion of cells that help moderate the immune response.[8] While T1DM is one of the most common chronic diseases in pediatric patients, patients are generally diagnosed at stage 3 disease. Stage 2 disease is considered to be presence of at least two islet autoantibodies and dysglycemia but not meeting diagnostic criteria for clinical diabetes.[9]

The antidiabetic agents, miscellaneous 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 November 2021.

Table 1. Antidiabetic Agents, Miscellaneous Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Mifepristone	tablet	Korlym®	none
Teplizumab	injection	Tzield®	none

PDL=Preferred Drug List

II. Evidence-Based Medicine and Current Treatment Guidelines

Current clinical guidelines are summarized in Table 2.

Table 2. Treatment Guidelines Using the Antidiabetic Agents, Miscellaneous

Clinical Guideline	Recommendation(s)

Endocrine Society: **Treatment of Cushing's Syndrome: An Endocrine Society Clinical Practice Guideline (2015)**[5]	Treatment goals for Cushing's syndrome
	• In patients with overt Cushing's syndrome (CS), normalizing cortisol levels or action at its receptors to eliminate the signs and symptoms of CS and treating comorbidities associated with hypercortisolism is recommended.
	• Treatment to reduce cortisol levels or action if there is not an established diagnosis of CS is not recommended.
	• Treatments designed to normalize cortisol or its action when there is only borderline biochemical abnormality of the hypothalamic-pituitary-adrenal (HPA) axis without any specific signs of CS is not suggested. The benefit of treating to normalize cortisol is not established in this setting.
	
	First-line treatment options
	• Initial resection of primary lesion(s) underlying Cushing's disease (CD), ectopic and adrenal (cancer, adenoma, and bilateral disease) etiologies is not recommended, unless surgery is not possible or is unlikely to significantly reduce glucocorticoid excess.
	
	Medical treatment
	• Steroidogenesis inhibitors are recommended under the following conditions: as second-line treatment after transsphenoidal selective adenomectomy in patients with CD, either with or without radiation therapy/radiosurgery; as primary treatment of ectopic adrenocorticotropic hormone (ACTH) secretion (EAS) in patients with occult or metastatic EAS; and as adjunctive treatment to reduce cortisol levels in adrenocortical carcinoma (ACC).
	• Pituitary-directed medical treatments are suggested in patients with CD who are not surgical candidates or who have persistent disease after transsphenoidal selective adenomectomy.
	• Administering a glucocorticoid antagonist (mifepristone) is suggested in patients with diabetes or glucose intolerance who are not surgical candidates or who have persistent disease after transsphenoidal selective adenomectomy.
	  ○ Cortisol levels remain unchanged or may increase during mifepristone treatment, and therefore practitioners cannot use hormonal measurements to guide efficacy or to diagnose adrenal insufficiency.
	  ○ Because practitioners must use clinical cortisol-dependent variables for these purposes, it is difficult to estimate the correct dose. For this reason, clinicians should start mifepristone at 300 mg/d, titrate it slowly, and base dose adjustment on clinical parameters, primarily glucose, and weight reduction.
	  ○ Adverse events include symptoms of cortisol insufficiency (fatigue, nausea, vomiting, arthralgias, and headache), evidence of increased mineralocorticoid action (hypertension, hypokalemia, edema), and antiprogestin effects (endometrial thickening).
	• Targeted therapies are suggested to treat ectopic ACTH syndrome.

American Diabetes Association: **Prevention or Delay of Type 2 Diabetes and Associated Comorbidities:**	Pharmacologic interventions for type 1 diabetes • Teplizumab-mzwv infusion to delay the onset of symptomatic type 1 diabetes should be considered in selected individuals aged ≥8 years with stage 2 type 1 diabetes. Management should be in a specialized setting with appropriately trained personnel.

Clinical Guideline	Recommendation(s)
Standards of Care in Diabetes (2023)[10]	

III. Indications

The Food and Drug Administration (FDA)-approved indication for mifepristone is noted in Table 2.

Table 2. FDA-Approved Indications for the Antidiabetic Agents, Miscellaneous[1-3,8]

Indication	Mifepristone	Teplizumab
To control hyperglycemia secondary to hypercortisolism in adult patients with endogenous Cushing's syndrome who have type 2 diabetes mellitus or glucose intolerance and have failed or who are not candidates for surgery	✔	
To delay the onset of Stage 3 type 1 diabetes (T1D) in adults and pediatric patients aged 8 years and older with Stage 2 T1D		✔

IV. Pharmacokinetics

The pharmacokinetic parameters of the antidiabetic agents, miscellaneous are listed in Table 3.

Table 3. Pharmacokinetic Parameters of the Antidiabetic Agents, Miscellaneous[1,2,8]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Half-Life
Mifepristone	69	96.1 to 99.2	Liver (extensive, % not reported)	20 to 85 hours
Teplizumab	Not reported	Not reported	Via catabolic pathways	4.5 days

V. Drug Interactions

Significant drug interactions with the antidiabetic agents, miscellaneous are listed in Table 4. Due to the long serum half-life of mifepristone, at least two weeks should elapse after cessation of mifepristone before initiating or increasing the dose of any interacting concomitant medication.[1]

Discontinuation or dose reduction of drugs whose metabolism is largely or solely mediated by cytochrome P450 (CYP) 3A may be necessary with mifepristone coadministration. Other drugs with similar high first pass metabolism in which CYP3A is the primary route of metabolism should be used with extreme caution if co-administered with mifepristone.[1] Medications that inhibit CYP3A could increase plasma mifepristone concentrations and dose reduction of mifepristone may be required. Avoid coadministration of mifepristone and CYP3A inducers.[1]

Table 4. Significant Drug Interactions with the Antidiabetic Agents, Miscellaneous[1,3]

Generic Name(s)	Interaction	Mechanism
Mifepristone	CYP2C8/2C9 metabolized drugs (e.g., fluvastatin, NSAIDs, warfarin, repaglinide)	Because mifepristone is an inhibitor of CYP2C8/2C9, concurrent use of mifepristone with a drug whose metabolism is largely or solely mediated by CYP2C8/2C9 is likely to result in increased plasma concentrations of the drug.
Mifepristone	CYP2B6 metabolized drugs	Mifepristone is an inhibitor of CYP2B6 and may cause significant increases in exposure of drugs that are metabolized by CYP2B6. Since no study has been conducted to evaluate the effect of

Generic Name(s)	Interaction	Mechanism
	(e.g., bupropion, efavirenz)	mifepristone on substrates of CYP2B6, the concomitant use of bupropion and efavirenz should be undertaken with caution.
Mifepristone	CYP3A metabolized drugs	Mifepristone is an inhibitor of CYP3A, concurrent use of mifepristone with a drug whose metabolism is largely or solely mediated by CYP3A is likely to result in increased plasma concentrations of the drug. Discontinuation or dose reduction of such medications may be necessary with mifepristone coadministration.
Mifepristone	CYP3A Inducers	Medications that inhibit CYP3A could increase plasma mifepristone concentrations and dose reduction of mifepristone may be required.
Mifepristone	Hormonal contraceptives.	Mifepristone is a progesterone-receptor antagonist and will interfere with the effectiveness of hormonal contraceptives. Therefore, non-hormonal contraceptive methods should be used.

VI. Adverse Drug Events

The most common adverse drug events reported with the antidiabetic agents, miscellaneous are listed in Table 5. The boxed warning for mifepristone is listed in Table 6.

Table 5. Adverse Drug Events (%) Reported with Antidiabetic Agents, Miscellaneous[1-3,8]

Adverse Event	Mifepristone	Teplizumab
Dermatologic		
Rash	-	36
Gastrointestinal		
Constipation	10	-
Diarrhea	12	5
Dry mouth	18	-
Nausea	48	5
Vomiting	26	-
General Disorders and Administration/Site Conditions		
Cytokine release syndrome	-	2
Edema peripheral	26	-
Fatigue	48	-
Pain	14	-
Serious infections	-	9
Hematologic		
Leukopenia	-	21
Lymphopenia	-	73
Neutropenia	-	5
Hepatic		
Increased serum alanine aminotransferase	-	5
Infections and Infestations		
Nasopharyngitis	12	5
Sinusitis	14	-
Investigations		
Blood potassium decreased	34	-
Thyroid function test abnormal	18	-
Metabolism and Nutrition Disorders		
Anorexia	10	-
Decreased appetite	20	-
Musculoskeletal and Connective Tissue Disorders		
Arthralgia	30	-
Back pain	16	-

Adverse Event	Mifepristone	Teplizumab
Myalgia	14	-
Pain in extremity	12	-
Nervous System		
Dizziness	22	-
Headache	44	11
Somnolence	10	-
Psychiatric Disorders		
Anxiety	10	-
Reproductive System and Breast Disorders		
Endometrial hypertrophy	38*	-
Respiratory, Thoracic, and Mediastinal Disorders		
Dyspnea	16	-
Vascular Disorders		
Hypertension	24	-

*The denominator was 26 females who had baseline and end-of-trial transvaginal ultrasound.
✓ Percent not specified.

Table 6. Boxed Warning for Korlym® (mifepristone)[1]

WARNING
Mifepristone is a potent antagonist of progesterone and cortisol via the progesterone and glucocorticoid (GR-II) receptors, respectively. The antiprogestational effects will result in the termination of pregnancy. Pregnancy must therefore be excluded before the initiation of treatment with mifepristone and prevented during treatment and for one month after stopping treatment by the use of a non-hormonal medically acceptable method of contraception unless the patient has had a surgical sterilization, in which case no additional contraception is needed. Pregnancy must also be excluded if treatment is interrupted for more than 14 days in females of reproductive potential.

VII. Dosing and Administration

The usual dosing regimen for the antidiabetic agents, miscellaneous are listed in Table 7.

Table 7. Usual Dosing Regimens for Antidiabetic Agents, Miscellaneous[1-2]

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
Mifepristone	Control hyperglycemia secondary to hypercortisolism in adult patients with endogenous Cushing's syndrome who have type 2 diabetes mellitus or glucose intolerance and have failed surgery or are not candidates for surgery: Tablet: initial, 300 mg once daily as a single dose with a meal; maximum, 1,200 mg QD or 20 mg/kg/day	Safety and efficacy in pediatric patients have not been established.	Tablet: 300 mg
Teplizumab	Delay of onset of stage 3 type 1 diabetes: Intravenous: Once daily for 14 consecutive days as follows: • Day 1: 65 mcg/m^2 • Day 2: 125 mcg/m^2 • Day 3: 250 mcg/m^2 • Day 4: 500 mcg/m^2 • Days 5 through 14: 1,030 mcg/m^2	Delay of onset of stage 3 type 1 diabetes in patients ≥8 years of age: Intravenous: Once daily for 14 consecutive days as follows: • Day 1: 65 mcg/m^2 • Day 2: 125 mcg/m^2 • Day 3: 250 mcg/m^2 • Day 4: 500 mcg/m^2 • Days 5 through 14: 1,030 mcg/m^2	Injection: 2 mg/2 mL

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the antidiabetic agents, miscellaneous are summarized in Table 8.

Table 8. Comparative Clinical Trials with Antidiabetic Agents, Miscellaneous

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Fleseriu et al.[11] (2012) Mifepristone 300 to 1,200 mg QD Patients started with 300 mg QD and if no significant clinical improvement, doses could be increased to 600 mg QD on day 14, 900 mg QD at week 6 and 1,200 mg QD at week 10.	MC, OL Adults with confirmed endogenous CS with type 2 diabetes mellitus, impaired glucose tolerance, or a diagnosis of hypertension in addition to ≥2 of the following symptoms: Cushingoid appearance (moon facies, dorsocervical fat pad, and plethora), increased body weight or central obesity, proximal muscle weakness, low bone mineral density (T score <-1.0), psychiatric symptoms, and skin changes (hirsutism, violaceous striae, or acne)	N=50 24 weeks	Primary: Change ≥25% in $AUC_{glucose}$ on oGTT from baseline (for patients with CS and type 2 diabetes mellitus or impaired glucose tolerance [C-DM cohort]) and change ≥5 mm Hg in DBP from baseline to week 24 (for patients with hypertension [C-HT cohort]) Secondary: Changes in glucose homeostasis, BP, lipids, weight, body composition change, clinical appearance, strength, neuropsychological and quality of life parameters and safety	Primary: In the C-DM mITT population, the $AUC_{glucose}$ was reduced by ≥25% on oGTT in 60% (15/25) of patients receiving mifepristone compared to baseline (P<0.001). In the C-HT mITT treatment group, 38.1% (8/21) of patients treated with mifepristone achieved ≥5 mm Hg decline in DBP compared to baseline (P<0.05). Secondary: Overall, the clinical responder rate was 87% at week 24 compared to baseline (P<0.0001). Specifically, 92% of patients in the C-DM group and 81% of those in the C-HT group achieved a median clinical improvement score of +1 (P values not reported). Overall, FPG decreased from 149.0±74.7 mg/dL at baseline to 104.7±37.5 mg/dL after 24 weeks (P<0.03). In the C-DM group, 72% of patients achieved ≥25% reduction from baseline in $AUC_{glucose}$ or a reduction in antidiabetic medication (95% CI, 50.6 to 87.9). The mean HbA_{1c} was significantly reduced from baseline following mifepristone treatment (6.29±0.99 vs 7.43±1.52%; P<0.001). Of the 12 patients with an HbA_{1c} >7.0% at baseline, nine were able to lover their HbA_{1c} below 7.0%, including six reaching an HbA_{1c} 6.0% or below. Patients in both the C-DM and C-HT treatment groups who were insulin resistant at baseline demonstrated rapid and significant improvements in $AUC_{insulin}$, which continued throughout the study. Insulin sensitivity was improved as evident by changes in HOMA-IR. In the mITT group, the mean±SD change in bodyweight from baseline to week 24 following mifepristone treatment was -5.7±7.4% (P<0.001). Overall, 24 mifepristone-treated patients lost ≥5% of their baseline weight, and 10 patients lost ≥10%.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Mifepristone treatment was associated with a statistically significant reduction in waist circumference in women (-6.8±5.8 cm; P<0.001) and men (-8.4±5.9 cm; P<0.001). At week 24, the mean total body fat declined by 3.6% (P<0.001), absolute fat mass declined by 13.9% (P<0.001), total body of the trunk declined by 15.6% (P<0.001) and by 17.1% (P<0.001) for the abdominal region. Overall, 52.5% of patients with hypertension at baseline had either a response in DBP or a reduction in antihypertensive medication use. There were no statistically significant differences in mean SBP and DBP from baseline after 24 weeks of treatment in C-HT patients (129.5±16.3/82.9±11.4 vs 129.9±19.0/82.8±13.2 mm Hg) or in C-DM patients who also had hypertension (137.7±24.0/86.4±15.3 vs 132.2±16.7/82.4±13.2 mm Hg). There were statistically significant improvements in the median BDI-II depression scores in the mITT population (P<0.001). For patients with at least mild depression at baseline, (BDI-II >14), the median score improved from 23 to 12 at 24 weeks (P<0.001). Similarly, improvements in cognition scores were also reported (P<0.01). Patients treated with mifepristone experienced statistically significant improvements in quality of life scores at 24 weeks compared to baseline in both mental (P=0.01) and physical (P=0.02) composite scores. Adverse events occurred in 88% of mifepristone-treated patients, with the most common being nausea (48%), fatigue (48%), headache (44%), decreased blood potassium (34%), arthralgia (30%), vomiting (26%), peripheral edema (26%), hypertension (24%), dizziness (22%), decreased appetite (20%), and endometrial thickening (20%). Seven patients discontinued mifepristone due to adverse events.
Herold et al.[12] TrialNet (2019)	DB, MC, PC, RCT Relatives of patients with type 1 diabetes who did not have	N=76 5 years	Primary: Elapsed time from randomization to the clinical diagnosis of	Primary: Treatment with a single course of teplizumab delayed the time to diagnosis of type 1 diabetes: 19 (43%) of the 44 participants who received teplizumab and 23 (72%) of the 32 participants who received placebo had type 1 diabetes diagnosed. The annualized rates of diagnosis of type 1

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Teplizumab 14 day course vs placebo	diabetes but were at high risk for development of clinical disease (two or more diabetes-related autoantibodies detected in two samples obtained within six months before randomization. In addition, participants had to have had evidence of dysglycemia during an oral glucose-tolerance test) and were ≥8 years of age		diabetes, determined with the use of criteria from the American Diabetes Association Secondary: Not reported	diabetes were 14.9% per year in the teplizumab group and 35.9% per year in the placebo group. The median time to diagnosis was 48.4 months in the teplizumab group and 24.4 months in the placebo group (hazard ratio, 0.41; 95% CI,, 0.22 to 0.78; two-sided P=0.006). Secondary: Not reported

Drug regimen abbreviations: QD=once daily
Study abbreviations: CI=confidence interval, MC=multicenter, OL=open label
Miscellaneous abbreviation: $AUC_{glucose}$=area under the curve for glucose, $AUC_{insulin}$= area under the curve for insulin, BDI-II-Beck depression inventory, BP=blood pressure, CS=Cushing's syndrome, DBP=diastolic blood pressure, FPG=fasting plasma glucose, HbA_{1c}=glycosylated hemoglobin A_{1c}, HOMA-IR=homeostatic model assessment of insulin resistance, mITT=modified intent to treat, oGTT=oral glucose tolerance test, QOL=quality of life, SBP=systolic blood pressure, SD=standard deviation

Additional Evidence

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

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

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

IX. Cost

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

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

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

Rx=prescription

Table 8. Relative Cost of Antidiabetic Agents, Miscellaneous

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Mifepristone	tablet	Korlym®	$$$$$	N/A
Teplizumab	injection	Tzield®	$$$$$	N/A

N/A=Not available

X. Conclusions

Mifepristone is the first agent Food and Drug Administration (FDA)-approved for the management of Cushing's syndrome.[1-3] Specifically, mifepristone is a cortisol receptor blocker indicated to control hyperglycemia secondary to hypercortisolism in adult patients with endogenous Cushing's syndrome who have type 2 diabetes or glucose intolerance and have failed surgery or are not candidates for surgery. Mifepristone should not be used for the treatment of type 2 diabetes unrelated to endogenous Cushing's syndrome.[1]

Based on the mechanism of action of mifepristone and its approved indication, the agent can only be used in certain patients with endogenous Cushing's syndrome and there is potential for it to be used in combination with other established treatments. Cushing's syndrome treatment goals include the reversal of clinical features, the normalization of biochemical changes with minimal morbidity, and long-term control without recurrence. Optimal treatment is surgical resection by selective adenomectomy, with second-line options that include repeated pituitary surgery, radiotherapy, or bilateral adrenalectomy.[5] Medical therapy plays an essential role in patients in whom surgery has failed to control the disease to reduce or normalize hypercortisolemia. Currently, adrenolytic therapies

(ketoconazole, metyrapone, aminoglutethimide [not available in the United States], mitotane, etomidate) are the most widely utilized agents, with ketoconazole considered first-line to treat hypercortisolism. The safety and efficacy of neuromodulatory therapies (somatostatin analogs, dopamine agonists, peroxisome proliferator-activated receptor-γ agonists, retinoic acid, glucocorticoid receptor antagonists) in Cushing's syndrome have not been established .[4-5] The Endocrine Society Clinical Practice Guidelines for the Treatment of Cushing's Syndrome suggests administering mifepristone in patients with diabetes or glucose intolerance who are not surgical candidates or who have persistent disease after transsphenoidal selective adenomectomy.[5]

FDA approval of teplizumab-mzwv was based on one clinical trial (N=76) that evaluated the safety and efficacy of teplizumab-mzwv for delay of onset of stage 3 type 1 diabetes in patients with stage 2 type 1 diabetes. Eligible participants were nondiabetic relatives of patients with T1DM and were at least eight years of age at the time of randomization and at high risk for development of clinical diabetes. Participants also had to have had two or more diabetes-related autoantibodies detected in two samples obtained within six months before randomization. In addition, participants had to have had evidence of dysglycemia during an oral glucose-tolerance test (defined as a fasting glucose level of 110 to 125 mg per deciliter, a 2-hour postprandial plasma glucose level of at least 140 mg per deciliter and less than 200 mg per deciliter, or an intervening postprandial glucose level at 30, 60, or 90 minutes of greater than 200 mg per deciliter) on two occasions, within 52 days before enrollment. The clinical trial demonstrated a median delay in time to diagnosis with stage 3 type 1 diabetes of 24 months.[8,12] Teplizumab-mzwv is administered as an intravenous infusion over a minimum of 30 minutes for 14 consecutive days. It is recommended to premedicate prior to teplizumab-mzwv infusion for the first five days of dosing with a nonsteroidal anti-inflammatory drug (NSAID) or acetaminophen, an antihistamine, and/or an antiemetic.[8]
The 2023 American Diabetes Association Standards of Care in Diabetes state that teplizumab-mzwv infusion to delay the onset of symptomatic type 1 diabetes should be considered in selected individuals aged ≥8 years with stage 2 type 1 diabetes. Management should be in a specialized setting with appropriately trained personnel.[10]

There is insufficient evidence to support that one brand antidiabetic agent, miscellaneous is safer or more efficacious than another within its given indication. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process. Tzield® (teplizumab-mzwv) is used in a specific patient population. Because this agent has a narrow indication with limited usage and very specific criteria must be met prior to initiating therapy, this agent should be managed through the clinical criteria portion of the prior authorization process.

Therefore, all brand products 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 antidiabetic agent, miscellaneous 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 Multivitamin Preparations: Prenatal Vitamins
AHFS Class 882800
November 8, 2023

I. Overview

Women of reproductive age should maintain good nutritional status prior to, during, and after pregnancy to minimize health risks to both the mother and child. This includes maintaining a healthy weight, participating in physical activity, consuming a variety of foods to meet the Dietary Reference Intake recommendations, as well as appropriate and timely supplementation with multivitamins.[1-3] There are several organizations that have published dietary guidelines for the perinatal period (preconception, pregnancy, and during lactation).[4-6] However, most women of childbearing age do not maintain a healthy diet and do not consume enough vitamins (A, C, B-6, and E), calcium, folic acid, iron, magnesium, or zinc.[1,2]

Women have an increased requirement for certain nutrients during pregnancy, including folate and iron. Folate is necessary for deoxyribonucleic acid (DNA) synthesis and cell division and is an important nutrient prior to and during pregnancy. Many studies have shown that folic acid supplementation is associated with a lower risk of neural tube defects, which are serious birth defects of the spine and brain.[1-10] The American Academy of Pediatrics (AAP), American Academy of Family Physicians (AAFP), American College of Obstetricians and Gynecologists (ACOG), American Dietetic Association (ADA), Centers for Disease Control and Prevention (CDC), and the United States Preventive Services Task Force (USPSTF) all recommend that women of reproductive age consume folic acid on a daily basis.[1,7-10] The amount of folic acid that is recommended varies slightly among the organizations; however, the most recent publication by the USPSTF recommends that all women planning pregnancy take a supplement containing 400 to 800 μg of folic acid on a daily basis.[8] A higher dose of folic acid (4 mg/day) is recommended for women who have had a previous pregnancy affected by a neural tube defect, which should begin one to three months prior to conception and continue throughout the first trimester of pregnancy.[2,8-9]

Iron deficiency is common in women of childbearing age due to menstruation, insufficient dietary intake, and multiple pregnancies.[2] There is an increase in iron requirements during pregnancy due to the expansion of blood volume and red blood cell mass.[11] Iron deficiency anemia during pregnancy can lead to fetal complications such as premature delivery, intrauterine growth restrictions, and neonatal mortality.[2,11] It is recommended that women consume 27 mg of elemental iron per day during pregnancy.[5] Pregnant women should be screened for iron deficiency anemia, and if present, be treated with supplemental iron (60 to 120 mg/day).[1-3,11]

There is evidence that maternal consumption of folic acid-containing multivitamins may reduce the risk of neural tube defects, cardiac defects, urinary tract defects, limb defects, as well as other birth defects.[2,12] The ADA recommends supplementation with a multivitamin for pregnant women with iron deficiency anemia, poor-quality diets, those who consume no or small amounts of animal source foods, women carrying two or more fetuses, those who smoke or abuse alcohol or drugs, and for women who are infected with human immunodeficiency virus.[1] In addition to a well-balanced diet, supplementation with a folic acid-containing multivitamin should be encouraged in all women of reproductive age to help support healthy pregnancy outcomes.[2]

There is a wide variety of prenatal vitamins currently available. Most of the preparations contain folic acid and iron; however, the amount varies among the products (refer to the dosing and administration section for comparison). The products also contain various combinations and quantities of vitamins and minerals. Additional nutrients which may be added to a prenatal vitamin include docusate, L-methylfolate, omega-3 fatty acids, and omega-6 fatty acids. Folic acid must be broken down to L-methylfolate to be used at the cellular level; however, some individuals are unable to convert folic acid to its active form. Some of the prenatal formulations contain L-methylfolate for women who are unable to fully metabolize folic acid. Omega-3 fatty acids include α-linolenic acid (ALA), docosahexaenoic acid (DHA), and eicosapentaenoic acid (EPA). Omega-3 and omega-6 fatty acids must be obtained from food because the human body cannot synthesize these nutrients. DHA and EPA can be synthesized de novo from ALA; however, intake of ALA has not been shown to increase maternal, fetal, or breast milk DHA levels.[2-3] Both DHA and EPA are considered essential fatty acids which are necessary for nervous

tissue growth and function.[13] Some studies suggest that they may play a role in fetal/neonatal visual and neural growth when taken during pregnancy, as well as help prevent low birth weight. There are recommended DRIs that have been established for ALA; however, it is unclear how much DHA or EPA a pregnant woman should consume through her diet and via supplementation.[2-3,14]

The prenatal vitamins that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. It should be noted that the products included in this review contain an extensive ingredient list, which can be found separately in the prescribing information. The term "prenatal vitamins" in Table 1 collectively refers to all of the active vitamin and mineral ingredients. Additional ingredients, including folic acid and iron, have been listed out separately. Many of the prenatal vitamins are available in a generic formulation, including products which contain omega-3 fatty acids. This class was last reviewed in November 2021.

Table 1. Prenatal Vitamins Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Iron, folic acid, B12, docusate	Tablet	Citranatal Bloom®	none
Prenatal vitamins, folic acid	Chewable tablet	Prenate Chewable®	none
Prenatal vitamins, folic acid, ginger oil	Tablet	Prenate AM®	none
Prenatal vitamins, iron, folic acid	Capsule, chewable tablet, tablet	Concept OB®*, Marnatal-F®, Nestabs®*, OB Complete®*, OB-Complete Premier®, Prenate Elite®, Prenate Star®, Provida OB®, Select-OB®, Thrivite Rx®*, Tricare®, Vinate II®, Vitafol Nano®, Vitafol-OB®	prenatal vitamins, iron, folic acid, Vitafol Nano®, Vitafol-OB®
Prenatal vitamins, iron, folic acid, DHA	Capsule, chewable tablet, combination package	Enbrace HR®, Nestabs DHA®*, Nestabs One®, OB Complete Caplet®*, OB Complete Petite®, Prenate DHA®, Prenate Enhance®, Prenate Essential®, Prenate Mini®, Prenate Pixie®, Prenate Restore®, Primacare®, Select-OB+DHA®, Tristart DHA®, Virt-PN® Plus, Vitafol Fe Plus®, Vitafol-OB+DHA®, Vitafol-One®, Vitafol Ultra®, Zatean-PN Plus®	prenatal vitamins, iron, folic acid, DHA, Select-OB+DHA®, Vitafol Fe Plus®, Vitafol-OB+DHA®, Vitafol-One®, Vitafol Ultra®
Prenatal vitamins, iron, folic acid, docusate	Tablet	Citranatal RX®	prenatal vitamins, iron, folic acid, docusate
Prenatal vitamins, iron, folic acid, omega-3 fatty acids	Capsule, combination package	Concept DHA®*, OB Complete With DHA®	prenatal vitamins, iron, folic acid, omega-3 fatty acids
Prenatal vitamins, iron, folic acid, vitamin B6	Tablet	Citranatal B-Calm®	prenatal vitamins, iron, folic acid, vitamin B6
Prenatal vitamins, iron, folic acid, DHA, docusate	Capsule, combination package	Citranatal 90 DHA®*, Citranatal Assure®*, Citranatal DHA®, Citranatal Harmony®, Extra-Virt Plus DHA®, Nexa Plus®, Vitafol Fe + Docusate®, VP-CH-PNV®, VP-CH Plus®	prenatal vitamins, iron, folic acid, DHA, docusate
Prenatal vitamins, iron, folic acid, DHA, EPA	Combination package	Nestabs ABC®	none

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Prenatal vitamins, iron, folic acid, DHA, fish oil	Capsule	OB Complete One®	none
Prenatal vitamins, iron, folic acid, DHA, omega-3 fatty acids	Combination package	N/A	prenatal vitamins, iron, folic acid, DHA, omega-3 fatty acids
Prenatal vitamins, iron, folic acid, DHA, EPA, omega-3 fatty acids	Chewable tablet	Vitafol Gummies®	Vitafol Gummies®
Prenatal vitamins, iron, L-methylfolate, algal oil blend, soy†	Capsule	Vinate DHA RF®†	none

*Generic is available in at least one dosage form or strength.
†Clinical information for this product is not available in the various drug databases.
DHA=Docosahexaenoic acid
EPA=Eicosapentaenoic acid
N/A=Not available

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the prenatal vitamins are summarized in Table 2. The recommended Dietary Reference Intakes for women are listed in Table 3.

Table 2. Treatment Guidelines Using the Prenatal Vitamins

Clinical Guideline	Recommendation(s)
United States Preventive Services Task Force: **Folic Acid for the Prevention of Neural Tube Defects: United States Preventive Services Task Force Recommendation Statement (2017)[8]**	• All women planning or capable of pregnancy should take a daily supplement containing 0.4 to 0.8 mg (400 to 800 µg) of folic acid. • This recommendation applies to women who are planning or capable of pregnancy, but it does not apply to women who have had a previous pregnancy affected by neural tube defects or women taking certain antiseizure medicines. Most organizations recommend that these women take higher doses of folic acid. • Most studies indicate the need to start folic acid supplementation at least one month before conception and to continue daily supplements through the first two to three months of pregnancy. Studies also indicate that 50% of pregnancies in the United States are unplanned, and clinicians should therefore advise all women who are capable of pregnancy to take folic acid supplements. • Good evidence from randomized trials in settings without fortification of food suggests that a multivitamin with 0.8 mg (800 µg) of folic acid reduces the risk for neural tube defects. Observational studies done before fortification report a reduction of neural tube defects in women taking a supplement with 0.4 mg (400 µg) of folic acid (the generally available dose). Evidence indicates that most women in the United States are not ingesting fortified foods at a level thought to provide optimal benefit. In a setting in which food is fortified with folic acid, the effective amount of additional folic acid supplementation is unclear.
Position of the Academy of Nutrition and Dietetics: **Nutrition and Lifestyle for a Healthy Pregnancy Outcome (2014)[1]**	• Women of childbearing age should adopt a lifestyle optimizing health and reducing risk of birth defects, suboptimal fetal development, and chronic health problems in both mother and child. Components leading to healthy pregnancy outcome include healthy prepregnancy weight, appropriate weight gain and physical activity during pregnancy, consumption of a wide variety of foods, appropriate vitamin and mineral supplementation, avoidance of alcohol and other harmful substances, and safe food handling. • During the first two trimesters of pregnancy, iron-deficiency anemia increases the risk for preterm labor, low birth weight, and infant mortality. Maternal and fetal demand for iron increases during pregnancy; this increase cannot be met without iron supplementation.

Clinical Guideline	Recommendation(s)
	• All women, including adolescents, who are capable of becoming pregnant should consume 400 µg/day folic acid from fortified foods and/or dietary supplements, in addition to eating food sources of folate. Pregnant women are advised to consume 600 µg dietary folate equivalents daily from all food sources. Folic acid is recognized as important before and during pregnancy because of its preventive properties against neural tube defects. Women who have had an infant with a neural tube defect should consult with their health care provider regarding the recommendation to take 4,000 µg folic acid daily before and throughout the first trimester of pregnancy. • Vitamin D supplementation during pregnancy has been suggested as an intervention to protect against adverse outcomes, including low birth weight; however, the need, safety, and effectiveness of vitamin D supplementation remains controversial. The Institute of Medicine recommends 600 IU per day of vitamin D, and ongoing research suggests higher levels are safe and effective for improving maternal and infant vitamin D status. • Although choline is found in many foods, the majority of pregnant women are not achieving the adequate intake for pregnancy of 450 mg/day. • Recommended calcium intake is equal for pregnant and nonpregnant women of the same age. Women with suboptimal intakes (<500 mg/day) may need additional amounts to meet maternal and fetal bone requirements. • The recommended amount of iodine from dietary and supplement sources is 150 µg/day before conception and 220 µg/day for pregnant women.
The American College of Obstetricians and Gynecologists Practice Bulletin: **Anemia in Pregnancy (2021)**[11]	• All pregnant women should be screened for anemia with a complete blood count in the first trimester and again at 24 0/7–28 6/7 weeks of gestation. • Patients who meet criteria for anemia based on hematocrit levels less than 33% in the first and third trimesters and less than 32% in the second trimester should be evaluated to determine the cause. If iron deficiency is ruled out, other etiologies should be investigated. • Those with iron deficiency anemia should be treated with supplemental iron, in addition to prenatal vitamins. • Low-dose supplementation of iron during pregnancy improves maternal hematologic parameters, reduces the likelihood of iron deficiency at term, and is not associated with harms. There is little evidence that iron supplementation results in morbidity beyond gastrointestinal symptoms, except in patients with hemochromatosis or certain other genetic disorders. Low-dose iron supplementation is recommended starting in the first trimester to decrease the prevalence of maternal anemia at delivery.

Centers for Disease Control and Prevention: **Recommendations to Improve Preconception Health and Health Care-United States (2006)**[7]	<u>Preconception risk factors for adverse pregnancy outcomes</u>
	• Alcohol misuse
	  ○ It is not safe to drink alcohol at any time during pregnancy, and harm can occur early, before a woman realizes that she is or might be pregnant. Fetal alcohol syndrome and other alcohol-related birth defects can be prevented if women stop drinking alcohol before conception.
	• Anti-epileptic drugs
	  ○ Certain anti-epileptic drugs (e.g., valproic acid) are known teratogens. Recommendations suggest that women who are on a regimen of these drugs and who are contemplating pregnancy should be prescribed a lower dosage of these drugs.
	• Diabetes (preconception)
	  ○ The threefold increase in the prevalence of birth defects among infants of women with type 1 and type 2 diabetes is substantially reduced through proper management of diabetes.
	• Folic acid

Clinical Guideline	Recommendation(s)
	○ Daily use of vitamin supplements containing folic acid has been shown to reduce the occurrence of neural tube defects by as much as two thirds. • Hepatitis B ○ Vaccination is recommended for men and women who are at risk for acquiring hepatitis B virus (HBV) infection. Preventing HBV infection in women of childbearing age prevents transmission of infection to infants and eliminates risks to the women of HBV infection and sequelae, including hepatic failure, liver carcinoma, cirrhosis, and death. • HIV/acquired immune deficiency syndrome ○ If HIV infection is identified before conception, timely antiretroviral treatment can be administered, and women (or couples) can be given additional information to help prevent mother-to-child transmission. • Hypothyroidism ○ The dosages of thyroxine (e.g., levothyroxine) need to be adjusted for proper neurologic development of the fetus. • Isotretinoins ○ Use of isotretinoins (e.g., Accutane®) to treat acne during pregnancy can result in miscarriage and birth defects. Effective pregnancy prevention should be implemented to avoid unintended pregnancies among women with childbearing potential who use this medication. • Maternal phenylketonuria ○ Women diagnosed with maternal phenylketonuria as infants have an increased risk for delivering infants with mental retardation or birth defects. However, this adverse outcome can be prevented when mothers adhere to a low-phenylalanine diet before conception and continue it throughout their pregnancy. • Rubella seronegativity ○ Rubella vaccination provides protective seropositivity and prevents congenital rubella syndrome. • Obesity ○ Adverse perinatal outcomes associated with maternal obesity include neural tube defects, preterm delivery, diabetes, cesarean delivery, and hypertensive and thromboembolic disease. Appropriate weight loss and nutritional intake before pregnancy reduces these risks.
The American College of Obstetricians and Gynecologists Practice Bulletin: **Neural Tube Defects (2017)[9]** **(Reaffirmed 2021)**	• All women planning a pregnancy or capable of becoming pregnant should take 400 µg of folic acid supplementation daily. Supplementation should begin at least one month before pregnancy and continue through the first 12 weeks of pregnancy. • Women at high risk of neural tube defects should supplement with a higher dose of folic acid than 400 µg. This group includes those with histories of previous pregnancies affected with neural tube defects, women who are affected with a neural tube defect themselves, those who have a partner who is affected, or those with a partner with a previous affected child. Women at high risk of neural tube defects should take 4 mg (4,000 micrograms) of folic neural tube defects daily. The daily supplement should be initiated three months before pregnancy and continued until 12 weeks of gestational age. • Some over-the-counter multivitamin supplements and most prenatal vitamins contain 400 µg of folic acid. Higher levels of supplementation should be achieved by taking an additional folic acid supplement and not by taking excess multivitamins. In particular, vitamin A is potentially teratogenic at high doses, and pregnant women should not take more than 5,000 international units per day, the amount that typically is found in one multivitamin and mineral supplement.

Clinical Guideline	Recommendation(s)
American Academy of Pediatrics: **Folic Acid for the Prevention of Neural Tube Defects (1999)[10]** **(Reaffirmed March 2017)**	• The American Academy of Pediatrics (AAP) endorses the United States Preventive Services Task Force recommendation that all women of childbearing age who are capable of becoming pregnant should consume 400 (0.4 mg) µg of folic acid daily. • Women with a history of a previous pregnancy resulting in a fetus with neural tube defects should be advised of the results of the Medical Research Council Vitamin (MRC) study. During times in which a pregnancy is not planned, these high-risk women should consume 4000 (4 mg) µg of folic acid per day. However, they should be offered treatment with 4000 µg of folic acid per day starting one month before the time they plan to become pregnant and throughout the first three months of pregnancy, unless contraindicated. Women should be advised not to attempt to achieve the 4000 µg daily dosage of folic acid by taking over-the-counter or prescription multivitamins containing folic acid because of the possibility of ingesting harmful levels of other vitamins, for example, Vitamin A. It should be noted that 4000 µg of folic acid did not prevent all neural tube defects in the MRC study. Therefore, high-risk patients should be cautioned that folic acid supplementation does not preclude the need for counseling or consideration of prenatal testing for neural tube defects.

Table 3. Dietary Reference Intake for Women[1,5,6]

Nutrient	Adult Women	Pregnancy	Lactation
Biotin	25 to 30 µg	30 µg	35 µg
Folate	400 µg DFE	600 µg DFE	500 µg DFE
Niacin	14 mg	18 mg	17 mg
Pantothenic acid	5 mg	6 mg	7 mg
Riboflavin	1.0 to 1.1 mg	1.4 mg	1.6 mg
Thiamin	1.0 to 1.1 mg	1.4 mg	1.4 mg
Vitamin A	700 µg RAE	750 to 770 µg RAE	1,200 to 1,300 µg RAE
Vitamin B_6	1.2 to 1.3 mg	1.9 mg	2.0 mg
Vitamin B_{12}	2.4 µg	2.6 µg	2.8 µg
Vitamin C	65 to 75 mg	80 to 85 mg	115 to 120 mg
Vitamin D	15 to 20 µg	15 µg	15 µg
Vitamin E	15 mg	15 mg	19 mg
Vitamin K	75 to 90 µg	75 to 90 µg	75 to 90 µg
Calcium	1,000 to 1,300 mg	1,000 to 1,300 mg	1,000 to 1,300 mg
Choline	400 to 425 mg	450 mg	550 mg
Chromium	24 to 25 µg	29 to 30 µg	44 to 45 µg
Copper	890 to 900 µg	1,000 µg	1,300 µg
Fluoride	3 mg	3 mg	3 mg
Iodine	150 µg	220 µg	290 µg
Magnesium	310 to 360 mg	350 to 400 mg	310 to 360 mg
Iron	15 to 18 mg	27 mg	9 to 10 mg
Manganese	1.6 to 1.8 mg	2.0 mg	2.6 mg
Molybdenum	43 to 45 µg	50 µg	50 µg
Phosphorus	700 to 1,250 mg	700 to 1,250 mg	700 to 1,250 mg
Selenium	55 µg	60 µg	70 µg
Zinc	8 to 9 mg	11 to 12 mg	12 to 13 mg
Alpha-linolenic acid	1.1 g	1.4 g	1.3 g
Linoleic acid	11 to 12 g	13 g	13 g

DFE=dietary folate equivalents, RAE=retinol activity equivalents

III. Indications

Indications for the prenatal vitamins are noted in Table 4. Dietary supplements do not need approval from the Food and Drug Administration (FDA) before they are marketed. These drugs have not been found by the FDA to be safe and effective, and the labeling has not been approved by the FDA.

Table 4. Indications for the Prenatal Vitamins[15-17]

Generic Name(s)	Nutritional supplement for use prior to conception, throughout pregnancy and during the postnatal period	Nutritional supplement to help ease nausea and vomiting of pregnancy
Iron, folic acid, B12, docusate	✔	
Prenatal vitamins, folic acid	✔	
Prenatal vitamins, folic acid, ginger oil		✔
Prenatal vitamins, iron, folic acid	✔	
Prenatal vitamins, iron, folic acid, DHA	✔	
Prenatal vitamins, iron, folic acid, docusate	✔	
Prenatal vitamins, iron, folic acid, omega-3 fatty acids	✔	
Prenatal vitamins, iron, folic acid, vitamin B6	✔	
Prenatal vitamins, iron, folic acid, DHA, docusate	✔	
Prenatal vitamins, iron, folic acid, DHA, EPA	✔	
Prenatal vitamins, iron, folic acid, DHA, fish oil	✔	
Prenatal vitamins, iron, folic acid, DHA, omega-3 fatty acids	✔	
Prenatal vitamins, iron, folic acid, DHA, EPA, omega-3 fatty acids	✔	

DHA=Docosahexaenoic acid
EPA=Eicosapentaenoic acid

IV. Pharmacokinetics

There is limited or no data available on the pharmacokinetic properties of the prenatal vitamins.[15-17]

V. Drug Interactions

There are no significant drug interactions reported with the prenatal vitamins.[15-17]

VI. Adverse Drug Events

Adverse reactions with iron therapy may include anorexia, constipation, diarrhea, nausea, vomiting, dark stools and abdominal pain, which are usually transient. Allergic sensitization has been reported following both oral and parenteral administration of folic acid.[15-17] Accidental overdose of iron containing products is a leading cause of fatal poisoning in children under the age of six. The boxed warning for the prenatal vitamins is listed in Table 5.

Table 5. Boxed Warning for the Prenatal Vitamins[15-17]

WARNING
Accidental overdose of iron-containing products is a leading cause of fatal poisoning in children under six. Keep this product out of the reach of children. In case of accidental overdose, call a doctor or poison control center immediately.

VII. Dosing and Administration

The usual dosing regimens for the prenatal vitamins are listed in Table 6.

Table 6. Usual Dosing Regimens for the Prenatal Vitamins[15-17]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Iron, folic acid, B12, docusate	Administer once daily.	Safety and effectiveness have not been established in pediatric patients.	Tablet: 90-1-0.012-50 mg
Prenatal vitamins, folic acid	Administer once daily.	Safety and effectiveness have not been established in pediatric patients.	Chewable tablet: 1 mg
Prenatal vitamins, folic acid, ginger oil	Administer once daily.	Safety and effectiveness have not been established in pediatric patients.	Tablet: 1-500 mg
Prenatal vitamins, iron, folic acid	Administer once daily.	Safety and effectiveness have not been established in pediatric patients.	Capsule: 40-1.25 mg 60-1 mg 85-1 mg 106-1 mg Chewable tablet: 29-1 mg 40-1 mg Tablet: 15-1 mg 18-1 mg 20-1 mg 27-1 mg 29-1 mg 30-20-1 mg 32-1 mg 50-1.25 mg 60-1 mg 65-1 mg
Prenatal vitamins, iron, folic acid, DHA	Administer once daily.	Safety and effectiveness have not been established in pediatric patients.	Capsule: 1.5-8.73-6.4 mg 10-1-200 mg 18-1-300 mg 18-1-350 mg 27-1-300 mg 27-1-400 mg 28-1-200 mg 28-1-300 mg 28-1-400 mg 29-1-200 mg 30-1-300 mg 31-1-200 mg 35-5-1-200 mg 38-1-225 mg 90-1-200 mg Combination package: 29-1-250 mg 32-1-230 mg 65-1-250 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Prenatal vitamins, iron, folic acid, docusate	Administer once daily.	Safety and effectiveness have not been established in pediatric patients.	Tablet: 27-1-50 mg 29-1-25 mg
Prenatal vitamins, iron, folic acid, omega-3 fatty acids	Administer once daily.	Safety and effectiveness have not been established in pediatric patients.	Capsule: 28-1-200 mg 30-10-1-200 mg 35-1-200 mg Combination package: 29-1-250 mg 29-1-400 mg
Prenatal vitamins, iron, folic acid, vitamin B6	Administer once daily.	Safety and effectiveness have not been established in pediatric patients.	Tablet: 20-1-25 mg
Prenatal vitamins, iron, folic acid, DHA, docusate	Administer once daily.	Safety and effectiveness have not been established in pediatric patients.	Capsule: 27-1-50-260 mg 29-1-50-265 mg 29-1.25-55-350 mg 30-1-50-200 mg 30-1-50-260 mg 30-1.2-55-265 mg 90-1-50-200 mg Combination package: 27-1-50-250 mg 30-1-50-300 mg 35-1-50-300 mg 90-1-50-300 mg
Prenatal vitamins, iron, folic acid, DHA, EPA	Administer once daily.	Safety and effectiveness have not been established in pediatric patients.	Combination package: 32-1-120-180 mg
Prenatal vitamins, iron, folic acid, DHA, fish oil	Administer once daily.	Safety and effectiveness have not been established in pediatric patients.	Capsule: 40-10-1-300-476 mg
Prenatal vitamins, iron, folic acid, DHA, omega-3 fatty acids	Administer once daily.	Safety and effectiveness have not been established in pediatric patients.	Combination package: 29-1-250-200 mg
Prenatal vitamins, iron, folic acid, DHA, EPA, omega-3 fatty acids	Administer once daily.	Safety and effectiveness have not been established in pediatric patients.	Chewable tablet: 3.33-0.33-34.83 mg (25-5.1-4.73 mg)
Prenatal vitamins, iron, L-methylfolate, algal oil blend, soy	Administer once daily.	Safety and effectiveness have not been established in pediatric patients.	Capsule: 27-1.13-581.28 mg

DHA=Docosahexaenoic acid
EPA=Eicosapentaenoic acid

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the prenatal vitamins are summarized in Table 7. There were no studies found in the medical literature that directly compared the various prenatal vitamin preparations.

Table 7. Comparative Clinical Trials with the Prenatal Vitamins

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Gupta et al.[18] (2007) Multivitamin supplementation plus folic acid 500 µg/day and iron 60 mg/day vs placebo plus supplementation with folic acid 500 µg/day and iron 60mg/day	DB, PC, RCT Pregnant women between 24 to 32 weeks gestation with a BMI <18.5 and/or a hemoglobin level 7 to 9 g/dL	N=200 Median 52 to 58 days	Primary: Birth weight, length, midarm, circumference, incidence of low birth weight, and early neonatal morbidity Secondary: Not reported	Primary Infants in the micronutrient supplement group were 98 g heavier (95% CI, -16 to 213) and 0.8 cm longer (95% CI, 0.03 to 1.57) than infants born to mothers who received placebo. Infants in the micronutrient supplement group were 0.2 cm larger in midarm circumference (95% CI, 0.04 to 0.36) than infants born to mothers who received placebo. Incidence of low birth weight decreased from 43.1 to 16.2% in those infants whose mothers received micronutrient supplementation (RR, 0.3; 95% CI, 0.13 to 0.71; P=0.006) compared to infants whose mothers received placebo. Early neonatal morbidity decreased from 28.0 to 14.8% in those infants whose mothers received micronutrient supplementation (RR, 0.42; 95% CI, 0.19 to 0.94; P=0.04) compared to infants whose mothers received placebo. Women who were anemic were not likely to benefit more from multivitamin supplementation in terms of birth size. There was no significant difference between birth size for women with hemoglobin levels of less than 9 g/dL and the rest in the micronutrient group. Secondary: Not reported
Liu et al.[19] (2013)	DB, RCT	N=18,775	Primary: Perinatal mortality	Primary: The perinatal mortality rate was 8.76 of 1000 births for the folic acid group, 8.73 of 1000 for the iron–folic acid group, and 8.25 of 1000 for the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Folic acid vs iron-folic acid vs multiple micronutrients (MMN)	Pregnant women in rural China ≥20 years old, ≤20 weeks gestation, nulliparous, hemoglobin >10.0 g/dL, and had not consumed micronutrient supplements other than folic acid in the prior 6 months	Variable duration	Secondary: Neonatal deaths, infant deaths, maternal hemoglobin and anemia, birth weight, birth length, duration of gestation	MMN group. Compared with prenatal folic acid alone, neither iron–folic acid (RR, 1.00; 95% CI, 0.68 to 1.46; P=0.99) nor MMN supplements (RR, 0.94; 95% CI, 0.64 to 1.39; P=0.76) affected the risk of perinatal mortality. Compared with iron–folic acid, MMN did not affect the risk of perinatal mortality (RR, 0.94; 95% CI, 0.64 to 1.39; P=0.77). Secondary: Risk of stillbirths, early neonatal deaths, neonatal deaths, or infant deaths did not differ by supplement group. Compared with folic acid alone, iron–folic acid and MMN increased third-trimester maternal hemoglobin concentration by 0.04 and 0.06 g/dL, respectively, and decreased the anemia prevalence by 28 and 29%, respectively, with a number needed to treat of 47 (95% CI, 33 to 81) for the iron–folic acid group and 46 (95% CI, 32 to 77) for the MMN group. Neither gestation duration nor birth weight or length differed significantly by supplement group.
Haider et al.[20] (2006) Multiple micronutrient supplementation of 3 or more micronutrients vs placebo, no supplementation or supplementation with 2 or less micronutrients	MA (9 RCTs) Pregnant women (varying duration of pregnancies)	15,378 Duration not specified	Primary: Preterm birth, small for gestational age, low birth weight, premature rupture of membranes, preeclampsia, miscarriage, maternal mortality, perinatal mortality Secondary: Maternal anemia	Primary: A significant decrease in the number of low birth weight babies was observed when comparing multiple micronutrient supplementation to placebo, no supplementation or two or less micronutrients (RR, 0.83; 95% CI, 0.76 to 0.91). No significant differences were observed in preterm birth and perinatal mortality (RR, 0.92; 95% CI, 0.82 to 1.04). When multiple micronutrient supplementation was compared to iron and folic acid supplementation, no significant differences were observed in any primary outcome. Secondary: A significant decrease in maternal anemia was observed when comparing multiple micronutrient supplementation with placebo, no supplementation or supplementation of two or less micronutrients (RR, 0.61; 95% CI, 0.52 to 0.71). No significant differences were observed in maternal anemia when multiple micronutrient supplementation was compared to iron and folic acid supplementation (RR, 1.23; 95% CI, 0.82 to 1.83).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
McNulty et al.[21] (2019) FASSTT Offspring Folic acid 400 µg vs placebo	Follow-up of DB, RCT Healthy pregnant women, 18 to 35 years of age with a singleton pregnancy and who had taken the recommended dose of 400 µg/d of folic acid in the first trimester, were recruited from antenatal clinics at the 14th week of gestation to study the impact of continuing folic acid after the first trimester of pregnancy	N=70 7 years	Primary: Cognitive performance of children at 7 years was evaluated using the Wechsler Preschool and Primary Scale of Intelligence (WPPSI-III) Secondary: Not reported	Primary: Following adjustment for child's sex, birth weight, breastfeeding, maternal age, and maternal education attainment, analysis showed that children born to mothers who had received folic acid in pregnancy scored higher in word reasoning compared to children from the placebo group (mean, 13.3; 95% CI, 12.4 to 14.2 vs mean, 11.9; 95% CI, 11.0 to 12.8; P=0.027). No other statistically significant differences in WPPSI-III scores were observed between the two groups. When compared with a nationally representative sample of British children at age 7 years, WPPSI-III scores were found to be higher in children from folic acid treated mothers for verbal IQ (107.7 vs 99.1, P<0.001), performance IQ (104.1 vs 98.7; P=0.035), general language (108.9 vs 101.8; P=0.002), and full scale IQ (106.4 vs 98.3; P=0.001). Comparison of the placebo group with British children however showed smaller differences in scores for verbal IQ (103.4 vs 99.1; P=0.034) and full scale IQ (103.5 vs 98.3; P=0.017) and no differences in performance IQ or general language scores. Secondary: Not reported
Lumley et al.[22] (2000) Multivitamins vs folate vs multivitamins plus folate	MA (4 RCTs) Periconceptual women	N=6,425 Variable duration	Primary: NTD Secondary: Not reported	Primary: Periconceptional folate supplementation reduced the prevalence of neural tube defects (RR, 0.28; 95% CI, 0.13 to 0.58). The reduction is similar for the first occurrence of defects (RR, 0.07; 95% CI, 0.00 to 1.32) and for recurrent defects (RR, 0.31; 95% CI, 0.14 to 0.66). The number needed to treat for folate prevention of an NTD is 847. The trials had very low power to identify differences in limb reduction defects (RR, 0.59; 95% CI 0.04 to 8.34), conotruncal defects (RR, 0.74; 95% CI, 0.16 to 3.32), orofacial clefts (RR, 0.76; 95% CI, 0.24 to 2.37) or all other major birth defects combined (RR, 0.76; 95% CI, 0.38 to 1.51). Folate supplementation was not associated with an increase in conception (RR, 1.02; 95% CI 0.97 to 1.07).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				No adverse effects of the folate supplementation were detected in terms of an increase in miscarriage (RR, 1.12; 95% CI, 0.98 to 1.29), or ectopic pregnancy (RR, 1.09; 95% CI, 0.47 to 2.55). There was no reduction in stillbirths (RR, 0.78; 95% CI, 0.34 to 1.78). There was no statistically significant reduction in NTD when multivitamins alone were compared with placebo (RR, 0.61; 95% CI, 0.26 to 1.45), when multivitamins were compared with multivitamins plus folate (RR, 2.05; 95% CI, 0.67 to 6.26), or when folate was compared with multivitamins plus folate (RR, 0.49; 95% CI, 0.09 to 2.66). When folate alone was compared with multivitamins alone there was a reduction with folate (RR, 0.27; 95% CI, 0.07 to 1.08), however this was not significant. Secondary: Not reported
Siega-Riz et al.[23] (2006) Multivitamin supplementation containing 30 mg of elemental iron (ferrous sulfate) vs multivitamin supplementation without iron	RCT Pregnant women who were less than 20 weeks of gestation with hemoglobin levels ≥110 g/L and ferritin levels ≥40 µg/L	N=429 >9 weeks	Primary: Third trimester iron status, birth weight, preterm birth, and small-for-gestational age Secondary: Not reported	Primary: There were no significant differences between the treatment groups in any of the iron status indicators measured. Women who received iron supplementation gave birth to infants who weighed 108 g heavier than women who did not receive iron supplementation (P=0.03). There were no significant differences among women who received iron supplementation compared to those who did not receive iron supplementation for the following outcomes: gestational age at delivery (P=0.43), low birth weight (4.8 vs 9.5%, respectively; P=0.09), preterm delivery (7.5 vs 13.9%, respectively; P=0.05), or small-for-gestational age (P=0.22). Secondary: Not reported
Goh et al.[24] (2006)	MA (6RCTs) Pregnant women	N=not specified Variable duration	Primary: Risk of pediatric cancer Secondary:	Primary: Use of prenatal multivitamins by the pregnant mothers was associated with a protective effect for childhood leukemia (OR, 0.64; 95% CI 0.53 to 0.78).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Prenatal multivitamin supplementation			Not reported	Ingestion of prenatal multivitamins was associated with a protective effect for acute lymphoblastic leukemia (OR, 0.61; 95% CI, 0.50 to 0.74). There was only one study that reported information regarding acute myeloid leukemia which suggested a protective effect of prenatal multivitamin use. Supplementation with prenatal vitamins was associated with a decreased risk for neuroblastoma (OR, 0.53; 95% CI, 0.42 to 0.68). Prenatal supplementation was associated with decreased risk for pediatric brain tumors (OR, 0.73; 95% CI, 0.60 to 0.88) Secondary: Not reported
Hofmeyr et al.[25] (2006) Calcium supplementation (1.5 to 2 g/day) vs placebo	MA (12 RCTs) Pregnant women	N=15,206 Variable duration	Primary: Hypertensive disorders of pregnancy and related maternal and child outcomes Secondary: Not reported	Primary: There was less high blood pressure with calcium supplementation rather than placebo (RR, 0.70; 95% CI, 0.57 to 0.86). There was a reduction in the risk of pre-eclampsia (RR, 0.48; 95% CI, 0.33 to 0.69). The relative risk of having the composite outcome maternal death or serious morbidity was reduced for women allocated calcium supplementation compared with placebo (RR, 0.80; 95% CI, 0.65 to 0.97). There was no difference in the rate of placental abruption between the groups (RR, 0.86; 95% CI, 0.55 to 1.34). There was no significant effect on the relative risk of caesarean section (RR, 0.95; 95% CI, 0.88 to 1.01). There was no overall difference in proteinuria between groups (RR, 1.04; 95% CI, 0.86 to 1.26).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				There was no difference in the rate of severe pre-eclampsia (RR, 0.74; 95% CI, 0.48 to 1.15) or eclampsia between the groups (RR, 0.73; 95% CI, 0.41 to 1.27). There was no difference in maternal deaths between the groups (RR, 0.17; 95% CI, 0.02 to 1.39). There was no overall effect on preterm birth (RR, 0.81; 95% CI, 0.64 to 1.03). There was no overall effect on the risk of having a baby with birthweight less than 2,500 g (RR, 0.84; 95% CI, 0.68 to 1.03). There was no overall effect on the relative risk of the baby being born small-for-gestational age (RR, 1.10; 95% CI, 0.88 to 1.37). There was no overall effect on the relative risk of admission to a neonatal intensive care unit (RR, 1.05; 95% CI, 0.94 to 1.18). There was no overall effect on the relative risk of a stillbirth or the baby dying before discharge from hospital (RR, 0.89; 95% CI, 0.73 to 1.09). Secondary: Not reported
Helland et al.[26] (2008) Omega-3 fatty acids in the form of cod liver oil (containing 1,183 mg of DHA and 803 mg of EPA) 10 mL/day from 18 weeks of pregnancy until 3 months after delivery	DB, RCT Healthy pregnant women 19 to 35 years of age	N=143 7 year follow-up of children born to pregnant women receiving treatment intervention	Primary: Cognitive function using the Kaufman Assessment Battery for Children Secondary: Not reported	Primary: There were no significant differences in Kaufman Assessment Battery for Children cognitive scores at seven years of age among children whose mothers received cod liver oil during pregnancy as compared to children whose mothers received corn oil during pregnancy. Maternal plasma levels of ALA and DHA at 35 weeks of pregnancy were positively associated with sequential processing scale at age seven. There was no significant correlation between fatty acid status at birth and BMI at age seven.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs corn oil (containing 4,747 mg of linoleic acid and 92 mg of ALA) 10 mL/day from 18 weeks of pregnancy until 3 months after delivery				Secondary: Not reported
Dunstan et al.[27] (2008) Fish oil (2.2 g DHA and 1.1 g EPA per day) from 20 weeks' gestation until delivery vs olive oil from 20 weeks' gestation until delivery	DB, RCT Pregnant women	N=98 2.5 year follow-up of children born to pregnant women receiving treatment intervention	Primary: Effects on infant growth and developmental quotients (Griffiths Mental Development Scales), receptive language (Peabody Picture Vocabulary Test) and behavior (Child Behavior Checklist) Secondary: Not reported	Primary: There was no significant difference in growth measurements between the fish oil group and the olive oil group. The mean age for both groups was 30 months; the mean height was 93.8 cm for the fish oil group vs 93.3 cm for the olive oil group (P=0.642); the mean weight was 14.5 vs 14.1 kg, respectively (P=0.456); and the head circumference was 49.4 vs 49.8 cm, respectively (P=0.304). Children from the fish oil group attained a significantly higher score for eye and hand coordination (P=0.021). There was no significant difference mean standard score obtained in the Peabody Picture Vocabulary Test between the fish oil group and the olive oil group (P=0.110). Results from the Child Behavior Checklist indicated no significant differences between the mean T scores of the fish oil and olive oil groups for internalizing (P=0.576), externalizing (P=0.706), total problem behavior scales (P=0.548), mean length of phrases (P=0.300) and vocabulary centile score (P=0.650). Secondary: Not reported
Makrides et al.[28] (2006)	MA (6 RCTs) Pregnant women	N=2,783 Variable follow-up	Primary: Risk of pre-eclampsia, preterm	Primary: There were no differences in the risk of high blood pressure (RR, 1.09; 95% CI, 0.90 to 1.33) or the incidence of pre-eclampsia (RR, 0.86; 95% CI, 0.59 to 1.27) between marine oil-treated and control groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Marine oil supplement (DHA and EPA dose ranged from 133 mg to 3 g per day) vs placebo or no treatment			birth, and birth weight Secondary: Not reported	Women allocated to a marine oil supplement had a mean gestation that was 2.6 days longer than women allocated to placebo or no treatment (difference, 2.55 days; 95% CI, 1.03 to 4.07 days). This was not reflected in a clear difference between the two groups in the relative risk of birth before 37 completed weeks (RR, 0.92; 95% CI, 0.79 to 1.07). Women allocated to marine oil had a lower risk of giving birth before 34 completed weeks' gestation compared with placebo (RR, 0.69; 95% CI, 0.49 to 0.99). Birthweight and birth length were slightly greater in infants born to women in the marine oil group compared with control. However, there was no overall difference between the groups in the relative risk for low birthweight or small-for-gestational babies. Secondary: Not reported
Carlson et al.[29] (2013) 3 capsules/day of a marine algae-oil source of DHA (200 mg DHA/capsule) vs placebo group received 3 capsules containing half soybean and half corn oil	DB, PC, RCT Women between 8 and 20 weeks of gestation, between 16 and 35.99 years of age, and planning to deliver at a hospital in the Kansas City metropolitan area	N=350 Enrollment until birth	Primary: Red blood cell (RBC)-phospholipid-DHA content, gestation duration, birth weight and length Secondary: Low and very low birth weight	Primary: RBC-phospholipid-DHA (percentage of total fatty acids by weight) was significantly higher in the DHA-supplemented group at birth and increased significantly from enrollment only in that group (P<0.001). Gestational age was also 2.87 days greater (P=0.041), and birth weight and length were higher by 172 grams and 0.7 cm, respectively (P=0.004 and P=0.022, respectively). Secondary: Cord RBC-phospholipid-DHA and head circumference were significantly higher in newborns of women assigned to DHA than to placebo. The incidence of preterm birth did not differ between the groups; however, significantly more infants in the placebo group had an early preterm birth (P=0.025). A trend toward fewer low birth weight deliveries was not statistically significant (P=0.059), but there was a significantly lower incidence of very low birth weight in the DHA-supplemented group (P=0.026).
Gould et al.[30] (2014)	DB, RCT	N=184	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Three 0.5 gram DHA-rich capsules/day, which provided 800 mg DHA/day and 100 mg EPA/day vs three 0.5 gram capsules that contained a blend of vegetable oils	Women with singleton pregnancies of 18 to 21-week gestation with no fetal abnormalities	Enrollment to delivery; follow-up when child 27 months of age	Average time it took to be distracted when playing with a toy (distractibility) and the accuracy of remembering a new hiding location while inhibiting a learned response to search in the previous location (working memory and inhibitory control [WMIC]) Secondary: Not reported	The primary outcome of distractibility did not differ between treatment and control groups. The primary outcome of the WMIC did not differ between treatment and control groups. However, the control group were more accurate at searching for the hidden toy during training trials than was the treatment group (14.4 mm; 95% CI, 20.2 to 29.1 mm; P=0.05). Secondary: Not reported
Makrides et al.[31] (2010) DHA supplementation (800 mg of DHA and 100 mg of EPA) vs vegetable oil capsules without DHA	DB, MC, RCT Pregnant women with singleton pregnancies less than 21 weeks gestation	N=2,399 (women) N=726 (children) 6 months post-partum	Primary: High level of maternal depressive symptoms as documented by a score >12 on the Edinburgh Postnatal Depression Scale at six weeks or six months postpartum, neurodevelopment at 18 months of age Secondary:	Primary: No significant differences were observed between groups in the percentage of women with high levels of depressive symptoms through six months postpartum (RR, 0.85; 95% CI, 0.70 to 1.02). No significant differences were observed between groups in mean cognitive composite scores or mean language composite scores (adjusted mean difference, 0.01; 95% CI, -1.36 to 1.37 and adjusted mean difference, -1.42; 95% CI, -3.07 to 0.22 respectively). Secondary: No difference was observed between groups in the percentage of women medically diagnosed with depression or receiving treatment for depression during the trial.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Percentage of women medically diagnosed with depression or receiving treatment for depression during pregnancy, at six weeks and six months postpartum	
Lewin et al.[32] (2005) Omega-3 fatty acid supplementation vs placebo or no treatment	MA Pregnant women, breastfeeding mothers, preterm and term infants	89 RCT Variable duration	Primary: Safety issues, pregnancy outcomes, growth pattern outcomes, neurological development outcomes, visual function outcomes, cognitive development outcomes Secondary: Not reported	Primary: *Safety* Omega-3 fatty acids supplementation in pregnant women, breastfeeding mothers, and preterm and term infants, was very well tolerated and did not generate any serious adverse events across the included RCTs. *Pregnancy Outcomes* There was no significant difference between intervention groups in the duration of gestation measured as mean of gestational age at delivery. Omega-3 fatty acids did not have a significant effect on the proportion of premature deliveries. There is inconsistent evidence of the use of omega-3 fatty acids supplements during the second or third trimester of pregnancy to reduce the incidence of premature pregnancies in high- and low-risk populations. The overall effect does not show a significant difference between study arms. Supplementation with omega-3 fatty acids did not have a significant effect on the incidence of preeclampsia. There was no significant difference in the incidence of gestational hypertension between treatment groups (OR, 1.07; 95% CI, 0.75 to 1.51). The mean birth weight was not influenced by the intervention.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Growth Pattern Outcomes There was no statistical difference between infants from mothers that were taking the supplementation with omega-3 and omega-6, or omega-6 fatty acids predominantly, on the weight, length, and head circumference from birth to 12 months of age. There was no effect of breast milk, with maternal intake of omega-3 (DHA) or omega-6 fatty acids, on the growth patterns at any time point. *Neurological Development Outcomes* One study failed to find a significant difference between groups in maturity as evaluated from the EEGs, neither at day one of life nor at three months of age. Two studies showed that maternal breast milk may not have an influence on the neurological outcome, measured with the Psychomotor Development Index scale of the Bayley's Index. *Visual Function Outcomes* One study failed to find a significant effect of DHA supplementation during pregnancy on the retinal sensitivity measured at birth in term infants. One cross-sectional study failed to find a statistically significant difference in mean visual function values between the exclusively breastfed group and the infants who were also receiving formula. Five studies found that the correlation between the DHA content in breast milk and visual function was not consistent with the clinical outcomes measured in breastfed term infants of mothers who were or were not taking supplements containing high DHA. *Cognitive Development Outcomes* There were no differences between groups in the novelty preference (Fagan Test of Infant Intelligence) at six and nine months of age. Two studies of breastfed children failed to find a difference in the mean Bayley's Mental Developmental Index score between groups at one or two years of age.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Harper et al.[33] (2010) Omega-3 fatty acid supplementation (800 mg of DHA and 1,200 mg of EPA) vs placebo	DB, MC, RCT Pregnant women between 16 and 22 weeks gestation with a history of previous singleton preterm birth	N=852 14 to 20 weeks	Primary: Delivery before 37 weeks gestation Secondary: Delivery before 35 weeks, delivery before 32 weeks, spontaneous preterm delivery, medically indicated preterm delivery, delivery after 40 weeks	Primary: No significant difference was observed between groups in the risk of delivery before 37 weeks (RR, 0.91; 95% CI, 0.77 to 1.07). Secondary: No significant differences were observed between groups for any secondary outcome measure.
Szajewska et al.[34] (2006) Omega-3 fatty acid supplementation	MA (6 RCTs) Pregnant women	N=1,278 Variable duration	Primary: Pregnancy and related maternal and child outcomes Secondary: Not reported	Primary: Omega-3 supplementation was associated with a significantly greater duration of pregnancy (difference, 1.57 days; 95% CI, 0.35 to 2.78). There was no significant difference between supplemented and non-supplemented subjects in the percentage of preterm deliveries (RR, 0.67; 95% CI, 0.41 to 1.10) or in the rate of low birth weight (RR, 0.66; 95% CI, 0.34 to 0.26). There was no significant difference between supplemented and non-supplemented subjects in the rate of preeclampsia or eclampsia (RR, 0.73; 95% CI, 0.22 to 2.37) or in the rate of cesarean delivery (RR, 1.17; 95% CI, 0.79 to 1.74). There was no significant difference between supplemented and non-supplemented subjects in the rate of gestational diabetes (RR, 0.73; 95% CI, 0.22 to 2.37).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				There was no significant difference between supplemented and non-supplemented subjects in the placental weight (difference, 10.9 g; 95% CI, 10.4 to 32.2). There was no significant difference in birth weight between supplemented and non-supplemented control subjects (difference, 54 g; 95% CI, -3.1 to 111). There was no significant difference between supplemented and non-supplemented subjects in the length at birth (difference, 0.23 cm; 95% CI, -0.04 to 0.5). Supplementation was associated with significantly greater head circumference of the infants in the supplemented group, as compared with those of the non-supplemented control group (difference, 0.26 cm; 95% CI, 0.02 to 0.49). Secondary: Not reported

Study design abbreviations: DB=double-blind, MA=meta-analysis, MC=multicenter, PC=placebo-controlled, RCT=randomized controlled trial
Miscellaneous abbreviations: ALA=α-linolenic acid, BMI=body mass index, CI=confidence interval, DHA=docosahexaenoic acid, EEG=electroencephalogram, EPA=eicosapentaenoic acid, NTD=neural tube defect, OR=odds ratio, RR=relative risk

Additional Evidence

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

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

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

IX. Cost

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

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

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

Rx=prescription

Table 8. Relative Cost of the Prenatal Vitamins

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Iron, folic acid, B12, docusate	Tablet	Citranatal Bloom®	$$$$	N/A
Prenatal vitamins, folic acid	Chewable tablet	Prenate®	$$$$$	N/A
Prenatal vitamins, folic acid, ginger oil	Tablet	Prenate AM®	$$$$$	N/A
Prenatal vitamins, iron, folic acid	Capsule, chewable tablet, tablet	Concept OB®*, Marnatal-F®, Nestabs®*, OB Complete®, OB-Complete Premier®, Prenate Elite®, Prenate Star®, Provida OB®, Select-OB®, Thrivite Rx®*, Tricare®, Vinate II®, Vitafol Nano®, Vitafol-OB®	$$-$$$	$
Prenatal vitamins, iron, folic acid, DHA	Capsule, chewable tablet, combination package	Enbrace HR®, Nestabs DHA®*, Nestabs One®, OB Complete Caplet®*, OB Complete Petite®, Prenate DHA®, Prenate Enhance®, Prenate Essential®, Prenate Mini®, Prenate Pixie®, Prenate Restore®, Primacare®, Select-	$$$	$

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
		OB+DHA®, Tristart DHA®, Virt-PN® Plus, Vitafol Fe Plus®, Vitafol-OB+DHA®, Vitafol-One®, Vitafol Ultra®, Zatean-PN Plus®		
Prenatal vitamins, iron, folic acid, docusate	Tablet	Citranatal RX®	$$$	N/A
Prenatal vitamins, iron, folic acid, omega-3 fatty acids	Capsule, combination package	Concept DHA®*, OB Complete With DHA®	$	$
Prenatal vitamins, iron, folic acid, vitamin B6	Tablet	Citranatal B-Calm®	$$$$	$
Prenatal vitamins, iron, folic acid, DHA, docusate	Capsule, combination package	Citranatal 90 DHA®*, Citranatal Assure®*, Citranatal DHA®, Citranatal Harmony®, Extra-Virt Plus DHA®, Nexa Plus®, Vitafol Fe + Docusate®, VP-CH-PNV®, VP-CH Plus®	$$$$	$
Prenatal vitamins, iron, folic acid, DHA, EPA	Combination package	Nestabs ABC®	$$$$	N/A
Prenatal vitamins, iron, folic acid, DHA, fish oil	Capsule	OB Complete One®	$$$$	N/A
Prenatal vitamins, iron, folic acid, DHA, omega-3 fatty acids	Combination package	N/A	N/A	$
Prenatal vitamins, iron, folic acid, DHA, EPA, omega-3 fatty acids	Chewable tablet	Vitafol Gummies®	$$$$	N/A
Prenatal vitamins, iron, L-methylfolate, algal oil blend, soy†	Capsule	Vinate DHA RF®†	$$$$	N/A

*Generic is available in at least one dosage form or strength.
† Clinical information for this product is not available in the various drug databases.
DHA=Docosahexaenoic acid
EPA=Eicosapentaenoic acid
N/A=Not available

X. Conclusions

Women of reproductive age should maintain good nutritional status prior to, during, and after pregnancy to minimize health risks to both the mother and child.[1-3] This includes maintaining a healthy weight, participating in physical activity, consuming a variety of foods to meet the Dietary Reference Intake recommendations, as well as appropriate and timely supplementation with multivitamins.[1-3]

It is recommended that that all women planning pregnancy take a supplement containing 400 to 800 µg of folic acid on a daily basis to reduce the risk of neural tube defects.[1,7-10] Women should receive at least 27 mg of elemental iron per day during pregnancy; however, higher amounts are necessary for pregnant women with iron deficiency anemia.[1-3,5,11] There is evidence that maternal consumption of folic acid-containing multivitamins may reduce the risk of neural tube defects, cardiac defects, urinary tract defects, limb defects, as well as other birth defects.[2,12,24] The American Dietetic Association recommends supplementation with a multivitamin for pregnant women with iron deficiency anemia, poor-quality diets, those who consume no or small amounts of animal source foods, women carrying two or more fetuses, those who smoke or abuse alcohol or drugs, and for women who are infected with human immunodeficiency virus.[1] In addition to a well-balanced diet, supplementation with a folic acid-containing multivitamin should be encouraged in all women of reproductive age to help support healthy pregnancy outcomes.[2]

There are many different prenatal vitamins currently available. The majority of the products contain folic acid and iron, as well as various combinations of vitamins and minerals. Additional nutrients which have been added to some of the prenatal vitamins include docusate, L-methylfolate, omega-3 fatty acids, and omega-6 fatty acids. Many of the prenatal vitamins are available in a generic formulation, including products which contain omega-3 fatty acids.

There were no clinical trials found in the medical literature that directly compared the various prenatal vitamin preparations. Supplementation with folic acid is clearly beneficial during pregnancy, and adequate intake of iron is necessary to reduce the risk of iron deficiency anemia. There has been recent interest in the health benefits associated with the use of supplemental omega-3 fatty acids during pregnancy. Omega-3 fatty acids are necessary for nervous tissue growth and function, and dietary intake has a variety of health benefits.[13] Some studies have suggested that omega-3 fatty acids may improve fetal/neonatal visual and neural growth and help prevent low birth weight when taken as a supplement during pregnancy.[2-3,14] Several meta-analyses have evaluated the use of supplemental omega-3 fatty acids during pregnancy. In general, the results of these analyses have not found a significant difference in pregnancy-related outcomes.[26-28,32-34] This includes assessment of maternal outcomes (blood pressure, preeclampsia, and preterm delivery) and child outcomes (neurological development, growth patterns, visual function, and cognitive development).[26-28,32,34] There is insufficient evidence regarding the supplemental use of omega-3 fatty acids and the effects on pregnancy-related maternal and child outcomes.

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

Therefore, all brand products 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 prenatal vitamin 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 Immunomodulatory Agents used to treat Multiple Sclerosis
AHFS Class 922000
November 8, 2023

I. Overview

Several immunomodulatory agents are Food and Drug Administration (FDA)-approved for the treatment of adult patients with relapsing forms of multiple sclerosis (MS), including both injectable products and oral products.[1-23] MS is a chronic and potentially disabling neurological disease characterized by repeated episodes of inflammation within the nervous tissue of the brain and spinal cord, resulting in injury to the myelin sheaths and subsequently the nerve cell axons.[24-25] MS is an autoimmune inflammatory demyelinating disease of the central nervous system.[24-25] There are several clinical subtypes of MS: clinically isolated syndrome (CIS), radiologically isolated syndrome (RIS), relapsing-remitting (RRMS), primary progressive (PPMS), and secondary progressive (SPMS).[24-25] The most common form is RRMS, characterized by acute relapses followed by partial or full recovery.[24-25] Patients with PPMS have a disease progression from onset. SPMS begins as RRMS, but as time progresses the attack rate declines and patients experience a gradual deterioration.[24-25]

The exact mechanisms of action of the immunomodulatory agents used to treat MS are generally not completely understood but are likely due to their antiproliferative and immuno-modulatory effects.[1-23] Alemtuzumab (Lemtrada®) is a CD52-directed cytolytic monoclonal antibody. Because of its safety risks, which include autoimmune conditions, infusion reactions, stroke, and increased risk of malignancies, the use of alemtuzumab should generally be reserved for patients who have had inadequate response to two or more drugs indicated for the treatment of MS. Alemtuzumab is only available through a limited distribution program.[1]

Glatiramer acetate is thought to act by modifying immune processes that are believed to be responsible for the pathogenesis of MS. Glatiramer acetate is a mixture of synthetic polypeptides, made through a chemical synthesis from four amino acids. The mixture is antigenically similar to myelin basic protein, a component of the myelin sheath of nerves. Experimental models suggest glatiramer may bind to major histocompatibility complex molecules and compete with various myelin antigens for their presentation to T cells. In addition, glatiramer is a potent inducer of specific T helper 2 type suppressor cells that migrate to the brain and lead to bystander suppression; these cells also express anti-inflammatory cytokines.[6,7,24]

Natalizumab is a recombinant monoclonal antibody directed against alpha-4 integrins. The formation of inflammatory lesions in patients with MS may involve lymphocytes and monocytes that gain access to the brain parenchyma from the circulation by first adhering to vascular endothelial cells. Alpha-4 integrin is expressed on the surface of inflammatory lymphocytes and monocytes and may play a critical role in their adhesion to the vascular endothelium. Natalizumab increases the risk of progressive multifocal leukoencephalopathy (PML). When initiating and continuing treatment with natalizumab, physicians should consider whether the expected benefit is sufficient to offset this risk. Natalizumab is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the TOUCH® Prescribing Program because of the risk of PML.[12,24]

Ocrelizumab (Ocrevus®) is a CD20-directed cytolytic antibody. The exact mechanism by which it exerts its therapeutic effect is not known. It binds to CD-20, a cell surface antigen present on pre-B and mature B lymphocytes, which results in antibody-dependent cellular cytolysis and complement-mediated lysis. Ocrelizumab is approved for the treatment of both relapsing and primary progressive forms of MS.[13,22]

IFNs are pleiotropic molecules with a wide range of proliferative, apoptotic, antiviral, and complex immunoregulatory activities.[8-10,16,19,24] Although first attempts to use IFNs as therapeutic agents in MS were based on their antiviral effect, more recent attention has focused on their direct effect on the blood-brain barrier and their immunomodulatory and antiproliferative effects.[27] These are the oldest treatments for RRMS, the first being approved in 1993.[24]

Oral products include fumarates, fingolimod (Gilenya teriflunomide (Aubagio®), and sphingosine 1-phosphate receptor modulators. Dimethyl fumarate may have neuroprotective and immunomodulatory properties, although the mechanism by which it exerts its therapeutic effect in multiple sclerosis is unknown.[2] Fingolimod is sphingosine analogue that modulates the sphingosine-1-phosphate receptor and thereby alters lymphocyte migration, resulting in sequestration of lymphocytes in lymph nodes. Initiation of fingolimod treatment results in a decrease in heart rate. The first dose of fingolimod should be administered in a setting in which resources to appropriately manage symptomatic bradycardia are available. In order to assess patient response to the first dose of fingolimod, observe all patients for six hours for signs and symptoms of bradycardia with hourly pulse and blood pressure measurement. In all patients, obtain an electrocardiogram prior to dosing, and at the end of the observation period.[4,24] Teriflunomide is the active metabolite of leflunomide that inhibits pyrimidine biosynthesis and disrupts the interaction of T cells with antigen presenting cells. The exact mechanism by which teriflunomide exerts its therapeutic effect is unknown but may involve a reduction in the number of activated lymphocytes in the central nervous system. Teriflunomide carries a boxed warning for the risks of hepatotoxicity and teratogenicity. The manufacturer recommends obtaining baseline transaminase and bilirubin levels before starting treatment with teriflunomide, and to monitor ALT levels monthly for at least six months once treatment is started.[20,23]

Vumerity® (diroximel fumarate) is approved for the treatment relapsing forms of MS in adults. Diroximel fumarate was approved as a new dosage form of dimethyl fumarate (Tecfidera®) via the 505(b)(2) drug approval pathway.[3] Diroximel fumarate, similar to dimethyl fumarate (Tecfidera®), is a fumaric acid ester prodrug that is metabolized to active monomethyl fumarate prior to systemic circulation.[2,3] Monomethyl fumarate is thought to act by modulating cell-signaling pathways, but the exact mechanism of action in MS is unknown. FDA-approval of diroximel fumarate was established based on bioavailability studies in patients with RMS comparing dimethyl fumarate and diroximel fumarate.[3] Monomethyl fumarate (Bafiertam DR®) is also indicated for the treatment of relapsing forms of MS. Similar to Vumerity®, because of its similarity to Tecfidera®, Bafiertam's approval was based largely on the FDA's findings of safety and efficacy for Tecfidera® and bioavailability studies in healthy subjects comparing dimethyl fumarate to Bafiertam®.[11]

Ofatumumab (Kesimpta®) is a recombinant human monoclonal immunoglobulin G1 (IgG1) antibody that binds to human CD20 expressed on B-cells. Following cell surface binding to B lymphocytes, ofatumumab results in antibody-dependent cellular cytolysis and complement-mediated lysis. Kesimpta® is the first B-cell therapy that can be self-administered once monthly at home. It is a subcutaneous injection indicated for the treatment of relapsing forms of MS.[14]

Ozanimod (Zeposia®) is a sphingosine-1-phosphate (S1P) receptor modulator approved by the FDA for the treatment of relapsing forms of MS in adults. The mechanism by which S1P modulators exert their therapeutic effects in MS is unknown, but is hypothesized to reduce lymphocyte migration into the central nervous system (CNS) via binding to the S1P-1 receptor subtype.[15] Siponimod (Mayzent®) is indicated for the treatment of adults with relapsing forms of MS, and it is also a S1P receptor modulator.[18] Ponesimod (Ponvory®) is the fourth S1P receptor modulator approved by the FDA for the treatment of relapsing forms of MS in adults.[17] In addition to ponesimod (Ponvory®), there are currently three other S1P modulators approved for RMS, fingolimod (Gilenya®), siponimod (Mayzent®) and ozanimod (Zeposia®).[22,23] The primary difference between agents is their affinity to different S1P receptor subtypes. Fingolimod binds with high affinity to four S1P subtypes (1, 3, 4 and 5), siponimod and ozanimod to two subtypes (1 and 5) and ponesimod to one subtype (1). While binding of S1P-1 is thought to be therapeutic in RMS, binding of S1P-3 is suspected to increase the risk of cardiac adverse events such as bradyarrhythmia and atrioventricular blocks. Because fingolimod binds S1P-3 with high affinity, the risk of cardiac adverse events is increased, particularly after the first dose. As such, first dose monitoring is required and fingolimod is contraindicated in patients with certain preexisting cardiac disease.[4] Ponesimod, siponimod, and ozanimod bind to S1P-3 with very low affinity, although some binding does still occur and thus potential for cardiac adverse events continue to exist. For siponimod and ponesimod, first dose cardiac monitoring is recommended only in higher-risk patients while first-dose monitoring is not required for ozanimod.[1-23] Differences is cardiac adverse events have not been directly compared and potential differences are not well defined. Serious, non-cardiac adverse events that are common among MS Agents (e.g., infections, fetal risks) and S1P receptor modulators (e.g., liver injury, respiratory effects, macular edema, rebound exacerbation after discontinuation, increased risk of malignancy) remain potential issues.[1-23]

Briumvi® (ublituximab-xiiy) is a CD20-directed cytolytic antibody indicated for the treatment of relapsing forms of MS, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive

disease, in adults. Maintenance infusions occur every 24 weeks.[21] Ublituximab-xiiy is the third anti-CD20 inhibitor approved for MS, along with Ocrevus® (ocrelizumab) and Kesimpta® (ofatumumab).[1-23]

The immunomodulatory agents used to treat multiple sclerosis included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Dimethyl fumarate, fingolimod, glatiramer acetate, and teriflunomide is available in a generic formulation. This class was last reviewed in November 2021.

Table 1. Products Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Alemtuzumab	injection	Lemtrada®	none
Dimethyl fumarate	delayed-release capsule	Tecfidera®*	dimethyl fumarate
Diroximel fumarate	delayed-release capsule	Vumerity DR®	none
Fingolimod	capsule, orally disintegrating tablet	Gilenya®*, Tascenso® ODT	none
Glatiramer acetate	injection	Copaxone®*, Glatopa®†	Copaxone®*
Interferon β-1a	injection	Avonex®, Avonex Pen®, Rebif®, Rebif Rebidose®	Avonex®, Rebif®
Interferon β-1b	injection	Betaseron®, Extavia®	Betaseron®
Monomethyl fumarate	delayed-release capsule	Bafiertam DR®	none
Natalizumab	injection	Tysabri®	Tysabri®
Ocrelizumab	injection	Ocrevus®	none
Ofatumumab	injection	Kesimpta®	none
Ozanimod	capsule	Zeposia®	none
Peginterferon β-1a	injection	Plegridy®	none
Ponesimod	tablet	Ponvory®	none
Siponimod	tablet	Mayzent®	none
Teriflunomide	tablet	Aubagio®*	teriflunomide
Ublituximab	injection	Briumvi®	none

PDL=Preferred Drug List
*Generic available in at least one dosage form or strength.
†Glatopa® is a generic equivalent of Copaxone®.

II. Evidence-Based Medicine and Current Treatment Guidelines

Current clinical guidelines are summarized in Table 2.

Table 2. Treatment Guidelines Using the Immunomodulatory Agents used to treat Multiple Sclerosis

Clinical Guideline	Recommendation(s)
American Academy of Neurology: **Evidence-based practice guideline: Disease-modifying Therapies for Adults with Multiple Sclerosis (2018)[29]** (Reaffirmed September 2021)	Starting Disease Modifying Therapy (DMT) • Clinicians should counsel patients just diagnosed with multiple sclerosis (MS) about specific treatment options with DMT at a dedicated treatment visit. • Clinicians must ascertain and incorporate/review preferences in terms of safety, route of administration, lifestyle, cost, efficacy, common side effects, and tolerability in the choice of DMT in patients with MS being considered for DMT. • Clinicians must engage in an ongoing dialogue regarding treatment decisions throughout the course of the disease with patients with MS. • Clinicians should counsel that DMTs are prescribed to reduce relapses and new MRI lesion activity. DMTs are not prescribed for symptom improvement in patients with MS. • Clinicians must counsel people with MS on DMTs to notify the clinicians of new or worsening symptoms. • Clinicians should evaluate readiness or reluctance to initiate DMT and counsel on its importance in patients with MS who are candidates to initiate DMT.

Clinical Guideline	Recommendation(s)
	• Clinicians should counsel about comorbid disease and adverse health behaviors, and potential interactions of the DMT with concomitant medications when patients with MS initiate DMTs. • Clinicians should evaluate barriers to adherence to DMT in patients with MS. • Clinicians should counsel on the importance of adherence to DMT when patients with MS initiate DMTs. • Clinicians should discuss the benefits and risks of DMTs for patients with a single clinical demyelinating event with two or more brain or spinal cord lesions that have imaging characteristics consistent with MS. • After discussing the risks and benefits, clinicians should prescribe DMT to people with a single clinical demyelinating event and two or more brain lesions characteristic of MS who decide they want this therapy. • Clinicians may recommend serial imaging at least annually for the first five years and close follow-up rather than initiating DMT in patients with clinically isolated syndrome (CIS) or relapsing forms of MS not on DMT who have not had relapses in the past two years and who do not have active new MRI lesion activity on recent imaging. • Clinicians should offer DMTs to patients with relapsing forms of MS with recent clinical relapses or MRI activity. • Clinicians should monitor for medication adherence, side effects, tolerability, safety, and effectiveness of the therapy in patients with MS on DMTs. • Clinicians should follow up either annually or according to medication-specific risk evaluation and mitigation strategies in patients with MS on DMT. • Clinicians should monitor patient's reproductive plans and counsel on reproductive risks and on use of birth control while on a DMT in women of childbearing years with MS. • Clinicians should counsel men with MS on their reproductive plans regarding treatment implications before initiating teriflunomide or cyclophosphamide. • Because of the high frequency of severe adverse events, clinicians should not prescribe mitoxantrone to people with MS unless the potential therapeutic benefits greatly outweigh the risks. • Clinicians should prescribe alemtuzumab, fingolimod, or natalizumab for patients with highly active MS. • Clinicians may direct patients with MS who are candidates for DMTs to support programs. • Clinicians may recommend azathioprine or cladribine for people with relapsing forms of MS who do not have access to approved DMTs. • Clinicians may initiate natalizumab treatment in people with MS with positive anti-John Cunningham virus (JCV) antibody indexes above 0.9 only when there is a reasonable chance of benefit compared with the low but serious risk of progressive multifocal leukoencephalopathy (PML). • Clinicians should offer ocrelizumab to people with primary progressive multiple sclerosis (PPMS) who are likely to benefit from this therapy unless there are risks of treatment that outweigh the benefits. <u>Switching DMT</u> • Clinicians should monitor MRI disease activity from the clinical onset of disease to detect the accumulation of new lesions in order to inform treatment decisions in people with MS using DMTs. • Clinicians should recognize that relapses or new MRI-detected lesions may develop after initiation of a DMT and before the treatment becomes effective in patients with MS on DMTs. • Clinicians should discuss switching from one DMT to another in patients who have been on a DMT long enough to take full effect and are adherent to their therapy when a patient has experienced one or more relapses, two or more

Clinical Guideline	Recommendation(s)
	unequivocally new MRI lesions, or increased disability on examination, over a one-year period on a DMT. • Clinicians should evaluate the amount of disease activity, adherence, adverse event profiles, and mechanism of action of DMTs when switching DMTs in patients with breakthrough disease activity during DMT use. • Clinicians should discuss a change to a non-injectable or less frequently injectable DMT in patients who report intolerable discomfort with the injections or in those who report "injection fatigue" on injectable DMTs. • Clinicians should inquire about medication adverse effects with patients with MS who are taking a DMT and attempt to manage these adverse effects, as appropriate. • Clinicians should discuss a medication switch with patients for whom these adverse effects negatively influence adherence. • Clinicians should monitor laboratory abnormalities found on requisite laboratory surveillance (as outlined in the medication's package insert) in patients with MS who are on a DMT. • Clinicians should discuss switching DMT or reducing dose or frequency (where there is data on different doses [e.g., interferons, teriflunomide, azathioprine]) when there are persistent laboratory abnormalities. • Clinicians should counsel people with MS considering natalizumab, fingolimod, rituximab, ocrelizumab, and dimethyl fumarate about the PML risk associated with these agents. • Clinicians should discuss switching to a DMT with a lower risk of PML in patients taking natalizumab who are or become JC virus antibody positive, especially with an index of above 0.9 while on therapy. • Clinicians should counsel that new DMTs without long-term safety data have an undefined risk of malignancy and infection in patients starting or using new DMTs. • If a patient with MS develops a malignancy while on a DMT, clinicians should promptly discuss switching to an alternate DMT, especially for patients on azathioprine, methotrexate, mycophenolate, cyclophosphamide, fingolimod, teriflunomide, alemtuzumab, or dimethyl fumarate. • Patients with serious infections potentially linked to their DMT should switch DMTs (note this does not pertain to management of PML in patients on DMT). • Clinicians should check for natalizumab antibodies in patients who have infusion reactions prior to subsequent infusions, or in patients who experience breakthrough disease activity on natalizumab. • Clinicians should switch DMTs in patients who have persistent natalizumab antibodies. • Physicians must counsel patients considering discontinuation of natalizumab that there is an increased risk of MS relapse or MRI-detected disease activity within six months of discontinuation. • Physicians and patients choosing to switch from natalizumab to fingolimod should initiate treatment within eight to 12 weeks after discontinuation of natalizumab (for reasons other than pregnancy or pregnancy planning) to diminish the return of disease activity. • Clinicians should counsel women to stop their DMT before conception for planned pregnancies unless the risk of MS activity during pregnancy outweighs the risk associated with the specific DMT during pregnancy. • Clinicians should discontinue DMTs during pregnancy if accidental exposure occurs, unless the risk of MS activity during pregnancy outweighs the risk of the specific DMT during pregnancy. • Clinicians should not initiate DMTs during pregnancy unless the risk of MS activity during pregnancy outweighs the risk associated with the specific DMT during pregnancy.

<table>
<tr><th>Clinical Guideline</th><th>Recommendation(s)</th></tr>
<tr><td></td><td>
<u>Stopping DMT</u>

In patients with relapsing remitting MS who are stable on DMT and wish to discontinue therapy, clinicians should counsel patients regarding the need for ongoing follow-up and periodic reevaluation of the decision to discontinue DMT.
Clinicians should advocate that people with MS who are stable (that is, no relapses, no disability progression, stable imaging) on DMT should continue on their current DMT unless the patient and physician decide a trial off therapy is warranted.
Clinicians should assess the likelihood of future relapse in individuals with secondary progressive (SP) MS by assessing patient age, disease duration, relapse history, and MRI-detected activity (e.g., frequency, severity, time since most recent relapse or gadolinium enhancing lesion).
Clinicians may advise discontinuation of DMT in people with SPMS who do not have ongoing relapses (or gadolinium-enhanced lesions on MRI activity) and have not been ambulatory (expanded disability status scale 7 or greater) for at least two years.
Clinician should review the risk of continuing DMTs vs the risk of stopping DMTs in patients with CIS using DMTs who have not been diagnosed with MS.

</td></tr>
<tr><td>American Academy of Neurology:
Comprehensive systematic review summary: Disease-modifying therapies for adults with multiple sclerosis (2018)[30]

(Reaffirmed September 2021)</td><td>
<u>In people with relapsing-remitting multiple sclerosis (RRMS), are disease-modifying therapies (DMTs) superior to placebo or other DMTs as measured by annualized relapse rates and the relative risk of relapse at two years?</u>
<table>
<tr><th colspan="3">Reduction of the annualized relapse rate</th></tr>
<tr><th>Confidence strength</th><th>Compared with placebo</th><th>Compared with other DMTs</th></tr>
<tr><td rowspan="8">High</td><td>Cladribine more effective</td><td>Alemtuzumab more effective than IFN-beta-1a SubQ 3x/week</td></tr>
<tr><td>Daclizumab more effective</td><td>Azathioprine more effective than beta-interferons</td></tr>
<tr><td>Dimethyl fumarate more effective</td><td>Fingolimod more effective than IFN-beta-1a once weekly</td></tr>
<tr><td>Glatiramer acetate more effective</td><td>Ocrelizumab more effective than IFN-beta-1a SubQ 3x/week</td></tr>
<tr><td>Natalizumab more effective</td><td></td></tr>
<tr><td>Peg-IFN more effective</td><td></td></tr>
<tr><td>Teriflunomide more effective</td><td></td></tr>
<tr><td rowspan="5">Moderate</td><td>Azathioprine probably more effective</td><td></td></tr>
<tr><td>IFN-beta-1a IM once weekly probably more effective</td><td></td></tr>
<tr><td>IFN-beta-1b SubQ alternate day probably more effective</td><td></td></tr>
<tr><td>Pulsed corticosteroids added to IFN-beta-1a probably more effective</td><td></td></tr>
<tr><td></td><td>Daclizumab probably more effective than IFN-beta-1a once weekly</td></tr>
<tr><td>Low</td><td>Cyclophosphamide possibly more effective</td><td></td></tr>
<tr><td rowspan="4">Very low</td><td>Azathioprine insufficient to support or refute</td><td></td></tr>
<tr><td>Immunoglobulins insufficient to support or refute</td><td></td></tr>
<tr><td>Pulsed corticosteroids insufficient to support or refute</td><td></td></tr>
<tr><td>Rituximab insufficient to support or refute</td><td></td></tr>
</table>
</td></tr>
</table>

Clinical Guideline	Recommendation(s)

Reduction of risk of relapse at two years		
Confidence strength	Compared with placebo	Compared with other DMTs
High	Daclizumab more effective (outcome measured at one year)	Alemtuzumab more effective than IFN-beta-1a SubQ 3x/week
	Dimethyl fumarate more effective	
	Fingolimod more effective	
	Immunoglobulins more effective	
	IFN-beta-1a IM once weekly more effective	
	IFN-beta-1a SubQ 3x/week more effective	
	Mitoxantrone more effective	
	Natalizumab more effective	
	Peg-IFN more effective (outcome measured at one year)	
Moderate	Cladribine probably more effective	Daclizumab probably more effective than IFN-beta-1a IM once weekly (outcome measured at three years)
	Glatiramer acetate probably more effective	
	IFN-beta-1b SubQ alternate day probably more effective	
	Pulsed corticosteroids added to IFN-beta-1a probably more effective	
	Rituximab probably more effective (outcome measured at one year)	
	Teriflunomide probably more effective	
Low		Mycophenolate mofetil plus IFN-beta-1a IM weekly possibly no more effective than IFN plus placebo (outcome measured at one year)
		Complex nonbiologic generic glatiramer acetate (Glatopa) possibly no more effective than glatiramer acetate (Copaxone)
		IFN-beta-1a IM once weekly possibly no more effective than glatiramer acetate (Copaxone)
		IFN-beta-1a SubQ 3x/week possibly no more effective than glatiramer acetate (Copaxone)
Very low		IFN-beta-1b SubQ alternate day possibly no more effective than glatiramer acetate (Copaxone)
	Azathioprine insufficient to support or refute	
	Cyclophosphamide insufficient to support or refute (outcome measured at 12 months)	
	Methotrexate insufficient to support or refute	
	Pulsed corticosteroids insufficient to support or refute	

Clinical Guideline	Recommendation(s)
Multiple Sclerosis Coalition: **The Use of Disease-Modifying Therapies in Multiple Sclerosis: Principles and Current Evidence (2019)**[31]	Treatment Considerations • Initiation of treatment with an FDA-approved disease-modifying therapy (DMT) is recommended: o As soon as possible following a diagnosis of relapsing MS, regardless of the person's age Relapsing MS includes: ▪ clinically isolated syndrome (CIS): People with a first clinical event and MRI features consistent with MS in whom other possible causes have been excluded. ▪ relapsing-remitting MS. ▪ active secondary progressive MS with clinical relapses of inflammatory activity on MRI. o For individuals with primary progressive multiple sclerosis, with an agent approved for this phenotype. • Clinicians should consider prescribing a high efficacy medication such as alemtuzumab, cladribine, fingolimod, ocrelizumab, or natalizumab for newly-diagnosed individuals with highly active MS. • Clinicians should also consider prescribing a high efficacy medication for individuals who have breakthrough activity on another DMT, regardless of the number of previously used agents. • Treatment with a given DMT should be continued indefinitely unless any of the following occur (in which case an alternative DMT should be considered): o Sub-optimal treatment response as determined by the individual and his or her treating clinician. o Intolerable side effects, including significant laboratory abnormalities. o Inadequate adherence to the treatment regimen. o Availability of a more appropriate treatment option. o The healthcare provider and patient determine that the benefits no longer outweigh the risks. • Movement from one DMT to another should occur only for medically appropriate reasons as determined by the treating clinician and patient. • When evidence of additional clinical or MRI activity while on consistent treatment suggests a sub-optimal response, an alternative regimen (e.g., different mechanism of action) should be considered to optimize therapeutic benefit. • The factors affecting choice of therapy at any point in the disease course are complex and most appropriately analyzed and addressed through a shared decision-making process between the individual and his or her treating clinician. Neither an arbitrary restriction of choice nor a mandatory escalation therapy approach is supported by data. Access Considerations • Due to significant variability in the MS population, people with MS and their treating clinicians require access to the full range of treatment options for several reasons: o MS clinical phenotypes may respond differently to different disease-modifying therapies. o Different mechanisms of action allow for treatment change in the event of a sub-optimal response. o Potential contraindications limit options for some individuals. o Risk tolerance varies among people with MS and their treating clinicians. o Route of delivery, frequency of dosing, and side effects may affect adherence and quality of life.

Clinical Guideline	Recommendation(s)
	○ Individual differences related to tolerability and adherence may necessitate access to different medications within the same class. ○ Pregnancy and breastfeeding limit the available options. • Individuals' access to treatment should not be limited by their frequency of relapses, level of disability, or personal characteristics such as age, sex or ethnicity. • Absence of relapses while on treatment is a characteristic of treatment effectiveness and should not be considered a justification for discontinuation of treatment. • Treatment should not be withheld to allow for determination of coverage by payers as this puts the patient at risk for recurrent disease activity.
Association of British Neurologists: **Revised Guidelines for Prescribing in Disease-Modifying Treatments for Multiple Sclerosis (2015)**[26]	<u>General Statements</u> • All of the licensed disease-modifying treatments for multiple sclerosis (MS)- β-interferons, glatiramer acetate, fingolimod, teriflunomide, dimethyl fumarate, natalizumab and alemtuzumab- reduce relapse rate and magnetic resonance imaging (MRI) lesion accumulation in relapsing–remitting MS, to varying extents. • Reducing relapse rate and MRI lesion accumulation data shows only a weak correlation between long-term disability and relapse frequency. • There is a consensus that none of the currently available disease-modifying therapies significantly modifies progressively increasing disability that is unrelated to relapses (progressive non-relapsing MS). • Long-term therapy with disease-modifying agents has not established the following: ○ Reduces the accumulation of disability by whatever mechanism. ○ Prevents or slows entry to the secondary progressive stage of the disease. • Immunotherapies appear particularly helpful when given early to people with active relapsing–remitting disease, before there is fixed disability or secondary progression. • Disease-modifying treatment should be started and supervised by an MS specialist neurologist. • When considering potential disease-modifying treatment options, it is important that patients and neurologists fully appreciate the risk and benefit of drugs, and of leaving the disease untreated. • Provide patients accurate information: ○ Expectations of treatment, including the evidence that disease-modifying treatment efficacy can be only partial, moderate and not curative. ○ Risk as well as expected benefit of treatment. ○ Monitoring requirements of treatment. • Discuss work, family and other factors that are personally important to them and take their views into account when making the treatment selection. <u>Initial Treatment Recommendations: Relapsing–Remitting MS (RRMS)</u> • Licensed agents are broadly divided into two classes: ○ Drugs of moderate efficacy (Category 1): ▪ β-interferons (including pegylated β-interferon) ▪ glatiramer acetate ▪ teriflunomide ▪ dimethyl fumarate ▪ fingolimod ○ Drugs of high efficacy (Category 2): ▪ alemtuzumab ▪ natalizumab

Clinical Guideline	Recommendation(s)

	• Consider starting treatment with disease-modifying agents in patients with "active" RRMS
	• Activity may be established on radiological/clinical grounds:
	• Active RRMS:
	  o Consider treatment in patients:
	  ▪ who have had two or more clinical relapses in the previous two years
	  ▪ who have had a single recent relapse and/or on radiological grounds, including both patients newly diagnosed according to the 2010 'MacDonald criteria'
	  ▪ with established disease who develop new MRI lesions without clinical relapse
	  o Usually start with a Category 1 drug.
	  ▪ Dimethyl fumarate and fingolimod appear to be most effective. β-Interferon, teriflunomide and glatiramer acetate appear to be similar (broadly), but are probably a little less effective.
	  ▪ Dimethyl fumarate and fingolimod have the additional benefit of being an oral agent.
	  ▪ β-interferons and glatiramer acetate have been used extensively for decades in MS, and there is a wealth of clinical experience confirming their general safety.
	• More Active RRMS
	  o Patients may be classified as having more active MS by frequent clinical relapses and/or MRI activity either when untreated or while on a Category 1 drug.
	  o The formal criteria for high-disease activity despite interferon-β or glatiramer requires one relapse in the previous year on interferon-β and either: ≥1 gadolinium-enhancing MRI lesions or at least nine T2-hyperintensive lesions on cranial MRI
	  o It is recommended to begin a Category 2 agent in patients with high disease activity: natalizumab or alemtuzumab.
	  ▪ Indirect comparison suggests that alemtuzumab and natalizumab have similar efficacy.
	  ▪ Appropriate where individuals and their neurologists are most concerned to achieve high efficacy, despite the more complex safety profile compared to Category 1 drugs.
	  o It may be appropriate to change from one Category 1 agent to another Category 1 agent:
	  ▪ Patients with infrequent or occasional minor relapses
	  ▪ Patient may be risk-averse to safety profile of Category 2 agents
	  ▪ Consider the increased potency of fingolimod and dimethyl fumarate
	
	<u>People aged under 18 years</u>
	• Minors aged between 16 and 18 years should be treated according to the above guidelines.
	• Children with MS aged <16 should be treated in specialist clinics, preferably under a combined team including adult and pediatric neurologists with a particular interest in MS.
	
	<u>Primary or secondary progressive MS</u>
	• None of the current disease-modifying treatments is recommended in non-relapsing secondary progressive MS or in primary progressive MS.

Clinical Guideline	Recommendation(s)
	• Some people with relapsing secondary progressive MS, whose relapses are their main cause of increasing disability, may benefit from disease-modifying treatment. <u>Recommendations for Stopping Disease-Modifying Treatment</u> • Mandatory stopping criteria that applies to all patients is not appropriate • The difficulty of stopping treatment in people with progressive disease is compounded by the absence of alternative options for disease modification • Clinicians should consider stopping disease-modifying treatment in the following scenarios: o Significant side effects specific to any individual agent o Development of non-relapsing secondary progressive MS o Pregnancy • If significant side effects develop to a specific agent, that agent should be discontinued and an alternative should be considered • Disease-modifying treatments should normally be stopped during pregnancy, as stated in the summary of product characteristics. Known risks and available information vary by agent. o Given the increased risk of relapse in the puerperium, treatment should be restarted early after delivery, depending on discussions concerning breast feeding.

III. Indications

The FDA-approved indications for immunomodulatory agents used to treat multiple sclerosis are noted in Table 3.

Table 3. FDA-Approved Indications for the Immunomodulatory Agents used to treat Multiple Sclerosis[1-23]

Generic Name	Treatment of patients with relapsing forms of multiple sclerosis	Treatment of patients with primary progressive forms of multiple sclerosis
Alemtuzumab	✔ *	
Dimethyl fumarate	✔	
Diroximel fumarate	✔	
Fingolimod	✔	
Glatiramer acetate	✔	
Interferon β-1a	✔	
Interferon β-1b	✔	
Monomethyl fumarate	✔	
Natalizumab§	✔	
Ocrelizumab	✔	✔
Ofatumumab	✔	
Ozanimod†	✔	
Peginterferon β-1a	✔	
Ponesimod	✔	
Siponimod	✔	
Teriflunomide	✔	
Ublituximab	✔	

*Because of its safety profile, the use of alemtuzumab should generally be reserved for patients who have had an inadequate response to two or more drugs indicated for the treatment of MS.
§Tysabri® is also indicated for inducing and maintaining clinical response and remission in adult patients with moderately to severely active Crohn's disease with evidence of inflammation who have had an inadequate response to, or are unable to tolerate, conventional Crohn's disease therapies and inhibitors of TNF-α. This indication is outside the scope of this review.
†Zeposia® is also indicated for moderately to severely active ulcerative colitis in adults. This indication is outside the scope of this review.

IV. Pharmacokinetics

The pharmacokinetic parameters of the immunomodulatory agents used to treat multiple sclerosis are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Immunomodulatory Agents used to treat Multiple Sclerosis[22]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life
Alemtuzumab	Not reported	Not reported	Not reported	Not reported	2 weeks
Dimethyl fumarate	Not reported	Active metabolite: 27 to 45	GI tract, blood, and tissues (extensive)	Renal (16), Feces (1), Respiratory (60)	Active metabolite: 1 hour
Diroximel fumarate	Not reported	Active metabolite: 27 to 45	GI tract, blood, and tissues (extensive)	Renal (58 to 63), Respiratory (primary)	Active metabolite: 1 hour
Fingolimod	93	>99.7	Liver (extensive)	Renal (81), Feces (<2.5)	6 to 9 days
Glatiramer acetate	Not reported	Not reported	Local hydrolysis	Not reported	Not reported
Interferon β-1a	Not reported	Not reported	Not reported	Not reported	IM: 19 hours SQ: 69 hours
Interferon β-1b	50	Not reported	Not reported	Renal (minimal)	Not reported
Monomethyl fumarate	Not reported	Not reported	Not reported	Renal (16), Feces (1), Respiratory (60)	0.5 hour
Natalizumab	Not reported	Not reported	Not reported	Not reported	11 days
Ocrelizumab	Not reported	Not reported	Not reported	Not reported	26 days
Ofatumumab	Not reported	Not reported	Proteolytic enzymes (extensive)	Not reported	16 days
Ozanimod	Not reported	98.2	Not reported	Renal (26), Feces (37)	21 hours
Peginterferon β-1a	Not reported	Not reported	Catabolism	Renal (extensive)	78 hours
Ponesimod	84	>99	Liver (extensive)	Renal (10 to 18), Feces (57 to 80)	33 hours
Siponimod	84	>99	Liver (extensive)	Feces (some), Bile (some)	30 hours
Teriflunomide	Not reported	>99	Hydrolysis	Renal (22.6), Feces (37.5)	18 to 19 days
Ublituximab	Not reported	Not reported	Enzymatic degradation	Not reported	22 days

V. Drug Interactions

Major drug interactions with the immunomodulatory agents used to treat multiple sclerosis are listed in Table 5.

Due to their potential to cause hepatic injury, patients must be monitored when interferon β (IFNβ) is administered in combination with another agent that can cause hepatic injury, or when new agents are added to a regimen of a patient already receiving IFNβ.[22-23]

Table 5. Major Drug Interactions with the Immunomodulatory Agents used to treat Multiple Sclerosis[1-22]

Generic Name(s)	Interaction	Mechanism
Alemtuzumab	Ozanimod, ponesimod, siponimod	Concurrent use may result in additive immunosuppressive effects during therapy and for weeks following administration.
Alemtuzumab	Tofacitinib	Concurrent use may result in increased risk of immunosuppression.
Biological response modifiers (alemtuzumab, interferon β, fingolimod, ocrelizumab, ofatumumab, teriflunomide, ublituximab)	Live vaccines	Concurrent use of may result in an increased risk of secondary transmission of infection and reduced effectiveness of immunization.
Fingolimod	Class Ia antiarrhythmic agents (flecainide, mexiletine, procainamide)	Concurrent use of fingolimod and Class Ia antiarrhythmic agents may result in increased risk of developing bradycardia or heart block.
Fingolimod	Class III antiarrhythmic agents (amiodarone, dronedarone, sotalol)	Concurrent use of fingolimod and Class III antiarrhythmic agents may result in increased risk of developing bradycardia or heart block.
Fingolimod	Drugs that slow heart rate (beta-blockers, diltiazem, verapamil, digoxin)	Initiation of fingolimod is associated with slowing of the heart rate and experience is limited when using drugs that slow heart rate. If patients cannot be switched, they should have overnight electrocardiogram monitoring after the first dose.
Fingolimod	Ketoconazole	Concomitant administration may result in an increase in fingolimod exposure and a greater risk of adverse events.
Fingolimod	QT prolonging drugs (citalopram, chlorpromazine, haloperidol, methadone, erythromycin)	Concomitant use may result in increased risk of QT-interval prolongation.
Ozanimod	Monoamine oxidase (MAO) inhibitors	Co-administration of ozanimod with MAO-B inhibitors may decrease exposure of the active metabolites of ozanimod. In addition, metabolites of ozanimod may inhibit MAO. The potential for a clinical interaction with MAO inhibitors has not been studied; however, the increased risk of nonselective MAO inhibition may lead to a hypertensive crisis.
Ozanimod	Strong CYP2C8 inhibitors	Co-administration of ozanimod with strong CYP2C8 inhibitors increases the exposure of the active metabolites of ozanimod, which may increase the risk of ozanimod adverse reactions.
Ozanimod	Strong CYP2C8 inducers	Co-administration of ozanimod with strong CYP2C8 inducers (e.g., rifampin) reduces the exposure of the major active metabolites of ozanimod, which may decrease the efficacy of ozanimod.
Ozanimod, ponesimod, siponimod	Anti-neoplastic, immune-modulating, or non-corticosteroid	Caution should be used during concomitant administration because of the risk of additive immune effects during such therapy and in the weeks following administration.

Generic Name(s)	Interaction	Mechanism
	immunosuppressive therapies	
Ozanimod, ponesimod, siponimod	Anti-arrhythmic drugs, QT prolonging drugs, drugs that may decrease heart rate	Because of the potential additive effects on heart rate, treatment with ozanimod/ponesimod should generally not be initiated in patients who are concurrently treated with QT prolonging drugs with known arrhythmogenic properties. If treatment initiation is considered in patients on QT prolonging drugs, advice from a cardiologist should be sought.
Ozanimod	Adrenergic and serotonergic drugs	Because an active metabolite of ozanimod inhibits MAO-B in vitro, there is a potential for serious adverse reactions, including hypertensive crisis with co-administration of ozanimod with drugs or over-the-counter medications that can increase norepinephrine or serotonin [e.g., opioid drugs, selective serotonin reuptake inhibitors, selective norepinephrine reuptake inhibitors, tricyclics, tyramine].
Ozanimod	Combination beta blocker and calcium channel blocker	Treatment with ozanimod should generally not be initiated in patients who are concurrently treated with both a heart rate lowering calcium channel blocker (e.g., verapamil, diltiazem) and beta blocker. If treatment initiation with ozanimod is considered in patients on both a heart rate lowering calcium channel blocker and beta blocker, advice from a cardiologist should be sought.
Ponesimod	Strong CYP3A4 and UGT1A1 inducers	In vitro assessments and limited clinical data indicated that concomitant use of strong CYP3A4 and UGT1A1 inducers (e.g., rifampin, phenytoin, carbamazepine) may decrease the systemic exposure of ponesimod. It is unclear whether this decrease in ponesimod systemic exposure would be considered of clinical relevance. Coadministration of PONVORY with strong CYP3A4 and UGT1A1 inducers is not recommended.
Siponimod	CYP2C9 and CYP3A4 inhibitors	Because of a significant increase in exposure to siponimod, concomitant use of siponimod and drugs that cause moderate CYP2C9 and moderate or strong CYP3A4 inhibition is not recommended. This concomitant drug regimen can consist of a moderate CYP2C9/CYP3A4 dual inhibitor (e.g., fluconazole) or a moderate CYP2C9 inhibitor in combination with a separate - moderate or strong CYP3A4 inhibitor. Caution should be exercised for concomitant use of siponimod with moderate CYP2C9 inhibitors.
Siponimod	CYP2C9 and CYP3A4 inducers	Because of a significant decrease in siponimod exposure, concomitant use of siponimod and drugs that cause moderate CYP2C9 and strong CYP3A4 induction is not recommended for all patients. This concomitant drug regimen can consist of moderate CYP2C9/strong CYP3A4 dual inducer (e.g., rifampin or carbamazepine) or a moderate CYP2C9 inducer in combination with a separate strong CYP3A4 inducer. Caution should be exercised for concomitant use of siponimod with moderate CYP2C9 inducers. Concomitant use of siponimod and moderate (e.g., modafinil, efavirenz) or strong CYP3A4 inducers is not recommended for patients with CYP2C9*1/*3 and *2/*3 genotype.
Teriflunomide	Breast Cancer Resistant Protein (BCRP) inhibitors (cyclosporine, eltrombopag, gefitinib)	BCPR inhibitors may increase exposure to teriflunomide and increase risk of adverse events.

Generic Name(s)	Interaction	Mechanism
Teriflunomide	CYP2C8 substrates (repaglinide, paclitaxel, pioglitazone)	Teriflunomide may be an inhibitor of CYP2C8, resulting in increased exposure of CYP2C8 substrates. Patient monitoring is recommended.
Teriflunomide	CYP1A2 substrates (duloxetine, alosetron, theophylline, tizanidine)	Teriflunomide may be a weak inducer of CYP1A2, resulting in reduced exposure of CYP1A2 substrates. Monitor for decreased efficacy of CYP1A2 substrates.
Teriflunomide	Oral contraceptives	Teriflunomide may increase exposure and risk of estrogen and progestin-related adverse effects. Consider type and dose of oral contraceptive.

VI. Adverse Drug Events

The most common adverse drug events reported with the immunomodulatory agents used to treat multiple sclerosis are listed in Tables 6 and 7. Boxed warnings are in Tables 8 through 10.

Table 6. Adverse Drug Events (%) Reported with the Immunomodulatory Agents used to treat Multiple Sclerosis, A-M[1-23]

Adverse Event	Alemtuzumab	Dimethyl Fumarate	Diroximel fumarate	Fingolimod	Glatiramer Acetate	Interferon β-1b*	Interferon β-1a (Rebif®)	Interferon β-1b (Extavia®)	Monomethyl fumarate
Cardiovascular									
Atrioventricular block	-	-	-	0.1[§]	-	-	-	-	-
Bradycardia	-	-	-	3	-	-	-	-	-
Chest pain	-	-	-	-	2 to 13	9	6 to 8	5	-
Dissection of artery	✔	-	-	-	-	-	-	-	-
Hypertension	-	-	-	6	-	6	-	-	-
Palpitations	-	-	-	-	9	-	-	-	-
Tachycardia	-	-	-	-	5	-	-	-	-
Vasodilatation	-	-	-	-	3 to 20	-	-	2	-
Central Nervous System									
Convulsions	-	-	-	-	-	-	4 to 5	-	-
Dizziness	10	-	-	7	-	-	-	14	-
Fatigue	18	-	-	-	-	-	33 to 41	-	-
Fever	29	-	-	-	-	31	20 to 28	31	-
Headache	52	-	-	25	-	50	65 to 70	50	-
Malaise	-	-	-	-	-	6	4 to 5	-	-
Migraine	-	-	-	5	4	-	-	5	-
Incoordination	16	-	-	-	-	17	4 to 5	-	-
Insomnia	-	-	-	-	-	21	-	21	-
Paresthesia	10	-	-	5	-	-	-	-	-
Pyrexia	-	-	-	-	6	-	-	-	-
Seizure	-	-	-	-	-	-	4 to 5	-	-
Somnolence	-	-	-	-	-	-	4 to 5	-	-
Speech disorder	-	-	-	-	2	-	-	-	-
Syncope	-	-	-	-	3	-	-	-	-
Tremor	-	-	-	-	4	-	-	-	-
Endocrine									
Diabetes mellitus type 1	0.1	-	-	-	-	-	-	-	-

Adverse Event	Alemtuzumab	Dimethyl Fumarate	Diroximel fumarate	Fingolimod	Glatiramer Acetate	Interferon β-1b*	Interferon β-1a (Rebif®)	Interferon β-1b (Extavia®)	Monomethyl fumarate
Thyroid cancer	0.3	-	-	-	-	-	-	-	-
Thyroid disorder	13 to 40.7	-	-	-	-	-	4 to 6	-	-
Gastrointestinal									
Abdominal pain	10	18	18	11	-	16	20 to 22	8	18
Diarrhea	12	14	14	13	-	-	-	-	14
Dry mouth	-	-	-	-	-	-	1 to 5	-	-
Dyspepsia	-	5	5	-	-	-	-	-	5
Nausea	21	12	12	-	2 to 15	-	23	23	12
Vomiting	10	9	9	-	7	-	-	-	9
Hematologic									
Anemia	-	-	-	-	-	-	3 to 5	4	-
Hypertriglyceridemia	-	-	-	3	-	-	-	-	-
Injection site ecchymosis	-	-	-	-	-	-	-	6	-
Leukopenia	-	-	-	3	-	10 to 18	28 to 36	10 to 18	-
Lymphadenopathy	-	-	-	-	7	6	11 to 12	-	-
Lymphomas	-	-	-	✔ ‖	-	-	-	-	-
Lymphopenia	-	2 to 6	2 to 6	7	-	86	-	86	2 to 6
Neutropenia	✔	-	-	-	-	13	-	-	-
Thrombocytopenia	-	-	-	-	-	-	2 to 8	-	-
Hepatic									
Abnormal hepatic function	-	-	-	-	-	-	4 to 9	-	-
Alanine aminotransferase liver enzymes increased	-	-	-	14	-	12	20 to 27	-	-
Aspartate aminotransferase liver enzymes increased	-	4	4	14	-	4	10 to 17	-	4
Autoimmune hepatitis	✔	-	-	-	-	-	-	-	-
Bilirubinemia	-	-	-	-	-	-	2 to 3	-	-
Gamma-glutamyl transpeptidase liver enzymes increased	-	-	-	5	-	-	-	-	-
Infections									-
Gastroenteritis	-	-	-	5	6	-	-	-	-
Herpes viral infection	-	-	-	9	-	-	-	-	-
Human papilloma virus infection	2	-	-	-	-	-	-	-	-
Influenza-like symptoms	-	-	-	11	3 to 14	57	56 to 59	49	-

Adverse Event	Alemtuzumab	Dimethyl Fumarate	Diroximel fumarate	Fingolimod	Glatiramer Acetate	Interferon β-1b*	Interferon β-1a (Rebif®)	Interferon β-1b (Extavia®)	Monomethyl fumarate
Nasopharyngitis	25	-	-	-	-	-	-	-	-
Serious infection	-	-	-	2.3	-	-	-	-	-
Sinusitis	-	-	-	-	-	-	14	-	-
Tinea infections	-	-	-	4	-	-	-	-	-
Upper respiratory tract infection	16	-	-	-	-	-	14	14	-
Vaginal candidiasis	-	-	-	-	4	-	-	-	-
Musculoskeletal									
Arthralgia or myalgia	12	-	-	-	24	23	25 to 29	9 to 29	-
Asthenia	-	-	-	3	41	53	24	53	-
Back pain	12	-	-	10	12	-	23 to 25	-	-
Chills	-	-	-	-	3	21	-	-	-
Hypertonia	-	-	-	-	22	40	6 to 7	-	-
Pain	-	-	-	-	20	42	23	42	-
Pain in limb	12	-	-	10	-	-	-	-	-
Shivering	-	-	-	-	-	21	19	21	-
Skeletal pain	-	-	-	-	-	-	10 to 15	-	-
Ophthalmic									
Abnormal vision	-	-	-	-	-	-	7 to 13	-	-
Blurred vision	-	-	-	4	-	-	-	-	-
Diplopia	-	-	-	-	3	-	-	-	-
Eye disorder	-	-	-	-	3	-	-	4	-
Eye pain	-	-	-	3	-	-	-	-	-
Macular retinal edema	-	-	-	0.5 to 1.5	-	-	-	-	-
Thyroid eye disease	1	-	-	-	-	-	-	-	-
Xerophthalmia	-	-	-	-	-	-	1 to 3	-	-
Psychiatric									
Anxiety	-	-	-	-	13	-	-	-	-
Depression	-	-	-	8	-	-	18	18	-
Nervousness	-	-	-	-	2	-	-	-	-
Suicidal behavior or ideation	0.6	-	-	-	-	-	-	-	-
Respiratory									
Bronchitis	-	-	-	8	6	-	-	8	-
Cough	-	-	-	12	6	-	-	-	-
Dyspnea	-	-	-	8	3 to 14	6	-	-	-

Adverse Event	Alemtuzumab	Dimethyl Fumarate	Diroximel fumarate	Fingolimod	Glatiramer Acetate	Interferon β-1b*	Interferon β-1a (Rebif®)	Interferon β-1b (Extavia®)	Monomethyl fumarate
Laryngospasm	-	-	-	-	2	-	-	-	-
Sinusitis	11	-	-	11	7	-	-	14	-
Throat Pain	11	-	-	-	-	-	-	-	-
Skin and Subcutaneous Tissue									
Alopecia	-	-	-	4	-	-	-	4	-
Basal cell carcinoma	-	-	-	2	-	-	-	-	-
Eczema	-	-	-	3	-	-	-	-	-
Edema	-	-	-	-	8	-	-	-	-
Erythema	-	5	5	-	-	-	-	-	5
Flushing	10	40	40	-	-	-	-	-	40
Hyperhidrosis	-	-	-	-	7	-	-	-	-
Hypersensitivity	-	-	-	-	3	-	-	-	-
Injection site necrosis	-	-	-	-	-	4	1 to 3	4 to 4.7	-
Injection site reactions	-	-	-	-	4 to 64	78	89 to 92	43.6 to 78	-
Malignant melanoma	0.3	-	-	0.7	-	-	-	-	-
Pruritus	14	8	8	3	5	-	-	-	8
Rash	53	8	8	-	19	21	4 to 7	21	8
Skin disorder	-	-	-	-	3	10	-	-	-
Urticaria	16	-	-	-	3	-	-	-	-
Vitiligo	0.3	-	-	-	-	-	-	-	-
Urogenital									
Albumin urine present	-	6	6	-	-	-	-	-	6
Impotence	-	-	-	-	-	8	-	-	-
Metrorrhagia	-	-	-	-	-	9	-	-	-
Micturition urgency	-	-	-	-	5	-	2 to 7	-	-
Urinary incontinence	-	-	-	-	-	-	2 to 4	-	-
Urinary tract infection	1 to 9	-	-	-	-	-	17	17	-
Urine constituents abnormal	-	-	-	-	-	-	-	3	-
Infusion reaction	92	-	-	-	-	-	-	-	-

✔ Percent not specified.
- Event not reported.
* Betaseron®, Extavia®
§ Initiation of fingolimod treatment has resulted in transient atrioventricular (AV) conduction delays. In clinical trials, first degree AV block (prolonged PR interval on electrocardiogram) following the first dose was reported in 0.1% of patients receiving fingolimod 0.5 mg, but in no patient receiving placebo. Second degree AV block following the first dose was also identified in 0.1% of patients receiving fingolimod 0.5 mg but in no patient receiving placebo.

‖Cases of lymphoma (cutaneous T-cell lymphoproliferative disorders or diffuse B-cell lymphoma) were reported in premarketing clinical trials in multiple sclerosis patients receiving fingolimod at, or above, the recommended dose of 0.5 mg. Based on the small number of cases and short duration of exposure, the relationship to fingolimod remains uncertain.

Table 7. Adverse Drug Events (%) Reported with the Immunomodulatory Agents used to treat Multiple Sclerosis, N-Z[1-23]

Adverse Event	Natalizumab	Ocrelizumab	Ofatumumab	Ozanimod	Peginterferon β-1a	Ponesimod	Siponimod	Teriflunomide	Ublituximab
Cardiovascular									
Atrioventricular block	-	-	-	-	-	3	5	-	-
Bradycardia	-	-	-	-	-	≤6	4 to 6	-	-
Chest pain	5	-	-	-	-	2	-	-	-
Hypertension	-	-	-	4	-	10	13	4	-
Orthostatic hypotension	-	-	-	4	-	-	-	-	-
Palpitations	-	-		-	-	-	-	2 to 3	-
Peripheral edema	-	-	-	-	-	≥2	8	-	-
Central Nervous System									
Burning sensation	-	-	-	-	-	-	-	2 to 3	-
Dizziness	-	-	-	-	-	5	7	-	-
Drowsiness	-	-	-	-	-	3	-	-	-
Falling	-	-	-	-	-	-	11	-	-
Fatigue	27	-	-	-	-	≥2	-	-	5
Fever	-	-	-	-	45	-	-	-	-
Headache	32 to 38	-	13	-	44	-	15	16 to 18	-
Migraine	-	-	-	-	-	≥2	-	-	-
Insomnia	-	-	-	-	-	≥2	-	-	6
Neuropathy	-	-	-	-	-	-	-	1.4 to 1.9	-
Paresthesia	-	-	-	-	-	-	-	9 to 10	-
Pyrexia	-	-	-	-	45	2	-	-	-
Sciatica	-	-	-	-	-	-	-	1 to 3	-
Seizure	-	-	-	-	-	1	2	-	-
Somnolence	2	-	-	-	-	-	-	-	-
Tremor	-	-	-	-	-	-	<5	-	-
Vertigo	6	-	-	-	-	2	-	-	-
Weight decreased	2	-	-	-	-	-	-	2 to 3	-
Weight increased	2	-	-	-	-	-	-	-	-
Gastrointestinal									
Abdominal pain	11	-	-	2	-	-	-	5 to 6	-
Diarrhea	10	6	-	-	-	-	6	13 to 14	-

Adverse Event	Natalizumab	Ocrelizumab	Ofatumumab	Ozanimod	Peginterferon β-1a	Ponesimod	Siponimod	Teriflunomide	Ublituximab
Dry mouth	-	-	-	-	-	≥2	-	-	-
Dyspepsia	-	-	-	-	-	≥2	-	-	-
Distension	-	-	-	-	-	-	-	1 to 2	-
Gastroenteritis	11	-	-	-	-	-	-	-	-
Nausea	17	-	-	-	9	-	7	8 to 11	-
Toothache	-	-	-	-	-	-	-	4	-
Vomiting	-	-	-	-	5	-	-	-	-
Hematologic									
C-reactive protein increased	-	-	-	-	-	2	-	-	-
Decreased serum immunoglobulins	-	-	6 to 8	-	-	-	-	-	2 to 21
Leukopenia	-	-	-	-	-	-	-	1 to 2	-
Lymphocytopenia	-	-	-	3	-	<2	<5	1 to 3	-
Neutropenia	-	-	-	-	-	-	-	4 to 16	15
Hepatic									
Abnormal hepatic function	5	-	-	-	-	-	-	-	-
Alanine aminotransferase liver enzymes increased	-	-	-	2 to 6	-	3 to 17	<1 to 6	12 to 14	-
Aspartate aminotransferase liver enzymes increased	-	-	-	-	-	-	1	2 to 3	-
Bilirubinemia	-	-	-	-	-	-	<10	-	-
Gamma-glutamyltransferase increased	-	-	-	-	-	-	-	3 to 5	-
Infections									
Bronchitis	-	-	-	-	-	-	-	5 to 8	-
Cystitis	-	-	-	-	-	-	-	2 to 4	-
Gastroenteritis	11	-	-	-	-	-	-	2 to 4	-
Herpes viral infection	8	6	-	-	-	5	5	2 to 4	6
Infection	-	-	-	-	-	-	-	-	56
Infection of skin and/or subcutaneous tissue	-	14	-	-	-	-	-	-	-
Influenza-like symptoms	-	-	-	-	47	-	-	9 to 12	-
Lower respiratory tract infection	17	8 to 10	-	-	-	-	-	-	9
Serious infection	-	-	3	1	-	≤2	-	-	5
Sinusitis	-	-	-	-	-	-	-	4 to 6	-
Tonsillitis	7	-	-	-	-	-	-	-	-
Tooth infections	9	-	-	-	-	-	-	-	-

Adverse Event	Natalizumab	Ocrelizumab	Ofatumumab	Ozanimod	Peginterferon β-1a	Ponesimod	Siponimod	Teriflunomide	Ublituximab
Upper respiratory tract infection	22	40 to 49	39	26	-	37	-	9	45
Vaginal candidiasis	10	-	-	-	-	-	-	-	-
Musculoskeletal									
Arthralgia or myalgia	19	-	-	-	11 to 19	-	-	3 to 4	-
Asthenia	-	-	-	-	13	-	<5	-	-
Back pain	-	6	8	4	-	≥2	-	-	-
Chills	-	-	-	-	17	-	-	-	-
Joint swelling	-	-	-	-	-	≥2	-	-	-
Pain	-	-	-	-	-	-	-	4 to 5	-
Pain in limb	16	5	-	-	-	4	6	-	6
Rigors	3	-	-	-	-	-	-	-	-
Shivering	-	-	-	-	17	-	-	-	-
Ophthalmic									
Blurred vision	-	-	-	-	-	-	-	3	-
Conjunctivitis	-	-	-	-	-	-	-	1 to 3	-
Macular retinal edema	-	-	-	-	-	1	2	-	-
Psychiatric									
Anxiety	-	-	-	-	-	-	-	3 to 4	-
Depression	19	8	-	-	-	≥2	-	-	-
Respiratory									
Cough	-	7	-	-	-	4	-	-	-
Dyspnea	-	-	-	-	-	5	-	-	-
Reduced forced expiratory volume	-	-	-	-	-	8	<5	-	-
Seasonal allergy	3	-	-	-	-	-	-	2 to 3	-
Sinusitis	-	-	-	-	-	≥2	-	-	-
Skin and Subcutaneous Tissue									
Acne	-	-	-	-	-	-	-	1 to 3	-
Alopecia	-	-	-	-	-	-	-	10 to 13	-
Dermatitis	7	-	-	-	-	-	-	-	-
Edema	-	6	-	-	-	-	-	-	-
Hypersensitivity	5	-	-	-	-	-	-	-	-
Hyperthermia	-	-	-	-	4	-	-	-	-
Injection site reactions	-	-	11 to 21	-	62	-	-	-	-
Pruritus	4	-	-	-	13	-	-	3 to 4	-

Adverse Event	Natalizumab	Ocrelizumab	Ofatumumab	Ozanimod	Peginterferon β-1a	Ponesimod	Siponimod	Teriflunomide	Ublituximab
Rash	12	-	-	-	-	-	-	-	-
Urogenital									
Amenorrhea	2	-	-	-	-	-	-	-	-
Dysmenorrhea	3	-	-	-	-	-	-	-	-
Irregular menstruation	5	-	-	-	-	-	-	-	-
Micturition urgency	9	-	-	-	-	-	-	-	-
Ovarian cyst	2	-	-	-	-	-	-	-	-
Urinary incontinence	4	-	-	-	-	-	-	-	-
Urinary tract infection	21	-	10	4	-	6	-	-	10
Other									
Hypercholesterolemia	-	-	-	-		2	-	-	-
Hyperkalemia	-	-	-	-		<2	-	-	-
Infusion reaction	-	34 to 40	-	-	-	-	-	-	48

ˇ Percent not specified.
- Event not reported.

Table 8. Black Box Warning for Lemtrada® (alemtuzumab)[1]

WARNING
Autoimmunity • Lemtrada causes serious, sometimes fatal, autoimmune conditions such as immune thrombocytopenia and anti-glomerular basement membrane disease. Monitor complete blood counts with differential, serum creatinine levels, and urinalysis with urine cell counts at periodic intervals for 48 months after the last dose of Lemtrada. **Infusion Reactions** • Lemtrada causes serious and life threatening infusion reactions. Lemtrada must be administered in a setting with appropriate equipment and personnel to manage anaphylaxis or serious infusion reactions. Monitor patients for two hours after each infusion. Make patients aware that serious infusion reactions can also occur after the 2-hour monitoring period. **Stroke** • Serious and life-threatening stroke (including ischemic and hemorrhagic stroke) has been reported within 3 days of Lemtrada administration. Instruct patients to seek immediate medical attention if symptoms of stroke occur. **Malignancies** • Lemtrada may cause an increased risk of malignancies, including thyroid cancer, melanoma, and lymphoproliferative disorders. Perform baseline and yearly skin exams.

WARNING
• Because of the risk of autoimmunity, infusion reactions, and malignancies, Lemtrada is available only through restricted distribution under a Risk Evaluation Mitigation Strategy (REMS) Program.

Table 9. Black Box Warning for Tysabri® (Natalizumab)[12]

WARNING
Progressive Multifocal Leukoencephalopathy Tysabri increases the risk of progressive multifocal leukoencephalopathy (PML), an opportunistic viral infection of the brain that usually leads to death or severe disability. Risk factors for the development of PML include duration of therapy, prior use of immunosuppressants, and presence of anti-JCV antibodies. These factors should be considered in the context of expected benefit when initiating and continuing treatment with Tysabri. • Healthcare professionals should monitor patients on Tysabri for any new sign or symptom that may be suggestive of PML. TYSABRI dosing should be withheld immediately at the first sign or symptom suggestive of PML. For diagnosis, an evaluation that includes a gadolinium-enhanced magnetic resonance imaging (MRI) scan of the brain and, when indicated, cerebrospinal fluid analysis for JC viral DNA are recommended. • Because of the risk of PML, Tysabri is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the TOUCH Prescribing Program.

Table 10. Black Box Warning for Aubagio® (Teriflunomide)[20]

WARNING
Hepatotoxicity Clinically significant and potentially life-threatening liver injury, including acute liver failure requiring transplant, has been reported in patients treated with teriflunomide in the postmarketing setting. Concomitant use of teriflunomide with other hepatotoxic drugs may increase the risk of severe liver injury. Obtain transaminase and bilirubin levels within 6 months before initiation of teriflunomide therapy. Monitor ALT levels at least monthly for six months after starting teriflunomide. If drug induced liver injury is suspected, discontinue teriflunomide and start an accelerated elimination procedure with cholestyramine or charcoal. Teriflunomide is contraindicated in patients with severe hepatic impairment. Patients with pre-existing liver disease may be at increased risk of developing elevated serum transaminases when taking teriflunomide. **Embryofetal Toxicity** Teriflunomide is contraindicated for use in pregnant women and in females of reproductive potential who are not using effective contraception because of the potential for fetal harm. Teratogenicity and embryolethality occurred in animals at plasma teriflunomide exposures lower than that in humans. Exclude pregnancy before the start of treatment with teriflunomide in females of reproductive potential. Advise females of reproductive potential to use effective contraception during teriflunomide treatment and during an accelerated drug elimination procedure after teriflunomide treatment. Stop teriflunomide and use an accelerated drug elimination procedure if the patient becomes pregnant.

VII. Dosing and Administration

The usual dosing regimens for the immunomodulatory agents used to treat multiple sclerosis are listed in Table 11.

Table 11. Usual Dosing Regimens for the Immunomodulatory Agents used to treat Multiple Sclerosis[1-23]

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
Alemtuzumab	Treatment of patients with relapsing forms of multiple sclerosis: Injection: First course: 12 mg/day on 5 consecutive days Second course: 12 mg/day on 3 consecutive days 12 months after first treatment course Injections should be administered over four hours for two or more treatment courses.	Safety and efficacy in children <18 years of age have not been established.	Injection: 12 mg/1.2 mL
Dimethyl fumarate	Treatment of patients with relapsing forms of multiple sclerosis: Delayed-release capsule: initial, 120 mg BID for seven days; maintenance, 240 mg BID	Safety and efficacy in children <18 years of age have not been established.	Delayed-release capsule: 120 mg 240 mg
Diroximel fumarate	Treatment of patients with relapsing forms of multiple sclerosis: Delayed-release capsule: initial, 231 mg BID; maintenance, 462 mg BID; maximum, 462 mg BID Temporary dose reduction to 231 mg BID may be considered in patients who cannot tolerate maintained dosing. Consider discontinuation if unable to return to maintenance dosing after four weeks.	Safety and efficacy in children have not been established.	Delayed-release capsule: 231 mg
Fingolimod	Treatment of patients with relapsing forms of multiple sclerosis: Capsule, ODT: 0.5 mg orally once daily [First dose monitoring: The first dose of fingolimod should be administered in a setting in which resources to appropriately manage symptomatic bradycardia are available. In order to assess patient response to the first dose of fingolimod, observe all patients for six hours for signs and symptoms of bradycardia with hourly pulse and blood pressure measurement. Obtain in all patients an electrocardiogram prior to dosing, and at the end of the observation period.]	Treatment of patients with relapsing forms of multiple sclerosis 10 to 18 years of age: Weight >40 kg: 0.5 mg orally once daily Weight ≤40 kg: 0.25 mg orally once daily	Capsule: 0.25 mg 0.5 mg Orally disintegrating tablet (ODT): 0.25 mg 0.5 mg
Glatiramer acetate	Treatment of patients with relapsing forms of multiple sclerosis: Prefilled syringe: 20 mg SC once daily or 40 mg SC three times per week at least 48 hours apart	Safety and efficacy in children <18 years of age have not been established.	Injection: 20 mg/mL 40 mg/mL
Interferon β-1a	Treatment of patients with relapsing forms of multiple sclerosis: Injection (Rebif®): initial, 20% of maintenance dose; maintenance, 22 or 44 µg SC three times a week Injection (Avonex®): 30 µg IM once a week	Safety and efficacy in children <18 years of age have not been established.	Injection, IM (Avonex®): 30 µg/0.5mL Injection, SubQ (Rebif®): 22 µg/0.5 mL

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
			44 µg/0.5 mL Titration pack: 8.8 µg/0.2 mL & 22 µg/0.5 mL
Interferon β-1b	Treatment of patients with relapsing forms of multiple sclerosis: Vial: initial, 0.0625 mg SC every other day; maintenance, 0.25 mg SC every other day	Safety and efficacy in children <18 years of age have not been established.	Injection: 0.3 mg
Monomethyl fumarate	Treatment of patients with relapsing forms of multiple sclerosis: Capsule: initial, 95 mg BID for 7 days; maintenance, 190 mg BID Temporary dosage reductions to 95 mg BID may be considered for individuals who do not tolerate the maintenance dosage. Within 4 weeks, the recommended dosage of 190 mg BID should be resumed. Discontinuation should be considered for patients unable to tolerate return to the maintenance dosage.	Safety and efficacy in pediatric patients have not been established.	Delayed-release capsule: 95 mg
Natalizumab	Treatment of patients with relapsing forms of multiple sclerosis: Vial: 300 mg intravenous infusion over one hour every four weeks	Safety and efficacy in children <18 years of age have not been established.	Injection: 300 mg/15 mL
Ocrelizumab	Treatment of patients with relapsing or primary progressive forms of multiple sclerosis: Injection: initial dose of 300 mg intravenous infusion followed two weeks later by a second 300 mg infusion subsequent doses of 600 mg every six months	Safety and efficacy in children <18 years of age have not been established.	Injection: 300 mg/10 mL
Ofatumumab	Treatment of patients with relapsing forms of multiple sclerosis: Injection: initial, 20 mg SC at weeks 0, 1, and 2; followed by maintenance dosing of 20 mg SC once monthly starting at week 4	Safety and efficacy in pediatric patients have not been established.	Injection: 20 mg/0.4 mL
Ozanimod	Treatment of patients with relapsing forms of multiple sclerosis: Capsule: 0.23 mg QD for four days, 0.46 mg QD for three days, then 0.92 mg QD thereafter	Safety and efficacy in children have not been established.	Capsule: 0.92 mg Dose packs: 0.23 mg (4)-0.46 mg (3) 0.23 mg (4)-0.46 mg (3)-0.92 mg (30)
Peginterferon β-1a	Treatment of patients with relapsing forms of multiple sclerosis: Pen, prefilled syringe: initial, 63 µg SC on day one, followed by 94 µg SC on day 15, followed by 125 µg SC on day 29 and then every 14 days thereafter	Safety and efficacy in children <18 years of age have not been established.	Injection: 125 µg/0.5 mL Starter pack: 63 µg/0.5 mL & 94 µg/0.5 mL

<table>
<tr><th>Generic Name</th><th>Usual Adult Dose</th><th>Usual Pediatric Dose</th><th>Availability</th></tr>
<tr><td>Ponesimod</td><td><u>Treatment of patients with relapsing forms of multiple sclerosis:</u>
Tablet: initial, 2 mg QD and titrate according to schedule; maintenance, 20 mg QD starting on day 15

Dose titration should occur based on the following schedule:
<table><tr><th>Titration Day</th><th>Daily Dose</th></tr><tr><td>Days 1 and 2</td><td>2 mg</td></tr><tr><td>Days 3 and 4</td><td>3 mg</td></tr><tr><td>Days 5 and 6</td><td>4 mg</td></tr><tr><td>Day 7</td><td>5 mg</td></tr><tr><td>Day 8</td><td>6 mg</td></tr><tr><td>Day 9</td><td>7 mg</td></tr><tr><td>Day 10</td><td>8 mg</td></tr><tr><td>Day 11</td><td>9 mg</td></tr><tr><td>Days 12, 13, and 14</td><td>10 mg</td></tr></table></td><td>Safety and efficacy in children have not been established.</td><td>Tablet:
20 mg

Dose pack:
2 mg(2)-3 mg(2)-4 mg(2)-5 mg-6 mg-7 mg-8 mg-9 mg-10 mg(3)</td></tr>
<tr><td>Siponimod</td><td><u>Treatment of patients with relapsing forms of multiple sclerosis</u>:
Patients with CYP2C9 Genotypes *1/*1, *1/*2, or *2/*2:
Tablet: initial, five-day titration (0.25 mg QD on day one and day two then 0.5 mg QD on day three then 0.75 mg QD on day four then 1.25 mg QD on day five); maintenance, 2 mg QD; maximum, 2 mg QD

Patients with CYP2C9 Genotypes *1/*3 or *2/*3:
Tablet: initial, four-day titration (0.25 mg QD on day one and day two then 0.5 mg on day three then 0.75 mg on day four); maintenance, 1 mg QD; maximum, 1 mg QD</td><td>Safety and efficacy in children have not been established.</td><td>Tablet:
0.25 mg
1 mg
2 mg</td></tr>
<tr><td>Teriflunomide</td><td><u>Treatment of patients with relapsing forms of multiple sclerosis:</u>
Tablet: 7 mg or 14 mg QD</td><td>Safety and efficacy in children <18 years of age have not been established.</td><td>Tablet:
7 mg
14 mg</td></tr>
<tr><td>Ublituximab</td><td><u>Treatment of patients with relapsing forms of multiple sclerosis:</u>
Injection: Infuse 150 mg on day 1 (over at least four hours) and 450 mg on day 14 (over at least one hour), then 450 mg every 24 weeks, starting 24 weeks after the first infusion (over at least one hour)</td><td>Safety and efficacy in children have not been established.</td><td>Vial:
150 mg/6 mL</td></tr>
</table>

BID=twice daily, IM=intramuscular, SC=subcutaneous, QD=once daily

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the immunomodulatory agents used to treat multiple sclerosis are summarized in Table 11.

Table 11. Comparative Clinical Trials with the Immunomodulatory Agents used to treat Multiple Sclerosis

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Relapsing-Remitting Multiple Sclerosis				
Hardova et al.[32] (2017) Alemtuzumab 12 mg/d IV on 3 consecutive days upon evidence of MS disease activity	ES Patients who completed the CARE-MS I study	N=335 60 months	Primary: ARR; 6-month confirmed disability worsening; 3-, 6-, or 12-month confirmed disability improvement; mean change from baseline EDSS score; proportions of patients with EDSS scores that were improved compared with baseline; and proportions of patients with new nonenhancing T1 hypointense lesions. Secondary: Not reported	Primary: The ARR was 0.18 between years zero to two and 0.16 between years three to five. Over five years, 79.7% (95% CI, 75.1 to 83.6%) of patients were free of 6-month confirmed disability worsening and 33.4% (95% CI, 27.5 to 40.1%) achieved 6-month confirmed disability improvement. The mean EDSS score changes from core study baseline was -0.16 at year two, -0.10 at year three, -0.09 at year four, and 0.00 at year five. Compared with core study baseline, 60.0% of patients at year five showed stable EDSS scores; 22.2% showed improved scores (≥1-point decrease) and 17.8% showed worsened scores (≥1-point increase). The proportion of patients that were free of T1 hypointense lesions was 89.2% at year 3; 85.4% at year 4; and 85.4% year 5. Secondary: Not reported
Kappos et al.[33] (2015) DECIDE Daclizumab 150 mg SC every four weeks plus IM placebo once weekly	AC, DB, DD, MC, PG, RCT Patients 18 to 55 years of age with a diagnosis of RRMS, MRI showing lesions,	N=1,841 96 to 144 weeks	Primary: Annualized relapse rate over a period of 144 weeks Secondary: Number of new or newly enlarged	Primary: The adjusted annualized relapse rate was 0.22 (95% CI, 0.19 to 0.24) in the daclizumab group and 0.39 (95% CI, 0.35 to 0.44) in the IFNβ-1a group. This represented a statistically significant, 45% reduction in the adjusted annualized relapse rate in favor of daclizumab compared to IFNβ-1a (P<0.001). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs IFNβ-1a 30 µg IM once weekly plus SC placebo every four weeks Patients were instructed to take prophylactic treatment for influenza-like symptoms during the first 24 weeks of therapy in order to reduce any potential for unbinding (interferon β-1a is associated with flu-like symptoms).	EDSS score 0 to 5, two or more clinical relapses within the previous three years, with one clinical relapse occurring in the 12 months before randomization or one or more clinical relapses and at least one new lesion on MRI that was not associated with the clinical relapse within the previous two years with at least one of these events occurring in the 12 months before randomization		hyperintense lesions on T2-weighted MRI scans of the brain (over a 96 week period), proportion of patients with confirmed progression of disability at 12 weeks (over a 144 week period), the proportion of patients who did not have a relapse (over a 144 week period), and the proportion of patients with an increase from baseline of at least 7.5 points on the MSIS-29 physical subscale at 96 weeks, safety	The number of new or newly enlarged hyperintense lesions on T_2-weighted images at week 96 was 4.3 (95% CI, 3.9 to 4.8) in the daclizumab group and 9.4 (95% CI, 8.5 to 10.5) in the IFNβ-1a group. This represented a statistically significant, 54% reduction in the number of new or newly enlarged in favor of daclizumab compared to IFNβ-1a (P<0.001). At week 144, the estimated percentage of patients who had disability progression confirmed at 12 weeks as measured by the EDSS was 16% in the daclizumab group and 20% in the IFNβ-1a group (HR, 0.84; 95% CI, 0.50 to 0.69; P=0.16). On the basis of the prespecified hierarchical testing plan, the results of the analyses of the third and fourth prespecified secondary end points were not considered to be significant. The estimated percentage of patients who were free from relapse at week 144 was 67% in the daclizumab group and 51% in the IFNβ-1a group (HR, 0.59; 95% CI, 0.50 to 0.69; P value no reported). Clinically meaningful worsening, defined as an increase of ≥7.5 points, in the patient-reported physical effect of multiple sclerosis, as assessed with the use of the MSIS-29 physical subscale, at week 96 was observed in 19% of the patients in the daclizumab group and 23% of those in the IFNβ-1a group. This represented a 24% (95% CI, 5 to 40) reduction in the odds of worsening in favor of daclizumab compared to IFNβ-1a (P value not reported).
Gold et al.[34] (2013) SELECT Daclizumab 150 mg SC every four weeks vs	DB, MC, PC, PG, RCT Patients 18 to 55 years of age with a diagnosis of RRMS, EDSS score 0 to 5, one clinical relapse occurring in the 12	N=621 52 weeks	Primary: Annualized relapsed rate at week 52 Secondary: Cumulative number of new gadolinium-enhancing lesions on brain MRI scans	Primary: The annualized relapse rate at 52 weeks was lower for patients in the daclizumab 150 mg group (0.21; 54% reduction), and in the daclizumab 300 mg group (0.23; 50 % reduction), compared to the placebo group (0.46; P<0.001 for both groups compared to placebo). Secondary: Cumulative number of new gadolinium-enhancing lesions on brain MRI scans done at weeks 8, 12, 16, 20 and 24, was lower in the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
daclizumab 300 mg SC every four weeks vs placebo	months before randomization or at least one new gadolinium-enhancing lesion on the brain MRI within the six weeks before randomization		done at weeks 8, 12, 16, 20 and 24, the number of new or newly enlarging T2 hyperintense lesions at week 52, the proportion of relapsing patients between baseline and week 52 and change in quality of life based on MSIS-29 score	daclizumab treatment groups compared to the placebo group (P<0.001). There was also a lower number of new or newly enlarging T2 hyperintense lesions, percentage change from baseline T2 hyperintense lesions percentage and change from baseline T1 hypointense lesions at week 52 at week 52 in the daclizumab treatment groups compared to the placebo group (P<0.001). From baseline to week 52, the estimated proportion of relapsing patients was reduced in the daclizumab treatment groups versus the placebo treatment groups (P=0.021 and P=0.091 in daclizumab 150 mg and daclizumab 300 mg groups, respectively). There was statistically significant improvement in the mean MSIS-29 physical score at week 52 for patients in the daclizumab 150 mg group versus those on placebo, but not for patients in the daclizumab 300 mg group (P=0.00082 and P=0.13 in daclizumab 150 mg and daclizumab 300 mg groups, respectively). There were similar improvements in other measure of quality of life, including measures of physical, psychological and overall health function.
Giovannoni et al.[35] (2014) SELECTION Daclizumab 150 mg or 300 mg SC every four weeks with washout period of 20 weeks (new start or re-initiation group) vs daclizumab 150 mg or 300 mg SC every four weeks without washout period of 20 weeks (continuous treatment)	DB, ES of SELECT[34] MC, RCT Patients who completed study treatment in the SELECT trial without a change in their overall health status that would preclude treatment with daclizumab	N=517 52 weeks	Primary: Safety and immunogenicity of treatment with daclizumab Secondary: Durability of daclizumab treatment effect on disease activity, based on relapse activity (AAR and proportion of patients who relapsed),	Primary: Frequency of adverse events was similar between the treatment initiation and continuous treatment groups. Secondary: In continuous treatment group, ARR was similar between year one and year two. The numbers of new gadolinium enhancing lesions in this group were also consistent. The number of new or newly enhancing T2 hyperintense lesions that formed during year two was lower than year one, as was the volume of new T1 hypointense lesions. The proportion of patients who had confirmed disability progression was similar between year one and year two. In treatment initiation group, ARR, proportion on patients who relapsed and proportion of patients with confirmed disability progression were significantly reduced in year two. The number of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			confirmed disability progression and MRI endpoints (new gadolinium enhancing lesions, new or enlarging T2 hyperintense lesions, total volume of T2 hyperintense lesions, volume of new T1 hypointense lesions, total volume of T1 hypointense lesions and whole brain volume)	new gadolinium-enhancing lesions and new or newly enlarging T2 lesions were also reduced in year two. Reductions were also recorded for the percentage change in volume of total T2 leases and the volume of new T1 hypointense lesions.
Gold et al.[36] (2016) SELECTED Daclizumab 150 mg SC every four weeks	OL extension of SELECT and SELECTION trials Patients must have completed 52 weeks of both SELECT and SELECTION, been compliant with the SELECTION protocol, provided informed consent for SELECTED, and met other general eligibility criteria	N=410 Up to 6.5 years	Primary: Safety Secondary: Efficacy	Primary: The yearly incidence of adverse events, serious adverse events, and adverse events leading to discontinuation did not increase over time and no deaths were reported. Forty-eight (12%) patients discontinued treatment due to adverse events. Common adverse events that occurred in 10% of patients or more were MS relapse (22%), nasopharyngitis (12%), and upper respiratory tract infection (12%). The most frequently reported serious adverse events excluding MS relapse, were hepatic enzyme elevations, pneumonia, ulcerative colitis, and urinary tract infection (each in three patients [each less than 1%]). Secondary: The adjusted ARR analyzed at 6-month intervals from the first dose of daclizumab was 0.21 (95% CI, 0.16 to 0.29) for weeks 0 to 24 and decreased to 0.15 (95% CI, 0.10 to 0.21) by the weeks 121 to 144 interval. The adjusted mean (95% CI) number of new/newly enlarging T2 hyperintense lesions was 1.95 (1.60 to 2.37) in year one and decreased to 1.26 (0.93 to 1.72) by year three of treatment with

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				daclizumab. The mean annualized PBVC was −0.77% in year one and decreased to −0.32% by year three of treatment with daclizumab.
Giovannoni et al.[37] (2014) Daclizumab 150 mg or 300 mg SC every four weeks in patients with highly active RRMS vs daclizumab 150 mg or 300 mg SC every four weeks in patients with less active RRMS	Post-hoc of SELECT[34] Patients 18 to 55 years of age with a diagnosis of RRMS, EDSS score 0 to 5, one clinical relapse occurring in the 12 months before randomization or at least one new gadolinium-enhancing lesion on the brain MRI within the six weeks before randomization	N=621 52 weeks	Primary: Annualized relapsed rate, new gadolinium-enhancing lesions, the number of new or newly enlarging T2 hyperintense lesions and disability progression Secondary: Not reported.	Primary: Treatment with daclizumab reduced ARR by 50% and 51% respectively in the highly active (P=0.0394) and less active (P<0.0001) treatment groups versus placebo, respectively. Treatment with daclizumab reduced new/newly-enlarging T2 lesions in highly active RRMS (76% reduction, P<0.0001) and less active RRMS (73% reduction, P<0.0001) Treatment with daclizumab reduced the risk of having more gadolinium-enhancing lesions in highly active RRMS (89% reduction, P<0.0001) and less active RRMS (86% reduction, P<0.0001) Treatment with daclizumab reduced the risk of sustained disability progression in highly active RRMS (88% reduction, P=0.0574) and less active RRMS (46% reduction, P=0.0383) Secondary: Not reported.
Cohan et al.[38] (2018) STRATEGY Dimethyl fumarate for at least one year following at least one year of natalizumab at FDA labeled doses	Phase IV, OS, RETRO Patients were ≥18 years of age with a diagnosis of RRMS and had received ≥12 months of therapy with natalizumab and had started dimethyl fumarate ≥1 year before the study initiation with no other	N=506 One year	Primary: Proportion of patients who relapsed during the 12 months after dimethyl fumarate initiation Secondary: ARR at 1 year after dimethyl fumarate initiation	Primary: Over the 12 months following dimethyl fumarate initiation 82% of patients experienced zero relapses, 15% experienced one relapse, 3% experienced two relapses, and 0.6% experienced three relapses. The Kaplan-Meier estimate of overall risk of relapse one year after dimethyl fumarate was calculated to be 19.6%. Secondary: The adjusted ARR for the first year following dimethyl fumarate therapy was 0.25 (95% CI, 0.20 to 0.30) as compared to 0.11 (95% CI, 0.08 to 0.14) for the first year of dimethyl fumarate therapy following natalizumab (rate ratio, 2.32; 95% CI, 1.69 to 3.16; P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	disease modifying treatments between the switch.			
Gold et al.[39] (2012) DEFINE Dimethyl fumarate 240 mg BID vs Dimethyl fumarate 240 mg TID vs placebo	DB, MC, PC, RCT Patients aged 18 to 55 years with a diagnosis of RRMS, an EDSS score of 0 to 5, and at least one clinically documented relapse in the previous 12 months or at least one gadolinium-enhancing lesion 0 to 6 weeks before randomization	N=1,237 96 weeks	Primary: Proportion of patients who had a relapse by two years Secondary: ARR, time to progression of disability, number of gadolinium-enhancing lesions and of new or enlarging hyperintense T2 lesions	Primary: Relapses after two years were observed in 27% and 26% of the patients in the twice daily and three times daily dimethyl fumarate groups, respectively, compared to 46% of patients in the placebo group (HR, 0.51; 95% CI: 0.39 to 0.65 and 0.50; 95% CI: 0.39 to 0.65, respectively). Secondary: Time to first relapse was prolonged by 87 and 91 weeks in patients in the twice and three times daily groups, respectively, compared to placebo. Relative to placebo, the ARR was reduced by 53% and 48% in the twice daily and three times daily groups, respectively (P=0.001). Additionally, the time to progression of disability was reduced by 38% in the twice daily group (HR, 0.62; 95% CI: 0.44 to 0.87) and by 34% in the three times daily group (HR, 0.66; 95% CI: 0.48 to 0.92. Relative to placebo, the number of new or enlarging hyperintense T2 lesions and the number of gadolinium-enhancing lesions was decreased by 85% and 90%, respectively in patients receiving dimethyl fumarate twice daily and by 74% and 73% in patients receiving dimethyl fumarate three times daily (P<0.001 for all) The most common adverse events in patients receiving dimethyl fumarate were flushing, gastrointestinal events, proteinuria and pruritus.
Naismith et al.[40] (2020) EVOLVE-MS-2 Diroximel fumarate (DRF) 462 mg BID	DB, RCT Patients 18 to 65 years of age with RRMS who were neurologically stable with no	N=504 5 weeks	Primary: Number of days with an Individual Gastrointestinal Symptom and Impact Scale (IGISIS) intensity	Primary: The number of days with an IGISIS intensity score of ≥ 2 relative to exposure was statistically significantly lower with DRF compared with DMF. The adjusted mean number of days with a patient-assessed event was 1.4 (95% CI, 1.1 to 1.9) days with DRF and 2.6 (95% CI, 2.0 to 3.3) days with DMF. The adjusted rate ratio was 0.54 (95% CI, 0.39 to 0.75), representing a 46% reduction (P=0.0003).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs dimethyl fumarate (DMF) 240 mg BID	evidence of relapse in the 30 days prior to screening		score ≥ 2 relative to exposure Secondary: Degree of gastrointestinal symptom severity and assessment of safety/tolerability	Secondary: The IGISIS worst symptom intensity scores were lower with DRF than DMF for events associated with the upper GI tract (with statistically significant reductions observed for nausea, vomiting, upper abdominal pain) but similar for events associated with the lower GI tract (diarrhea, lower abdominal pain; Table 3). Lower rates of gastrointestinal adverse events (including diarrhea, nausea, vomiting, and abdominal pain) were observed with DRF than DMF (34.8% vs 49.0%). Fewer patients discontinued DRF than DMF because of adverse events (1.6% vs 5.6%) and gastrointestinal adverse events (0.8% vs 4.8%).
Comi et al.[41] (2017) GOLDEN Fingolimod 0.5 mg/day vs IFN β-1b 250 µg SC every other day	MC, OL, rater blinded, randomized, parallel-group Patients were 18 to 60 years of age who were diagnosed with RRMS and had active disease and cognitive impairment at the time of screening.	N=157 18 months	Primary: Cognitive function assessed by Selective Reminding Test (SRT), 10/36 Spatial Recall Test (10/36 SPART), Symbol Digit Modalities Test (SDMT), Paced Auditory Serial Addition test (PASAT) and Word List Generation (WLG); executive function assessed by the Delis–Kaplan Executive Function System (DKEFS) Sorting test; depression assessed by the Montgomery–	Primary: Both treatment groups demonstrated improvements in mean changes of all parameters used to assess cognitive function from screening to Month 18. No significant differences were detected between the treatment groups in the mean changes in all parameters. Both treatment groups showed improvements in executive function assessed by the DKEFS Sorting test; however, no significant differences were detected between the treatment groups. At month 18, the change in MADRS was -0.68±7.57 (95% CI, -2.45 to 1.08) in the fingolimod group compared to a change of 0.30±5.63 (95% CI, -1.93 to 2.52) in the IFN β-1b group; however, the difference was not statistically significant (P=0.3291). At month 18, patients in the IFN β-1b group presented with greater new T2 lesions on MRI scans (3.33±4.44) as compared to the fingolimod group (1.25±2.05) (P=0.0276).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Åsberg Depression Rating Scale (MADRS); and lesions identified by MRI	
Chitnis et al.[42] (2018) PARADIGMS Fingolimod 0.5 mg once daily for patients >40 kg or 0.25 mg once daily for patients ≤40 kg vs IFNβ-1a 30 µg IM once weekly	AC, DB, MC, RCT Patients were 10 to 17 years of age with a diagnosis of MS and had at least one relapse of MS in the year proceeding screening or two relapses in the two years preceding screening or had evidence of at least one gadolinium-enhancing lesion on T1-weighted MRI in the six months before randomization, and who had an EDSS score of 0.0 to 5.5	N=215 24 months	Primary: ARR Secondary: Annualized rate of new or newly enlarged lesions detected on T2-weighted MRI as compared with baseline; percentage of patients free of relapse; the number of gadolinium-enhancing lesions, and the safety and side-effect profile	Primary: The adjusted ARR at 24 months was 0.12 in the fingolimod group and 0.67 in the IFNβ-1a group (rate ratio, 0.18; 95% CI, 0.11 to 0.30; P<0.001) (absolute difference, 0.55 relapses; 95% CI, 0.36 to 0.74; P<0.001). Secondary: The annualized rate of new or newly enlarged lesions on T2-weighted MRI at up to 24 months was 4.39 with fingolimod and 9.27 with IFNβ-1a (rate ratio, 0.47; 95% CI, 0.36 to 0.62; P<0.001) (absolute difference, 4.88 lesions; 95% CI, 2.91 to 6.84; P<0.001). The percentage of patients in the fingolimod group who were free of relapse was 85.7% (95% CI, 79.0 to 50.3%) as compared to 38.8% (95% CI, 27.4 to 50.3%) in the with IFNβ-1a group (difference, 46.9%; 95% CI, 33.7 to 60.1%). The mean number of gadolinium-enhancing lesions per scan at up to 24 months was 0.44 with fingolimod and 1.28 with IFNβ-1a (rate ratio, 0.34; 95% CI, 0.22 to 0.54). The overall incidence of adverse events was 88.8% in the fingolimod group and 95.3% in the IFNβ-1a group.
Kappos et al.[43] (2010) FREEDOMS Fingolimod 0.5 mg once daily vs fingolimod 1.25 mg once daily	DB, MC, PC, RCT Patients 18 to 55 years of age with RRMS and an EDSS score 0 to 5.5 and ≥1 relapse in the past year or	N=1,272 24 months	Primary: ARR Secondary: Time to first relapse, proportion of patients relapse free after 24 months, time to	Primary: The aggregate ARR was lower with fingolimod 0.5 (0.18; 95% CI, 0.15 to 0.22) and 1.25 mg (0.16; 95% CI, 0.13 to 0.19) compared to placebo (0.40; 95% CI, 0.34 to 0.47; P<0.001 for both comparisons). This represents a reduction of 54 and 60%, respectively, in the ARR for fingolimod.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo	≥2 relapses in the past 2 years		confirmed disability (an increase ≥1 in EDSS) progression confirmed after three and six months, changes in EDSS and MSFC score from baseline to 24 months, number of gadolinium-enhancing lesions, proportion of patients free from gadolinium-enhancing lesions, number of new or enlarged lesions on T2-weighted MRI scans, proportion of patients free from new or enlarged lesions on T2-weighted scans, volumes of hyperintense lesions on T2-weighted scans and hypointense lesions on T1-weighted scans, change in brain volume between baseline and 24 months, safety and tolerability	A subgroup analysis comparing ARRs among treatment naïve patients and those previously treated found significant reductions compared to placebo (P<0.01 for all comparisons). Secondary: In the fingolimod groups compared to the placebo group, the time to a first relapse was longer (P<0.001 for both comparisons), the risk of relapse was reduced (0.5 mg vs placebo: HR, 0.48; 95% CI, 0.39 to 0.61; P<0.001 and 1.25 mg vs placebo: HR, 0.38; 95% CI, 0.30 to 0.48; P<0.001) and significantly more patients remained free of relapse during the 24 month period (0.5 mg: 70.4±2.3%; 95% CI, 66.0 to 74.8; P<0.001, 1.25 mg: 74.7±2.2%; 95% CI, 70.4 to 2.3; P<0.001, placebo: 45.6±2.3%; 95% CI, 40.7 to 50.6). The time to disability progression was longer in patients treated with fingolimod compared to patients treated with placebo. Treatment with fingolimod reduced the risk of disability progression, confirmed after three months, over the 24 month study period (HR, 0.70 for 0.5 mg and HR, 0.68 for 1.25 mg; P values not reported). The cumulative probability of disability progression (confirmed after three months) was 17.7% for fingolimod 0.5 mg, 16.6% for fingolimod 1.25 mg and 24.1% for placebo (P values not reported). Regarding disability progression that was confirmed after six months, the risk was also reduced with fingolimod over the 24 month study period (HR, 0.63 for 0.5 mg and HR, 0.60 for 1.25 mg; P values not reported), and the cumulative probability of progression was 12.5% for fingolimod 0.5 mg, 11.5% for fingolimod 1.25 mg and 19.0% for placebo (P values not reported). During the study period, the EDSS and MSFC scores remained stable or improved slightly in the fingolimod groups and worsened in the placebo group (P<0.02 for all comparisons). All MRI based secondary endpoints including number and proportion of patients demonstrating gadolinium-enhancing lesions, changes in hypointense and hyperintense lesions on T1- or T2-weighted scans

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				and changes in brain volume favored the fingolimod groups compared to the placebo group (P≤0.03 for all comparisons). The rates of adverse events were reported to be similar (93 to 94%) among the three treatment groups. Adverse events that led to treatment discontinuation were more common with fingolimod 1.25 mg (14.2%) compared to fingolimod 0.5 mg (7.5%) and placebo (7.7%). The most common serious adverse events, each reported for eight patients, were bradycardia, MS relapse and basal-cell carcinoma. The overall incidence of infection was similar in the fingolimod and placebo groups (69 to 72%); serious infections occurred in 1.6 and 2.6% of patients. Transient, dose-related decreases in heart rate occurred after the first dose of fingolimod was administered. Bradycardia was reported in nine patients receiving 0.5 mg of fingolimod, 14 patients receiving 1.25 mg of fingolimod and three patients receiving placebo. Macular edema was diagnosed in seven patients, all of whom were receiving 1.25 mg of fingolimod. Three of these events were reported as serious adverse events. Peripheral-blood lymphocyte counts were reduced from the baseline counts by an average of 73% with 0.5 mg of fingolimod and 76% with 1.25 mg of fingolimod, remaining stable after one month. Increases in ALT to three times the upper limit of normal or more were more frequent in the fingolimod groups (8.5% of patients in the 0.5 mg group and 12.5% of patients in the 1.25 mg group) than in the placebo group (1.7% of patients) and occurred predominantly in men.
Devonshire et al.[44] (2012) Subgroup analysis of FREEDOMS Fingolimod 0.5 mg once daily	DB, MC, PC, RCT Patients 18 to 55 years of age with RRMS and an EDSS score 0 to	N=1,272 24 months	Primary: ARR Secondary:	Primary: Fingolimod 0.5 mg treatment significantly reduced ARR compared to placebo in all subgroups except for patients older than 40 years of age. ARR

<table>
<tr><th>Study and Drug Regimen</th><th>Study Design and Demographics</th><th>Study Size and Study Duration</th><th>End Points</th><th>Results</th></tr>
<tr><td>vs

placebo

Subgroup analysis based on demographic factors (sex, gender, treatment history), disease characteristics (baseline disability scores, relapse rates, and lesion parameters), and response to previous therapy.</td><td>5.5 and ≥1 relapse in the past year or ≥2 relapses in the past 2 years</td><td></td><td>Confirmed disability progression</td><td>
<table>
<tr><th>Subgroup</th><th>HR, (95% CI)</th></tr>
<tr><td>Sex</td><td></td></tr>
<tr><td>Men</td><td>0.33, (0.22 to 0.50)</td></tr>
<tr><td>Women</td><td>0.50, (0.39 to 0.65)</td></tr>
<tr><td>Age</td><td></td></tr>
<tr><td>>40 years</td><td>0.76, (0.54 to 1.09)</td></tr>
<tr><td>≤40 years</td><td>0.33, (0.25 to 0.43)</td></tr>
<tr><td>Treatment history</td><td></td></tr>
<tr><td>Previously treated</td><td>0.54, (0.39 to 0.74)</td></tr>
<tr><td>Treatment naïve</td><td>0.36, (0.27 to 0.49)</td></tr>
<tr><td>Number of relapses in year before study</td><td></td></tr>
<tr><td>>1</td><td>0.37, (0.27 to 0.51)</td></tr>
<tr><td>≤1</td><td>0.52, (0.39 to 0.69)</td></tr>
<tr><td>Number of relapses in two years before study</td><td></td></tr>
<tr><td>>2</td><td>0.50, (0.34 to 0.72)</td></tr>
<tr><td>2</td><td>0.45, (0.32 to 0.63)</td></tr>
<tr><td>1</td><td>0.37, (0.24 to 0.58)</td></tr>
<tr><td>Baseline disability</td><td></td></tr>
<tr><td>EDSS >3.5</td><td>0.34, (0.20 to 0.58)</td></tr>
<tr><td>EDSS 0 to 3.5</td><td>0.48, (0.38 to 0.60)</td></tr>
<tr><td>Number of gadolinium-enhancing lesions</td><td></td></tr>
<tr><td>≥1</td><td>0.40, (0.29 to 0.55)</td></tr>
<tr><td>0</td><td>0.48, (0.36 to 0.65)</td></tr>
<tr><td>T2 lesion volume</td><td></td></tr>
<tr><td>>3,300 mm</td><td>0.47, (0.36 to 0.63)</td></tr>
<tr><td>≤3,300 mm</td><td>0.40, (0.29 to 0.57)</td></tr>
<tr><td>Disease activity in treatment-naïve or previously treated patients</td><td></td></tr>
<tr><td>Group A*</td><td>0.29, (0.16 to 0.52)</td></tr>
<tr><td>Group B†</td><td>0.38, (0.24 to 0.62)</td></tr>
<tr><td>Group C‡</td><td>0.38, (0.21 to 0.68)</td></tr>
<tr><td>Group D§</td><td>0.49, (0.31 to 0.78)</td></tr>
<tr><td>Group E‖</td><td>0.33, (0.18 to 0.62)</td></tr>
</table>

Secondary:
Disability progression confirmed after three months
<table>
<tr><th>Subgroup</th><th>HR, (95% CI)</th></tr>
<tr><td>Sex</td><td></td></tr>
<tr><td>Men</td><td>0.43, (0.22 to 0.81)</td></tr>
<tr><td>Women</td><td>0.77, (0.53 to 1.10)</td></tr>
</table>
</td></tr>
</table>

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

Age	
>40 years	0.74, (0.46 to 1.19)
≤40 years	0.68, (0.45 to 1.02)
Treatment history	
Previously treated	0.70, (0.43 to 1.14)
Treatment naïve	0.63, (0.41 to 0.95)
Number of relapses in year before study	
>1	0.62, (0.37 to 1.05)
≤1	0.70, (0.47 to 1.03)
Number of relapses in two years before study	
>2	0.40, (0.21 to 0.77)
2	0.71, (0.44 to 1.13)
1	0.84, (0.46 to 1.52)
Baseline disability	
EDSS >3.5	0.32, (0.14 to 0.73)
EDSS 0 to 3.5	0.77, (0.55 to 1.09)
Number of gadolinium-enhancing lesions	
≥1	0.62, (0.37 to 1.04)
0	0.75, (0.50 to 1.11)
T2 lesion volume	
>3,300 mm	0.59, (0.38 to 0.90)
≤3,300 mm	0.85, (0.53 to 1.36)
Disease activity in treatment-naïve or previously treated patients	
Group A*	0.64, (0.27 to 1.51)
Group B†	0.59, (0.29 to 1.20)
Group C‡	0.68, (0.29 to 1.62)
Group D§	0.54, (0.26 to 1.10)
Group E‖	0.73, (0.25 to 2.07)

*Patients who received interferon beta during the year before study enrollment but who had as many or more relapses in the year immediately before the study than in the two years before the study.
†Patients who received any disease modifying therapy during the year before study enrollment but who had as many or more relapses in the year immediately before the study than in the two years before the study.
‡ Patients who received interferon beta during the year before study enrollment and had at least one relapse in the previous year plus at least either one gadolinium-enhancing T1 lesion or nine T2 lesions at baseline.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				§ Patients who received any disease modifying therapy during the year before study enrollment and had at least one relapse in the previous year plus at least either one gadolinium-enhancing T1 lesion or nine T2 lesions at baseline. ‖Treatment-naïve rapidly evolving severe RRMS with at least two relapses within the year before baseline and at least one gadolinium-enhancing lesion at baseline.
Kappos et al.[45] (2006) Fingolimod 1.25 mg once daily vs fingolimod 5 mg once daily vs placebo Patients who were randomized to placebo for the first six months were randomized to active treatment during the six month ES (placebo/fingolimod group).	DB, ES, MC, PC, RCT Patients 18 to 60 years of age with RRMS, an EDSS score 0 to 6, neurologically stable condition with no evidence of relapse for ≥30 days before screening and ≥2 documented relapses during the previous two years; ≥1 documented relapse in the year before enrollment or ≥1 gadolinium-enhanced lesions detected by MRI at screening	N=281 6 months (followed by a 6 month ES)	Primary: Total number of gadolinium-enhanced lesions/ patient recorded on T1-weighted MRI intervals for six months Secondary: Total number of gadolinium-enhanced lesions per patient, the proportion of patients with gadolinium-enhanced lesions, total number of new lesions per patient on T2-weighted images, changes in lesion volume on T2-weighted images, brain volume from baseline to month six, number of patients remaining free of relapse,	Primary: The total cumulative numbers of lesions per patient on post-baseline, monthly gadolinium-enhanced T1-weighted MRI scans were lower in both fingolimod groups compared to the placebo group (P<0.001 for 1.25 mg and P=0.006 for 5 mg). Secondary: At 12 months, the number of lesions remained low in the two groups of patients who received continuous treatment with fingolimod, whereas the number decreased significantly in the placebo-to-fingolimod group (P value not reported). At six months, the proportion of patients who were free of gadolinium-enhanced lesions was greater in both fingolimod groups than with the placebo group (P<0.001 for both comparisons), with a separation between the curves becoming evident after two months of treatment. With the exception of the change in brain volume from baseline, all secondary MRI endpoints differed significantly between the fingolimod groups and the placebo group, in each case favoring treatment with fingolimod. At 12 months, MRI variables consistently demonstrated that fingolimod continued to have a marked effect on inflammatory activity, as reflected by MRI findings. At 12 months, more than 80% of patients who received fingolimod were free of gadolinium-enhanced lesions.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			ARR, time to first relapse, disability scores	The trial was not powered to detect a treatment effect on relapse endpoints; however, in both groups of patients who received continuous fingolimod, 79% were free of relapse at month 12, whereas 65 to 67% were free of relapse in the placebo-to-fingolimod group. Significant improvements over placebo were observed in the fingolimod groups, including a reduction in the ARR (by 53% in the 5 mg group and by 55% in the 1.25 mg group). For the placebo-to-fingolimod group, the ARR was lower during the period of treatment with fingolimod. The relapse rates for patients who received continuous fingolimod remained low during months seven to 12, with overall 12 month relapse rates of 0.31 and 0.29 for the 1.25 and 5 mg dose, respectively. The estimated time to a first relapse was significantly prolonged in the fingolimod groups (P value not reported). There were no significant differences in EDSS scores at 12 months between the fingolimod groups and the placebo/fingolimod group (P=0.74 for 1.25 mg and P=0.64 for 5 mg).
Radue et al.[46] (2012) Fingolimod 0.5 mg QD vs Fingolimod 1.25 mg QD vs placebo	DB, MC, PC, RCT Patients 18 to 55 years of age with RRMS and an EDSS score 0 to 5.5 and ≥1 relapse in the past year or ≥2 relapses in the past 2 years	N=1,272 2 years	Primary: Proportion of patients free from gadolinium-enhancing lesions, proportion of patients free from gadolinium-enhancing T1 lesions or new anti-inflammatory activity, proportion of patients free from new or enlarged T2 lesions, change from	Primary: Both fingolimod 0.5 mg and 1.25 mg significantly decreased the number of new/newly enlarged T2 lesions, the number of gadolinium-enhancing lesions and the volume of gadolinium-enhancing lesions from baseline over 24 months compared to placebo (P<0.001 for all). Additionally, the proportion of patients free from new/newly enlarged T2 lesions, gadolinium-enhancing lesions or both was significantly greater in patients receiving fingolimod compared to placebo (P<0.001 for all) Change in T2 lesion volume was significantly reduced in each fingolimod group compared to placebo at both 12 and 24 months (P<0.001 for all). The actual T2 lesions volume slightly decreased in each fingolimod group, but increased in the placebo group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			baseline in the total volume of T2 lesions or T1 hypointense lesions, change in PBVC Secondary: Not reported	After 24 months, T1 hypointense lesion volume increased in the placebo group, but remained stable in each fingolimod group (absolute change vs placebo, P<0.001 for each). Both fingolimod groups significantly reduced PBVC compared to placebo from months 0 to 6, 0 to 12 and 12 to 24 (P<0.05 for all). Secondary: Not reported
Saida et al.[47] (2012) Fingolimod 0.5 mg QD vs Fingolimod 1.25 mg QD vs placebo	PC, PG, RCT Patients aged 18 to 60 years, a diagnosis of MS according to the revised McDonald criteria and a relapsing course of the disease	N=171 6 months	Primary: Percentage of patients free from gadolinium-enhanced lesions at months three and six Secondary: Relapses over six months, safety	Primary: The proportion of patients who were free from gadolinium-enhanced lesions at months three and six was significantly greater in the fingolimod 0.5 mg (70%) and 1.25 mg (86%) groups compared to placebo (40%; P<0.004 and P<0.001, respectively). Secondary: The proportion of patients who were relapse free in the fingolimod 0.5 mg and 1.25 mg groups was 78.9% and 83.3%, respectively, compared to 64.9% in the placebo group (OR, 1.94; 95% CI: 0.82 to 4.63 and OR, 2.49; 95% CI: 0.99 to 6.29, respectively). An adverse event was reported in 91.2% and 94.4% of patients receiving fingolimod 0.5 mg and 1.25 mg, respectively, compared to 78.9% of patients receiving placebo (No P values reported). Additionally, a serious adverse event was reported in 8.8% and 20.4% of patients receiving fingolimod 0.5 mg and 1.25 mg, respectively, compared to 5.3% of patients receiving placebo (No P values reported). Adverse events related to fingolimod included transient bradycardia and atrioventricular block at treatment initiation and elevated liver enzymes.
Cohen et al.[48] (2010) TRANSFORMS Fingolimod 0.5 mg once daily vs	DB, DD, MC, PG, RCT Patients 18 to 55 years of age with RRMS, EDSS score 0 to 5.5 and	N=1,292 12 months	Primary: ARR Secondary: The number of new or enlarged hyperintense	Primary: There were significantly greater reductions in ARR for both fingolimod groups compared to the IFNβ-1a group (fingolimod 1.25 mg: ARR, 0.20; 95% CI, 0.16 to 0.26; P<0.001, fingolimod 0.5 mg: ARR, 0.16; 95% CI, 0.12 to 0.21; P<0.001, IFNβ-1a: ARR, 0.33; 95% CI, 0.26 to 0.42).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
fingolimod 1.25 mg once daily vs IFNβ-1a (Avonex®) 30 µg IM once-weekly Previous or recent therapy with any type of IFNβ or GA was not a criterion for exclusion.	≥1 relapse in the past year or ≥2 relapses in the past two years		lesions on T2-weighted MRI scans at 12 months, time to confirmed disability progression and adverse events	There was no significant difference in the magnitude of the treatment effect between patients who had previously undergone disease treatment and those who had not. Secondary: Patients in the two fingolimod groups had significantly fewer new or enlarged hyperintense lesions on T2-weighted images at 12 months compared to those in the IFN group (fingolimod 1.25 mg: 1.5±2.7; P<0.001, fingolimod 0.5 mg: 1.7±3.9; P=0.004 and IFNβ-1a: 2.6±5.8). Confirmed disability progression was infrequent in all the treatment groups. There were no significant differences in the time to the progression of disability or in the proportion of patients with confirmed progression among the treatment groups (P values not reported). Adverse events were reported in similar proportions of patients in the three treatment groups, ranging from 86 to 92%. Serious adverse events and those leading to the discontinuation of a study drug were most frequent in patients assigned to fingolimod 1.25 mg. The most common adverse events observed were bradycardia and atrioventricular block. The overall incidence of infection was similar across the treatment groups (ranging from 51 to 53%). Increases in mean arterial pressure occurred in both fingolimod groups (3 mm Hg in the 1.25 mg group and 2 mm Hg in the 0.5 mg group) during the first six months and remained stable between six and 12 months. Macular edema was confirmed in six patients receiving fingolimod; four patients in the 1.25 mg group (1%) and two patients in the 0.5 mg group (0.5%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				A mild reduction (2 to 3%) in the mean forced respiratory volume in one second was observed in both fingolimod groups at one month, with no further reductions for the remainder of treatment.
Khatri et al.[49] (2011) TRANSFORMS Fingolimod 0.5 mg once daily vs fingolimod 1.25 mg once daily Patients initially randomized to either fingolimod dose in the core study continued treatment throughout the extension period. Patients initially randomized IFNβ-1a 30 µg IM once-weekly were randomly reassigned (1:1) to receive fingolimod 0.5 or 1.25 mg daily for the duration of the extension period.	DB, DD, ES, MC, PG, RCT A 12-month extension of TRANSFORMS; patients 18 to 55 years of age with RRMS, EDSS score 0 to 5.5 and ≥1 relapse in the past year or ≥2 relapses in the past two years; all patients must have completed the core study on assigned treatments	N=1,027 24 months	Primary: ARR Secondary: The number of new or enlarged hyperintense lesions on T2-weighted MRI scans at 12 months, time to confirmed disability progression, adverse events	Primary: Patients initially randomized to fingolimod 0.5 or 1.25 mg in the core study continued to experience reductions in ARR throughout the extension study (months 13 to 24). The estimated ARR for patients receiving fingolimod 0.5 mg was not different between the core study and 12 month extension period (0.12 vs 0.11, respectively; P=0.80). Similarly, there was no difference in the ARR for patients continuing the 1.25 mg dose through month 24 compared to the core study (0.15 vs 0.11 for, respectively; P=0.12). Patients switched from IFNβ-1a to either fingolimod dose in the extension period experienced greater reductions in ARR compared to initial treatment with IFNβ-1a. Patients switched to fingolimod 0.5 mg experience a lower ARR in the extension period compared to treatment with IFNβ-1a during the core trial (0.22 vs 0.31; P=0.049). Patients switched from IFNβ-1a to fingolimod 1.25 mg had lower ARR in the extension period with fingolimod treatment compared to treatment with IFNβ-1a in the core trial (0.18 vs 0.29; P=0.024). Switching from IFNβ-1a to fingolimod 0.5 mg was associated with a 30% reduction in relapse rates (ARR, 0.70; 95% CI, 0.49 to 1.00), while patients switched to the 1.25 mg dose experienced a 36% reduction in relapses (ARR, 0.64; 95% CI, 0.43 to 0.94). Secondary: Patients in the fingolimod 1.25 mg continuous treatment group had significantly fewer (mean) new or enlarged hyperintense lesions on T2-weighted images at 24 months compared to the end of the core study (1.0±2.3 vs 1.4±2.37; P=0.0003). Significant reductions in new or enlarged lesions were also observed in patients treated with the 0.5 mg dose at 24 months compared to month 12 (0.9±1.87 vs 1.6±3.60; P=0.0001). Patients switched from IFNβ-1a to either fingolimod dose for the extension period experienced significant reductions in new or

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				enhanced T2 lesions at 24 months compared to initial treatment with IFNβ-1a in the core study (1.0 vs 2.4 and 0.7 vs 2.1 for the 1.25 and 0.5 mg doses, respectively; P<0.0001 for both comparisons). There were no significant changes in EDSS scores in the extension period compared to the core study for any of the treatments. Patients switched from IFNβ-1a to fingolimod experienced fewer adverse events compared to treatment with IFNβ-1a in the core study (86 vs 91% and 91 vs 94% for the 0.5 and 1.25 mg groups, respectively; P values not reported). Fewer patients continuing fingolimod from the core study reported adverse events in the extension period compared to the core study. (72 vs 86% and 71 vs 90% for the 0.5 and 1.25 mg doses, respectively; P values not reported). There was a rise in serious cardiac-related adverse events after switching to fingolimod 1.25 mg (from 0% with IFNβ-1a to 2% with fingolimod) but not with the 0.5 mg dose (1% for both time periods).
Cohen et al.[50] (2016) TRANSFORMS Fingolimod 0.5 mg once daily vs fingolimod 1.25 mg once daily Patients initially randomized to either fingolimod dose in the core study continued treatment throughout the extension period. Patients initially randomized IFNβ-1a 30 µg IM once-weekly were randomly	DB, DD, ES, MC, PG, RCT A long-term extension of TRANSFORMS; patients 18 to 55 years of age with RRMS, EDSS score 0 to 5.5 and ≥1 relapse in the past year or ≥2 relapses in the past two years; all patients must have completed the core study on assigned treatments	N=772 Up to 4.5 years	Primary: ARR Secondary: The number of new or enlarged hyperintense lesions on T2-weighted MRI scans at 12 months, time to confirmed disability progression, adverse events	Primary: Patients in the continuous-fingolimod group who received treatment for up to 4.5 years demonstrated significantly lower ARR compared with those in the IFN-switch group (0.17 vs 0.27), with an associated 35% reduction in the risk of relapse (HR, 0.65; P<0.001). Within-group comparisons in the IFN-switch group showed a reduction in ARR from 0.40 to 0.20 after patients switched to fingolimod. In the continuous-fingolimod group, the low relapse rate during the extension phase (0.16) was comparable with that observed in the core phase (0.19). Secondary: New/newly enlarging T2 lesion counts remained low in the continuous-fingolimod group throughout the extension phase. The percentage of patients free of new/newly enlarging T2 lesions between the groups was similar throughout the extension study (continuous-fingolimod group: 42%; IFN-switch group: 45%; P=0.63).

<table>
<tr><th>Study and
Drug Regimen</th><th>Study Design and
Demographics</th><th>Study Size
and Study
Duration</th><th>End Points</th><th>Results</th></tr>
<tr><td>reassigned (1:1) to receive fingolimod 0.5 or 1.25 mg daily for the duration of the extension period.</td><td></td><td></td><td></td><td>HRs for confirmed disability progression were not statistically different at end of study in the continuous-fingolimod versus the IFN-switch group (HR 3-month confirmed disability progression, 0.94; CI, 0.71 to 1.26; P=0.687; 6-month confirmed disability progression, 1.08; CI, 0.77 to 1.51; P=0.674).

The highest incidence of adverse events during the extension phase was reported for nasopharyngitis, lymphocyte count decrease and headache. The proportion of patients who discontinued the study because of adverse events was similar between the treatment groups (8.4% in the continuous-fingolimod group, 7.8% in the IFN-switch group), mostly due to an increase in liver enzymes by >5-fold of the upper limit of normal.</td></tr>
<tr><td>Meca-Lallana et al.[51]
(2012)

GA

Patients must have switched from treatment with IFNβ and been on GA for at least 24 weeks.</td><td>MC, OS

Patients aged 18 to 60 years with a diagnosis of RRMS, a score of ≤5.5 on the Kurtzke EDSS and confirmed spasticity</td><td>N=68

6 months</td><td>Primary:
Changes on the PSFS, MAS, ATRS and GPS after three and six months

Secondary:
Change in disability, number of relapses, working days' leave, adverse events</td><td>Primary:
Significant reductions from baseline in mean scores on all spasticity measurement scales were observed after three and six months.

<table><tr><th>Scale</th><th>Baseline</th><th>Three Months</th><th>P Value (Three Months)</th><th>Six Months</th><th>P Value (Six Months)</th></tr><tr><td>PSFS</td><td>1.7</td><td>1.4</td><td><0.01</td><td>1.3</td><td><0.01</td></tr><tr><td>MAS</td><td>0.7</td><td>0.6</td><td><0.01</td><td>0.5</td><td><0.01</td></tr><tr><td>ATRS</td><td>1.6</td><td>1.4</td><td><0.01</td><td>1.3</td><td><0.01</td></tr><tr><td>GPS</td><td>29.4</td><td>24.7</td><td><0.01</td><td>19.1</td><td><0.01</td></tr></table>
Secondary:
EDSS scores were significantly decreased after three months but not after six months (P<0.05 and P=0.385, respectively). A relapse was observed in 10.3% of patients over six months.

After three months, 19.1% of patients reported missing work and after SIX months, 13.2% more patients reported missing work. The mean number of working days' leave used was 15.4 and 26.5 days, at three and six months, respectively.

At least one adverse event was reported in five (7.4%) of patients, however only one was considered possibly related to GA.</td></tr>
</table>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Ford et al.[52] (2010) GA 20 mg SC daily vs placebo	ES, OL, PRO Patients with RRMS who had experienced ≥2 medically documented relapses in the previous two years and had EDSS scores 0 to 5 at study entry	N=100 180 months	Primary: Change from baseline in ARR, change in EDSS scores, yearly EDSS scores Secondary: Not reported	Primary: The cohort of patients continuing to receive GA for 15 year had a lower ARR compared to their baseline values (0.25±0.34 vs 1.12±0.82; P value not reported). These results appear to be lower compared to reductions in AAR for patients completing the original study but who did not remain on treatment for 15 years (0.43±0.58 vs 1.18±0.82; P value not reported), although the significance the lowered relapse rate in these patients is unknown. Of patients who withdrew from the original study, the ARR associated with GA treatment was 0.56±0.68 compared to baseline relapse rates of 1.23±0.83 (P value not reported). The cohort of patients continuing GA treatment for 15 years had a slower progression in EDSS scores compared to the modified ITT population of patients completing the original study, and the population of patients who withdrew from the original study (0.6±2.0 vs 0.9±1.8 and 1.0±1.7 points, respectively; P value not reported). Moreover, the average yearly change in EDSS was smaller with the cohort of patients continuing GA treatment for 15 years compared to the original modified ITT population completing the original study, and the population of patients who withdrew from the original study (0.1±0.2 vs 0.2±0.6 and 0.5±0.8, respectively; P value not reported) Secondary: Not reported
Boneschi et al.[53] (2003) GA 20 mg SC daily vs placebo	MA DB, PC, RCTs of patients 18 to 50 years of age with RRMS for at least one year with ≥1 relapse in the previous two years	N=540 (3 studies) Up to 35 months	Primary: ARR Secondary: Total number of relapses, time to first relapse and disability progression	Primary: Treatment with GA was associated with a statistically significant 28% reduction in the ARR compared to treatment with placebo (0.82 vs 1.14; P=0.004). Secondary: Treatment with GA was associated with a statistically significant 36% reduction in the total number of relapses compared to treatment with placebo (P<0.0001).

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				Treatment with GA was associated with a statistically significant 32% delay in the time to first relapse compared to treatment with placebo (322 vs 219 days; P=0.01). Treatment with GA was associated with a beneficial effect on disability progression compared to treatment with placebo (RR, 0.6; 95% CI, 0.4 to 0.9; P=0.02).
Caon et al.[54] (2006) GA 20 mg SC daily Administered for up to 42 months to patients who had previously received IFNβ-1a 30 µg IM once-weekly therapy for up to 24 months.	OL, PRO Patients 18 years of age or older with RRMS	N=85 Up to 24 months	Primary: ARR Secondary: Change in EDSS	Primary: Switching to GA was associated with a statistically significant 57% reduction in the ARR from 1.23 to 0.53 (P=0.0001). In a subgroup of patients who switched to GA due to lack of efficacy with IFNβ-1a, the ARR was reduced from 1.32 to 0.52 (61%; P=0.0001). There was no statistically significant reduction in the ARR among patients who switched from IFNβ-1a to GA due to adverse effects (P=NS). Secondary: After 37.5 months of GA there was a statistically significant improvement in mean EDSS scores (P=0.0001).
Zwibel et al.[55] (2006) GA 20 mg SC daily administered to treatment naive patients vs GA 20 mg SC daily administered to patients who had previously received IFNβ-1b therapy	MC, OL, PRO Patients 18 years of age or older with RRMS and an EDSS disability score ≤6	N=805 3.5 years	Primary: ARR, proportion of relapse-free patients, time to first relapse, progression of neurological disability (measured by change in EDSS score from baseline) and proportion of patients with sustained	Primary: There was no significant difference between the prior IFNβ-1b and treatment-naïve groups in the reduction of ARR from two years before study entry (75% in both groups; P=0.148). No significant difference was reported between the prior IFNβ-1b and treatment-naïve groups in the proportion of relapse-free patients throughout the study (68.4 vs 69.5%; P>0.90). There were no differences in the estimated time to first relapse for 25% of patients in the prior IFNβ-1b and treatment-naïve groups (245 vs 328 days, respectively; P=0.28). Patients with a prior history of IFNβ-1b therapy exhibited a higher rate of neurological disability progression at 12 and 18-months and

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			progression (≥1 EDSS point increase for six months) Secondary: Not reported	last observation compared to treatment-naïve patients (P=0.0070, P=0.0155 and P=0.0018, respectively). There were no significant differences between the study groups in regards to the proportion of patients with sustained progression (P=0.209). Secondary: Not reported
Miller et al.[56] (2008) GA 20 mg SC daily	OL, PRO Patients with RRMS	N=46 Up to 22 years	Primary: ARR, percentage of relapse-free patients, change in EDSS and adverse events Secondary: Not reported	Primary: Throughout the course of the study patients experienced a statistically significant reduction in the ARR from 2.9 to 0.1 at last observation (P<0.0001). Of patients who continued therapy through the end of the study 72% were free of relapses (P value not reported). There were no significant changes in the mean EDSS scores from baseline (P=0.076) with the majority (67%) of continuing patients exhibiting improved or stable EDSS scores. The most commonly reported adverse events were injection site reactions. Six patients who received GA for up to 22 years reported lipoatrophy. Skin necrosis was not observed. A discontinuation rate of 61% was observed. The most common reason for discontinuing the study was withdrawal of consent. Secondary: Not reported
La Mantia et al.[57] (2010) GA 20 mg SC daily vs placebo	MA RCTs comparing GA and placebo in patients of any age or gender with definite MS of any	N=1,458 (540 with RRMS) Up to 35 months	Primary: Patient disease progression (defined as worsening of at least one point in EDSS for six months), mean	Primary: Treatment with GA did not significantly reduce the risk of disease progression at two years (RR, 0.75; 95% CI, 0.51 to 1.12; P=0.16) or at 35 months (RR, 0.81; 95% CI, 0.50 to 1.29; P=0.37). Patients randomized to receive GA experienced small yet significant decreases in EDSS scores at two years (WMD, -0.33; 95% CI, -0.58

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	severity according to Poser criteria		changes in EDSS score, frequency of clinical relapses, patients who remained relapse-free, frequency of adverse events and quality of life Secondary: Number of patients requiring steroid courses, hospital admissions and length of stay	to -0.08; P=0.009) and at 35 months (WMD, -0.45; 95% CI, -0.77 to -0.13; P=0.006). Compared to placebo, there was a significant reduction in the frequency of clinical relapses reported with GA use at one year (-0.35; P=0.0002), at two years (-0.51; P=0.0006) and at 35 months (-0.64; P=0.002). Patients randomized to receive GA were more likely to remain relapse- free after one year of treatment compared to patients randomized to receive placebo (RR, 1.28; 95% CI, 1.02 to 1.62; P=0.03). The risk of being relapse-free after two years and 35 months continued to be higher in the GA treatment group, although the difference was not statistically significant (RR, 1.39; 95% CI, 0.99 to 1.94; P=0.06 and RR, 1.33; 95% CI, 0.86 to 2.06; P=0.19, at two years and 35 months, respectively). Injection-site reactions including itching, swelling, redness and pain occurred more frequently with GA compared to placebo (P<0.05 for all comparisons). Secondary: There was a significantly lower risk of requiring steroids in patients treated with GA compared to patients treated with placebo over nine months (RR, 0.65; 95% CI, 0.52 to 0.82; P=0.0002), although only one study evaluated this outcome. Data from hospital admission rates showed that patients receiving GA experienced fewer hospitalization by the end of follow-up compared to patients who were treated with placebo (RR, 0.54; 95% CI, 0.31 to 0.93; P=0.02).
Khan et al.[58] (2013) GALA GA 40 mg SC three times weekly	DB, MC, PC, PG, Phase III, RCT Patients 18 to 55 years of age with RRMS with at least	N=1,404 12 months	Primary: Total number of confirmed relapses during the 12-month PC phase	Primary: GA group had a 34% reduction in the risk of relapse compared to placebo group (mean ARR, 0.331 vs 0.505; RR, 0.656; 95% CI, 0.539 to 0.799; P<0.0001). Secondary:

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vs placebo	1 documented relapse in the 12 months before screening, or at least 2 documented relapses in the 24 months before screening, and an EDSS score ≤5.5 with relapse-free for ≥30 days		Secondary: Cumulative number of new/newly enlarging T2 lesions as months 6 and 12, cumulative number of Gd-enhancing lesions on T1-WI taken at months 6 and 12, brain atrophy defined as the percentage brain volume change from baseline to month 12, time to the first confirmed relapse, proportion of relapse-free patients, total number of severe confirmed relapses defined as those requiring hospitalizations or intravenous steroids	The time to first confirmed relapse was significantly longer in the GA group compared to placebo group (393 days vs 377 days; HR, 0.606; 95% CI, 0.493 to 0.744; P<0.0001). GA group (77.0%) compared to placebo group (65.5%) had a greater proportion of relapse-free patients (OR, 1.928; 95% CI, 1.491 to 2.494; P<0.0001). GA group was associated with 35% reduction in annualized rate of severe relapse (0.301 vs 0.466; RR, 0.644; 95% CI, 0.526 to 0.790; P<0.0001). Patients in the GA group experienced 45% reduction in the cumulative number of Gd-enhancing T1 lesions compared to placebo (RR, 0.552; 95% CI, 0.436 to 0.699; P<0.0001) and 35% reduction in the cumulative number of new or newly enlarging T2 lesions (RR, 0.653; 95% CI, 0.546 to 0.780; P<0.0001) at months 6 and 12. The percentage change in normalized brain volume at month 12 from baseline was similar between treatment arms (20.706 with GA group vs 20.645 with placebo group; P=0.2058). The most common adverse reactions were injection-site reactions with 35.2% in the GA group vs 5.0% in the placebo group with 99.9% reactions being mild or moderate in severity. The most common injection-site reactions with an incidence of >5% in the GA group were erythema (20.9%), injection site pain (10.4%) and pruritics (5.9%). Total number of severe confirmed relapses defined as those requiring hospitalizations or intravenous steroids results were not noted.
Khan et al.[59] (2017) GA 40 mg SC three times weekly	OL extension of the GALA study Patients from either treatment arm who	N=1,041 36 months	Primary: ARR Secondary:	Primary: The ARR during the OL extension phase was similar between patients who has received GA and were continued on therapy compared to those who had originally been in the placebo group and were switched to GA. At Year two RR=0.944 (95% CI, 0.716 to

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	completed the GALA study.		Time to first relapse; time to confirmed disability progression; number of MRI lesions; changes in brain volume; and safety	1.245; P=0.68) and at Year three RR=1.043 (95% CI, 0.782 to 1.391; P=0.78). Secondary: Time to first relapse was significantly longer in patients who continued GA therapy as compared to patients who had been treated with placebo and were switched to GA (HR=0.746; 95% CI, 0.628 to 0.887; P=0.0009). The percent of patients who experienced six-month confirmed disability progression was 11% in patients who continued GA therapy and 13% in patients who were switched from placebo to GA (HR=0.759; 95% CI, 0.552 to 1.044; P=0.09). The number of GdE T1 lesions and new or enlarging T2 lesions was similar between the two groups at Year three (GdE T1 lesions: RR=1.19; 95% CI, 0.728 to 1.946; P=0.49) (new or enlarging T2 lesions: RR=0.907; 95% CI, 0.677 to 1.214; P=0.51). The change loss of whole brain volume from baseline to 36 months for the patients who continues on GA as compared to those who were switched from placebo to GA was -1.81% and -1.98%, respectively (P= 0.12). Between Months 12 to 36: the changes were -1.13% and -1.27%, respectively (P=0.08). At Month 36, patients who continued GA had a gray matter volume loss of -2.01 compared to baseline and patients who were switched from placebo to GA had a loss of -2.33% (P=0.07). Between Months 12 and 36 the loses were -1.16% and -1.53%, respectively (P=0.015). No significant differences were observed in white matter, thalamic, or deep gray matter volume changes between groups. There were no new safety signals identified. Over three-quarters of patients exposed to GA experienced at least one adverse effect. Of those treated with GA 8% experienced a serious adverse effect.
Lubin et al.[60] (2017)	Blinded, ES, RCT	N=584 Seven years	Primary: ARR	Primary: The ARR based on protocol defined exacerbations was 0.10 in the GA plus IFNβ-1a group, 0.13 in the IFNβ-1a group, and 0.09 in the

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GA 20 mg SC once daily + IFNβ-1a (Avenox®) 30ug IM weekly vs GA 20 mg SC once daily vs IFNβ-1a (Avenox®) 30ug IM weekly	Patients were 18 to 60 years of age with an EDSS score of ≤6, and with at least two relapses in the prior three years during enrollment in the original study. Patients who completed the three-year core study were eligible for the extension study.		Secondary: Confirmed worsening measured by EDSS; MRI outcomes; clinical activity free status; and safety	GA group. Statistical significance was only observed in between the GA plus IFNβ-1a and IFNβ-1a groups (P=0.019). Secondary: The proportion of patients with 6-month worsening over the core phase of the study was 23.9% in the GA plus IFNβ-1a group, 21.6% in the IFNβ-1a group and 24.8% in the GA group. The absolute percent increases in the extension phase were 5.5% for the GA plus IFNβ-1a group, 6.6% for the IFNβ-1a group and 6.9% for the GA group. These values were not statistically significant. The proportion of participants cumulatively Gd+ free at years 3, 4 and 6 was higher in the GA plus IFNβ-1a group compared to the IFNβ-1a group (P=0.0002, <0.008 and <0.02). There were no differences in the proportion of participants who were clinical activity free No new safety issues arose during the extension.
Carmona et al.[61] (2008) IFNβ-1b (Betaseron®) 0.25 mg SC every other day vs no treatment	OL, PRO Patients with clinically definite RRMS and a history of ≥2 relapses in the previous two years	N=159 Up to 5 years	Primary: Percentage of relapse-free patients, ARR, time to first relapse, disability progression (assessed by change in EDSS scores) and time to progression Secondary: Not reported	Primary: The percentage of patients treated with IFNβ-1b who were relapse-free at the end of follow-up was 21.7% (P value not reported). At two years of follow-up, 32.5% of patients in the IFNβ-1b group were relapse-free compared to 22.7% of patients in the control group (P=NS). The mean ARR in the IFNβ-1b group was 0.70 relapses per year (P value not reported). The mean ARR at two year follow-up in the IFNβ-1b group was 0.74 compared to 2.20 in the control group (P=0.001). The median time to first relapse in the IFNβ-1b group was 375 days compared to 313 days in the control group (P=0.26). The mean number of relapses after two years of treatment decreased by 47% (from 3.2 at baseline to 1.7; P value not reported).

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				At 59 months of follow-up, 25% of IFNβ-1b treated patients progressed by one point on the EDSS from baseline (P value not reported). The mean time that it took for the IFNβ-1b treated patients to progress by one point on the EDSS was longer compared to the control group (72.94 vs 36.94 months; P=0.002). Higher EDSS scores were observed at the end of follow-up among patients who had experienced a relapse during the first 12 months of treatment compared to those patients who did not have a relapse (3.37 vs 2.36; P=0.003). At the end of follow-up, 70% of patients remained on IFNβ-1b therapy with sustained efficacy and good tolerance. Secondary: Not reported
PRISMS study group[62] (1998) IFNβ-1a (Rebif®) 22 µg SC three times weekly vs IFNβ-1a (Rebif®) 44 µg SC three times weekly vs placebo	DB, I, MC, PC, RCT Adult patients, median age 34.9 years, with RRMS and EDSS scores 0 to 5 and ≥2 relapses in the preceding two years	N=560 2 years	Primary: Mean number of relapses Secondary: Relapse rate, percentage of patients relapse-free at one and two years, mean number of moderate to severe relapses, mean number of hospital admissions, mean change in EDSS, median time to first relapse, time to sustained progression, burden	Primary: Patients randomized to IFNβ-1a 22 and 44 µg groups experienced significantly fewer mean number of relapses compared to patients receiving placebo at two years of therapy (1.82 and 1.73 vs 2.56, respectively; P<0.005). Secondary: Compared to the placebo group, the relapse rate was reduced by 29% in the IFNβ-1a 22 µg group and 32% in the IFNβ-1a 44 µg group (P value not reported). At one year, a significantly greater percentage of patients in the IFNβ-1a 22 and 44 µg groups were relapse-free compared to those receiving placebo (37 and 45 vs 22%, respectively; P<0.005). At two years, a significantly greater percentage of patients in the IFNβ-1a 22 µg (27 vs 16%; P≤0.05) and IFNβ-1a 44 µg (32 vs 16%; P<0.005) groups were relapse-free compared to those receiving placebo.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			of disease and adverse events	The mean number of moderate to severe relapses was significantly lower in the IFNβ-1a 22 and 44 µg groups compared to the placebo group (0.71 and 0.62 vs 0.99; P<0.005). The mean number of hospital admissions was significantly lower in the IFNβ-1a 44 µg group compared to patients receiving placebo (0.25 vs 0.48, respectively; P<0.005). The mean change in EDSS was significantly smaller in the IFNβ-1a 22 and 44 µg groups compared to patients receiving placebo (0.23 and 0.24 vs 0.48, respectively; P≤0.05). The median time to first relapse was delayed by three and five months in the IFNβ-1a 22 and 44 µg groups, respectively (P value not reported). The time to sustained progression was significantly longer in both the IFNβ-1a 22 and 44 µg groups compared to the placebo group (P<0.05). The burden of disease was significantly increased in the placebo group compared to the IFNβ-1a 22 and 44 µg groups (10.9 vs -1.2 and -3.8%, respectively; P<0.0001 for both compared to placebo). The following adverse events occurred more frequency with IFNβ-1a treatment compared to placebo: injection-site reactions, lymphopenia, increased ALT, leukopenia and granulocytopenia (P≤0.05).
Kappos et al.[63] (2006) PRISMS IFNβ-1a (Rebif®) 22 µg SC three times weekly vs	DB, ES, I, PC, RCT This was a PRISMS extension study; patients with RRMS and EDSS scores 0 to 5 and ≥2 relapses within	N=382 Up to 8 years	Primary: Mean change in EDSS scores, progression to SPMS, ARR, percentage of relapse-free patients, annualized change in T2 burden of disease,	Primary: Among patients returning for follow-up after eight years of therapy, mean EDSS scores increased by 1.1 points. Approximately 31.3% of patients progressed by two EDSS points. The longest time to reach disability progression was observed among patients initially randomized to IFNβ-1a 44 µg (2.3 vs 1.0 year for the late treatment group). Progression to SPMS occurred in 19.7% of patients. The time to developing SPMS was 5.3 years.

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IFNβ-1a (Rebif®) 44 µg SC three times weekly vs placebo for initial two years, followed by IFNβ-1a 22 or 44 µg (Rebif®) SC three times a week for additional six years (later treatment group)	two years prior to study onset		change in brain parenchymal volume, adverse events and antibody development Secondary: Not reported	The ARR was lower in the IFNβ-1a 44 µg (0.60 vs 0.78; P=0.014) and IFNβ-1a 22 µg (0.63 vs 0.78; P<0.001) treatment groups compared to patients in the late treatment group. The greatest percentage of patients remaining relapse-free at follow-up were those receiving IFNβ-1a 44 µg (15.4%) compared to patients in the IFNβ-1a 22 µg (8.1%) and late treatment groups (6.5%; P value not reported). Compared to the late treatment group, patients initially randomized to IFNβ-1a 44 µg therapy had a lower increase in T2 burden of disease (5.0 vs 24.5%; P=0.002). At two years of follow-up, patients receiving placebo experienced a greater median annualized increase in T2 burden of disease compared to the IFNβ-1a 22 and 44 µg groups (6.5 vs -0.7 and -2.8%, respectively; P value not reported). At eight-year follow-up, all treatment groups experienced a median relative reduction in brain parenchymal volume of 3.9% from baseline (P value not reported). At eight-year follow-up, the most frequently reported adverse events were injection-site disorders, reported by 44% of patients. Flu-like symptoms occurred in 11.7% of patients. Elevated ALT was the most common liver abnormality, affecting approximately 8.4% of patients on IFNβ-1a therapy. Lymphopenia and leukopenia were reported by 19.6 and 14.0% of patients receiving IFNβ-1a therapy, respectively. Of patients who developed antibodies, 90% did so during the first two years of therapy. Of patients returning for follow-up after eight years of therapy 72% remained on SC IFNβ-1a. Secondary:

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				Not reported
Rice et al.[64] (2009) IFNα-2a (Roferon-A®) 9 MIU IM every other day vs IFNβ-1a (Avonex®) 6 to 12 MIU IM once-weekly vs IFNβ-1a (Rebif®) 6 to 12 MIU SC three times weekly vs IFNβ-1b (Betaseron®) 0.6 to 8 MIU SC every other day vs placebo	MA DB, PC, RCTs of patients with RRMS who were treated with recombinant IFN, given by the SC or the IM route	N=1,301 (8 studies) Up to 24 months	Primary: Exacerbation rate during treatment and follow-up, percent of patients who progressed during treatment, mean change in EDSS score and the percent of patients unable to walk without aid at the end of treatment (EDSS >5.5) Secondary: Time to first exacerbation, time to progression in disability, percent of patients requiring steroid administration during IFN treatment and follow-up, hospitalizations during treatment and follow-up, number of patients reporting adverse events, mean change of total lesion load on T2 weighted images, and the number of	Primary: Patients treated with IFN therapy were significantly less likely to experience an exacerbation during the first year of treatment compared to patients receiving placebo (pooled RR, 0.73; 95% CI, 0.55 to 0.97; P=0.03). During the first two years, IFN treatment was associated with lower rates of exacerbations compared to placebo (55 vs 69%; RR, 0.80; 95% CI, 0.73 to 0.88; P<0.001). The type of IFN administered or route of administration did not appear to affect the number of patients experiencing exacerbations. Disease progression, defined as ≥1 EDSS point increase for three to six months, occurred in 20% of the patients receiving IFN treatment compared to 29% of patients receiving placebo over two years (RR, 0.69; 95%CI, 0.55 to 0.87; P=0.002). Patients treated with IFN experienced a small but significant decrease in EDSS score relative to patients treated with placebo (WMD, -0.25; 95% CI, -0.05 to -0.46; P=0.01). Notably, this outcome was only reported in two studies. No data was available for the number of patients who were unable to walk without aid. Secondary: The frequency of steroid administration over the first year of treatment was only reported in two studies. Result from one study found a non-significant reduction in steroid requirements between IFN treatment and placebo, while the second study reported no difference between treatments. One study evaluated steroid requirements over two years and concluded that patients treated with IFN were less likely to require steroid administration compared to patients treated with placebo (RR, 0.70; 95% CI, 0.56 to 0.87; P=0.001). There was no reduction in the frequency of hospitalization between participants treated with IFN and those treated with placebo (RR,

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			patients continuing to show gadolinium-enhancing lesions during treatment and follow-up	0.44; 95% CI, 0.08 to 2.36; P=0.30). Flu-like symptoms, injection site reactions, development of psychiatric disorders, leukopenia, lymphopenia and elevated liver enzymes were all reported more frequently in IFN groups compared to the placebo group (P<0.05 for all). The evolution in MRI technology in the decade in which these studies were conducted and varied data reporting in the studies made it impossible to perform a quantitative analysis of the MRI results. A reduction in gadolinium enhancing lesions was apparent after one year of treatment in two studies, but the benefit was not apparent at two years. No data were available for the time to first exacerbation or time to progression in disability.
Freedman et al.[65] (2008) GA 20 mg SC weekly vs IFNβ-1b (Betaseron®) 0.25 mg SC every other day vs IFNβ-1a (Rebif®) 22 to 44 µg SC three times weekly vs IFNβ-1a (Avonex®) 30 µg IM once-weekly vs	MA DB, MC, PC, RCTs with a sample size >30 patients, that included patients at least 18 years of age diagnosed with a clinically-definite RRMS	N=2,351 (6 studies) Up to 2 years	Primary: The proportion of patients relapse-free at one year, proportion of patients relapse-free at two years, proportion of patients progression-free at two years, proportion of patients free of gadolinium-enhancing lesions at one year Secondary: Not reported	Primary: Compared to placebo, a significantly greater proportion of patients receiving IFNβ-1a 22 to 44 µg SC (AAR, 0.23; 95% CI, 0.14 to 0.33; P value not reported) and natalizumab were relapse-free at one year (AAR, 0.23; 95% CI, 0.17 to 0.30; P value not reported). The proportion of patients receiving IFNβ-1a 30 µg IM or GA that were relapse-free at one year of therapy was not statistically different from those receiving placebo (P value not reported). Compared to placebo, a significantly greater proportion of patients receiving IFNβ-1a 22 to 44 µg SC (AAR, 0.17; 95% CI, 0.09 to 0.26; P value not reported), IFNβ-1b (AAR, 0.14; 95% CI, 0.04 to 0.25; P value not reported), and natalizumab were relapse-free at two years (AAR, 0.26; 95% CI, 0.20 to 0.33; P value not reported). The proportion of patients receiving GA who were relapse-free at two years of therapy was not statistically different from those receiving placebo (P value not reported). Compared to placebo, a significantly greater proportion of patients were progression-free at two years among patients receiving IFNβ-1a 22 to 44 µg SC (AAR, 0.11; 95% CI, 0.01 to 0.20; P value not reported), IFNβ-1a 30 µg IM (AAR, 0.13; 95% CI, 0.03 to 0.23; P

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natalizumab 300 mg IV infusion every four weeks vs placebo				value not reported) and natalizumab (AAR, 0.12; 95% CI, 0.06 to 0.18; P value not reported). The proportion of patients progression-free at two years among patients receiving IFNβ-1b or GA was not statistically different from those receiving placebo (P value not reported). Compared to placebo, a significantly greater proportion of patients were free of gadolinium-enhancing lesions at one year among patients receiving IFNβ-1a 22 to 44 µg SC (AAR, 0.31; 95% CI, 0.17 to 0.44; P value not reported), IFNβ-1a 30 µg IM (AAR, 0.12; 95% CI, 0.01 to 0.24; P value not reported) and natalizumab (AAR, 0.28; 95% CI, 0.23 to 0.33; P value not reported). The proportion of patients free of gadolinium-enhancing lesions at one year among patients receiving GA was not statistically different from patients receiving placebo (P value not reported). Secondary: Not reported
Coppola et al.[66] (2006) IFNβ-1a (Avonex®) 30 µg IM once-weekly	OS, PRO Patients with a clinically definite or laboratory-confirmed MS	N=255 Mean of 31.7 months	Primary: Percentage of patients progression-free, percentage of patients relapse-free, relapse rate, change in EDSS scores and estimated time to disability progression Secondary: Not reported	Primary: At three years of therapy, 58% of patients remained progression-free, and 39.6% of patients remained relapse-free (P values not reported). At three years of therapy, 88% of patients had an improved relapse rate compared to baseline (P value not reported). After three years of therapy, mean EDSS scores increased by 0.4 points from baseline (P value not reported). The estimated median time to disability progression among patients receiving IFNβ-1a therapy was 4.5 years (P value not reported). Within the three-year follow-up period, 31% of patients discontinued the study. Reasons for discontinuation were disease activity (66%), voluntary decision (23%) and adverse events (11%). Secondary: Not reported
Polman et al.[67]	DB, RCT	N=942	Primary:	Primary:

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(2006) AFFIRM Natalizumab vs placebo	Patients 18 to 50 years of age with a diagnosis of relapsing MS who had a score of 0 to 5.0 on the EDSS scale who had undergone MRI showing lesions consistent with MS, who had had at least one medically documented relapse within the 12 months before the study began	≥2 years	Rate of clinical relapse at one year, cumulative probability of sustained progression of disability at two years Secondary: Number of new or enlarging hyperintense lesions as detected by T2-weighted MRI, the number of lesions as detected by gadolinium-enhanced MRI, and the proportion of relapse-free patients	After one year of treatment, natalizumab reduced the annualized rate of relapse to 0.26 relapse per year, as compared with 0.81 relapse per year in the placebo group (P<0.001). The 68% relative reduction in the annualized rate of relapse produced by natalizumab was maintained at two years (P<0.001). Subgroup and sensitivity analyses showed results consistent with the primary analysis. A sustained progression of disability over two years was significantly less likely in the natalizumab group than in the placebo group. At two years, the cumulative probability of progression (on the basis of Kaplan–Meier analysis) was 17% in the natalizumab group and 29% in the placebo group (HR, 0.58; 95% CI, 0.43 to 0.77; P<0.001). Secondary: The proportion of relapse-free patients was significantly higher in the natalizumab group than in the placebo group at one year (77 vs 56%, P<0.001) and at two years (67 vs 41%, P<0.001). Natalizumab reduced the mean number of new or enlarging hyperintense lesions detected by T2-weighted MRI over two years by 83%, as compared with placebo (P<0.001). Over two years, no new or enlarging hyperintense lesions developed in 57% of patients in the natalizumab group, as compared with 15% of patients in the placebo group. In contrast, 68% of patients in the placebo group had at least three new or enlarging hyperintense lesions, as compared with only 18% of patients in the natalizumab group. Natalizumab reduced the mean number of lesions as detected by gadolinium-enhanced MRI by 92% as compared with placebo at both one year and two years (P<0.001). In addition, lesions detected by gadolinium-enhanced MRI were absent in 97% of patients in the natalizumab group as compared with 72% of patients in the placebo group on MRI scanning at two years.
Lublin et al.[68] (2014) Natalizumab vs	PH of AFFIRM study Adult patients (18 to 50 years of age) with a diagnosis of RRMS, who had a	N=283 Up to 120 weeks	Primary: 1) Relapse clinical severity, defined as the change in EDSS score between pre-relapse and at-relapse	Primary: At relapse, an increase in EDSS score of ≥0.5 points was seen in 71% of natalizumab patients and 84% of placebo (P=0.0088), while an increase of ≥1.0 point was seen in 49% of natalizumab patients and 61% of placebo (P=0.0349). Treatment effects on the clinical severity of relapses were most apparent in patients with baseline EDSS score <3.0. In this subgroup, 74% of natalizumab versus 91% of placebo

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo	score of 0.0 to 5.0 on the EDSS, cranial MRI showing lesions consistent with MS, and at least one medically documented relapse within the 12 months before the baseline visit		assessments; 2) Relapse-induced residual disability, defined as the change in EDSS score between pre-relapse and post-relapse assessments; 3) Probability of 12-week and 24-week confirmed complete EDSS recovery from disabling relapses Secondary: Not reported	patients experienced an increase in EDSS score of ≥0.5 points at first relapse assessment (P=0.0019), while 50% of natalizumab versus 71% of placebo patients showed an increase of ≥1.0 point (P=0.0048). Among those with baseline EDSS score ≥3.0, there was no significant difference between the percentage of natalizumab and placebo patients who experienced an increase in EDSS of either 0.5 (natalizumab, 68%; placebo, 70%; P=0.8259) or 1.0 point (natalizumab, 48%; placebo, 43%; P=0.5976) at relapse. Residual disability (≥0.5-point increase in EDSS from pre- to post-relapse) remained in 31% and 45% of patients in the natalizumab and placebo groups, respectively (P=0.0136). A significant difference was observed among those with a baseline EDSS score <3.0; 33% of those who received natalizumab showed a pre- to post-relapse residual EDSS increase of ≥0.5 points versus 47% of those given placebo (P=0.0478). The difference was not significant in relapse-induced residual EDSS impairment between natalizumab and placebo patients with a baseline EDSS score ≥3.0 (natalizumab, 29%; placebo, 40%; P=0.1930). In patients with an increase in EDSS of ≥0.5 points during relapse, natalizumab increased the cumulative probability of 12-week and 24-week confirmed complete recovery from relapse by 55% (HR, 1.554; 95% CI, 1.085 to 2.226; P=0.0161) and 61% (HR, 1.609; 95% CI, 1.066 to 2.430; P=0.0236) relative to placebo, respectively. In patients with an increase in EDSS of ≥1.0 point during relapse, natalizumab increased the cumulative probability of 12-week and 24-week confirmed complete recovery from relapse by 67% (HR, 1.673; 95% CI, 1.046 to 2.678; P=0.0319) and 66% (HR, 1.656; 95% CI, 0.968 to 2.832; P=0.0655) relative to placebo, respectively. Secondary: Not reported
Fox et al.[69] (2014) RESTORE	MC, PG, RCT Patients 18 to 60 years of age with	N=175 52 weeks	Primary: Radiographic and clinical disease activity in patients	Primary: During the randomized treatment period, 49 of 122 patients (40%) randomized to placebo or other therapies had MRI activity meeting disease recurrence criteria, while none of the patients randomized to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Natalizumab vs placebo vs alternate immunomodulatory therapy (IM interferon β-1a [Avonex®], glatiramer acetate [Copaxone®], or methylprednisolone)	relapsing MS who were relapse-free for one year on natalizumab therapy		with MS undergoing up to a 24-week interruption of natalizumab therapy Secondary: Not reported	natalizumab had MRI activity meeting the criteria (P<0.001). Thirty-four percent (23/68) of patients with high disease activity prior to natalizumab treatment had MRI activity meeting criteria during the randomized treatment period; the proportion was 26% (26/99) for those with low disease activity prior to natalizumab treatment (P=0.305). No MRI activity meeting defined disease recurrence criteria was detected prior to week 12. A total of 49 patients developed MRI findings that met defined criteria for disease recurrence; three patients (6%) at week 12, 37 patients (76%) at week 16 or 20, and nine patients (18%) after week 20. Twenty-three of 122 patients (19%) off natalizumab and 2 of 45 patients (4%) on natalizumab experienced relapses during the randomized treatment period (P=0.026). Relapses occurred in 21% (14/68) of patients with high disease activity and in 11% (11/99) of patients with low disease activity prior to starting natalizumab (P=0.122). Of 25 relapses occurring during the randomized treatment period, two (8%) occurred between weeks four and eight, nine (44%) occurred between weeks eight and 16, and 14 (56%) occurred between weeks 16 and 28. Two patients with high disease activity (in glatiramer and methylprednisolone groups) experienced a relapse in both the randomized treatment period and in the follow-up period. Secondary: Not reported
Outteryck et al.[70] (2014) BIONAT Natalizumab	Cohort, MC, PRO Patients with relapsing–remitting MS starting natalizumab therapy at 18 MS centres in France since June 2007 were included and were followed prospectively	N=793 ≥2 years	Primary: Clinical and radiological response to natalizumab after 2 years of treatment Secondary: Not reported	Primary: Natalizumab was discontinued in 17.78% of patients. The most frequent causes, together representing more than half the discontinuations, were pregnancy planning (24.82%), cutaneous allergy (17.02%), always occurring in the first year, conversion to a secondary progressive form of MS (12.06%) and serious adverse event (8.51%). The proportion of patients without combined disease activity was 45.59% during the first two successive years of treatment. Systematic dosage of anti-natalizumab antibodies detected only two supplementary patients with anti-natalizumab antibodies compared with strict application of recommendations. A significant

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				decrease of IgG and IgM concentrations at two years of treatment was found. Secondary: Not reported
Rudick et al.[71] (2006) SENTINEL Natalizumab added to interferon β-1a (Avonex®) vs interferon β-1a (Avonex®) alone	DB, PC, PG, RCT Patients were 18 to 55 years of age; had a diagnosis of relapsing–remitting multiple sclerosis, a score on the EDSS (possible scores range from 0 to 10, with higher scores indicating more severe disease) between 0 and 5.0, and an MRI scan revealing lesions consistent with a diagnosis of MS; had received treatment with interferon beta-1a for at least 12 months before randomization; and had had at least one relapse during the 12-month period before randomization	N=1,171 ≥116 weeks	Primary: Rate of clinical relapse at one year; cumulative probability of sustained disability progression at two years Secondary: Number of new or enlarging T2-hyperintense lesions, the number of gadolinium-enhancing lesions, and the proportion of patients free of relapse	*SENTINEL was stopped approximately one month early because of two reports of progressive multifocal leukoencephalopathy (PML).* Primary: Combination therapy reduced the annualized rate of relapse at one year, which was 0.82 with interferon beta-1a alone, compared to 0.38 (P<0.001) — a 54% reduction. Kaplan–Meier estimates of the cumulative probability of sustained disability progression at two years were 23% with combination therapy and 29% with interferon β-1a alone. Combination therapy resulted in a 24% decrease in the risk of sustained disability progression (HR, 0.76; 95% CI, 0.61 to 0.96; P=0.02). In the sensitivity analysis of the risk of disability progression sustained for 24 weeks, estimates of the cumulative probability of progression by two years were 15% for combination therapy and 18% for interferon β-1a alone (representing an 18% reduction with combination therapy); however, this difference was not statistically significant (P=0.17). Secondary: The number of new or enlarging T2-hyperintense lesions over the two-year period was reduced from 5.4 with interferon β-1a alone to 0.9 with combination therapy (P<0.001), representing an 83% reduction with combination therapy. The mean number of gadolinium-enhancing lesions at two years was 0.9 with interferon β-1a alone and 0.1 with combination therapy, representing an 89% reduction (P<0.001). The proportion of patients who were relapse-free at two years was 54% in the combination-therapy group, as compared with 32% in the group assigned to interferon β-1a alone (P<0.001). The risk of relapse

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				was 50% lower with combination therapy (HR, 0.50; 95% CI, 0.43 to 0.59; P<0.001).
Kalincik et al.[72] (2015) Natalizumab vs fingolimod	OBS, PRO Patients with relapsing–remitting MS in the MSBase registry who had switched therapy from interferon β or glatiramer acetate to either natalizumab or fingolimod (treatment gap < 3 months; no unified escalation protocol was used) after on-treatment relapse and/or progression of disability documented within the preceding six months (i.e., clinical breakthrough activity)	N=792 12 months	Primary: Relapse (defined as occurrence of new symptoms or exacerbation of existing symptoms persisting for at least 24 hours, in the absence of concurrent illness or fever, and occurring at least 30 days after a previous relapse), Progression of EDSS (defined as increase of ≥1 EDSS step (≥1.5 EDSS steps if baseline EDSS was 0) sustained for ≥6 months), ARR Secondary: Not reported	Primary: Treatment persistence following the baseline did not differ between the compared therapies, with the proportion of patients discontinuing therapy at 24 months reaching 27% and 31% in the natalizumab and fingolimod groups, respectively (P=0.9). The proportion of relapse-free patients was higher among those switching to natalizumab than fingolimod (HR, 1.5; 95% CI, 1.1 to 2.2; P=0.02), and the cumulative hazard of relapses was relatively lower in the natalizumab group (HR, 0.6; 95% CI, 0.4 to 0.8, P=0.002). ARR decreased in both groups, with a more prominent drop after switching to natalizumab (1.5 to 0.2) compared to fingolimod (1.3 to 0.4; P=0.002). The difference in ARR was sustained throughout the two years post-switch. Secondary: Not reported
Hauser et al.[73] (2020) ASCLEPIOS Ofatumumab subcutaneous (20 mg every 4 weeks after 20-mg loading doses at days 1, 7, and 14) vs	Two DB, MC, RCTs Patients aged 18 to 55 years of age with a diagnosis of MS with a relapsing–remitting course or a secondary	N=1,882 Median follow-up 1.6 years	Primary: ARR Secondary: Disability progression, change in MRI findings	Primary: In ASCLEPIOS I, the adjusted ARR was 0.11 with ofatumumab and 0.22 with teriflunomide (difference, −0.11; 95% CI, −0.16 to −0.06; P<0.001). The corresponding rates in ASCLEPIOS II were 0.10 and 0.25 (difference, −0.15; 95% CI, −0.20 to −0.09; P<0.001). Secondary: In the pooled trials, the percentage of patients with disability worsening confirmed at three months was 10.9% with ofatumumab and 15.0% with teriflunomide (HR, 0.66; P=0.002); the percentage

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teriflunomide oral (14 mg daily)	progressive course with disease activity, EDSS score ≤5.5			with disability worsening confirmed at six months was 8.1% and 12.0%, respectively (HR, 0.68; P=0.01); and the percentage with disability improvement confirmed at six months was 11.0% and 8.1% (HR, 1.35; P=0.09). The number of gadolinium-enhancing lesions per T1-weighted MRI scan, the annualized rate of lesions on T2-weighted MRI, and serum neurofilament light chain levels, but not the change in brain volume, were in the same direction as the primary end point. Injection-related reactions occurred in 20.2% in the ofatumumab group and in 15.0% in the teriflunomide group (placebo injections). Serious infections occurred in 2.5% and 1.8% of the patients in the respective groups.
Hauser et al.[74] (2022) ALITHIOS Patients on continuous ofatumumab treatment and patients newly switched from teriflunomide	OL Patients completing ASCLEPIOS I/II (phase 3), APLIOS, or APOLITOS (phase 2) trials	N=1,969 Up to 3.5 years	Primary: Adverse events Secondary: Not reported	Primary: The safety population had 1,969 patients: 1,292 continuously treated with ofatumumab and 677 newly switched. A total of 1650 patients (83.8%) had ≥1 adverse events and 191 (9.7%) had ≥1 serious adverse events. No opportunistic infections or progressive multifocal leukoencephalopathy events were identified. Mean serum immunoglobulin (Ig) G levels remained stable. Mean IgM levels decreased but remained above the lower limit of normal in most. Serious infection incidence was low; decreased Ig levels were not associated with serious infections. Secondary: Not reported
Comi et al.[75] (2019) SUNBEAM Ozanimod 0.46 mg QD + placebo IM injection or ozanimod 0.92 mg QD + placebo IM injection vs	AC, DB, DD, PG, MC, RCT Patients 18 to 55 years of age with a diagnosis of RMS, with ≥1 relapse in the past year or ≥1 relapse in the past two years with ≥1 gadolinium-enhancing lesion,	N=1,346 Variable duration (patients were treated until all enrolled subjects were treated for at least one year)	Primary: ARR at the end of the treatment period (after all enrolled subjects treated for one year) Secondary: Number of new or enlarging T2 brain lesions over 12 months, number of gadolinium-	Primary: Adjusted ARRs were 0.18 (95% CI, 0.14 to 0.24) for ozanimod 0.92 mg, 0.24 (95% CI, 0.19 to 0.31) for ozanimod 0.46 mg, and 0.35 (95% CI, 0.28 to 0.44) for IFN β-1a. When compared to IFN β-1a, the rate ratio was 0.52 (95% CI, 0.41 to 0.66) with ozanimod 0.92 mg (P<0.0001) and 0.69 (95% CI, 0.55 to 0.86) with ozanimod 0.46 mg (P=0.0013). Secondary: The mean number of new or enlarging T2 lesions over 12 months was 1.47 for ozanimod 0.92 mg, 0.75 for ozanimod 0.46 mg and 2.84 for IFN β-1a. When compared to IFN β-1a rate ratio was 0.52 for

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
IFN β-1a 30 mcg IM weekly + placebo capsule Dose titration was used for all patients (ozanimod and placebo capsules).	and a baseline EDSS score ≤5.0		enhancing lesions at month 12, percent change in brain volume from baseline to month 12, proportion of patients free of gadolinium-enhancing or new or enlarging T2 lesions at month 12, change from baseline to month 12 in MSFC and MSQOL-54 scores	ozanimod 0.92 mg (P<0.001) and 0.75 for ozanimod 0.46 mg (P=0.0032). The mean number of gadolinium-enhancing lesions at month 12 month was 0.16 for ozanimod 0.92 mg, 0.29 for ozanimod 0.46 mg and 0.43 for IFN β-1a. When compared to IFN β-1a rate ratio was 0.37 for ozanimod 0.92 mg (P<0.001) and 0.66 for ozanimod 0.46 mg (P=0.0182). Mean percent change from baseline to month 12 in brain volume was -0.41 for ozanimod 0.92 mg, -0.49 for ozanimod 0.46 mg and -0.61 for IFN β-1a. Although P values are nominal, differences were statistically significant for ozanimod 0.92 mg and 0.46 mg when compared to IFN β-1a (P<0.0001 and P=0.0092, respectively). At month 12, 74.05%, 68.29% and 63.17% of ozanimod 0.92 mg, 0.46 mg and IFN β-1a were free of gadolinium-enhancing lesions. Although P values are nominal, differences were statistically significant for ozanimod 0.92 mg but not 0.46 mg when compared to IFN β-1a (P=0.0006 and P=0.1130, respectively). At month 12, 27.96%, 26.39% and 23.44% of ozanimod 0.92 mg, 0.46 mg and IFN β-1a were free of new or enlarging T2 lesions. There were no significant differences between ozanimod 0.92 or 0.46 mg when compared to IFN β-1a (P=0.1180 and P=0.3023, respectively). Mean change from baseline in MSFC scores were 0.006, 0.019 and -0.024 for ozanimod 0.92 mg, 0.46 mg and IFN β-1a respectively. There were no significant differences for ozanimod 0.92 mg or 0.46 mg when compared to IFN β-1a (P=0.1091 and P=0.4394, respectively). Mean change from baseline in MSQOL-54 physical health composite scores were 1.925, 1.024 and 0.046 for ozanimod 0.92 mg, 0.46 mg and IFN β-1a respectively. When compared to IFN β-1a, there was a nominally significant difference for ozanimod 0.92 mg (P=0.0364) but not ozanimod 0.46 mg (P=0.1905).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Mean change from baseline in MSQOL-54 mental health composite scores were 0.260, 0.283 and -0.123 for ozanimod 0.92 mg, 0.46 mg and IFN β-1a respectively. There were no significant differences for ozanimod 0.92 mg or 0.46 mg when compared to IFN β-1a (P=0.7104 and P=0.8587, respectively).
Cohen et al.[76] (2019) RADIANCE Ozanimod 0.46 mg QD + placebo IM injection or ozanimod 0.92 mg QD + placebo IM injection vs IFN β-1a 30 mcg IM weekly + placebo capsule Dose titration was used for all patients (ozanimod and placebo capsules).	AC, DB, DD, PG, MC, RCT Patients 18 to 55 years of age with a diagnosis of RMS, with ≥1 relapse in the past year or ≥1 relapse in the past two years with ≥1 gadolinium-enhancing lesion, and a baseline EDSS score ≤5.0	N=1,313 24 months	Primary: ARR over 24 months Secondary: Number of new or enlarging T2 brain lesions over 24 months, number of gadolinium-enhancing lesions at month 24, time to onset of disability progression, proportion of patients free of gadolinium-enhancing or new or enlarging T2 lesions at month 24, change from baseline to month 24 in MSFC and MSQOL-54 scores, and percent change in whole brain atrophy from baseline to month 24	Primary: Adjusted ARRs over 24 months were 0.17 (95% CI, 0.14 to 0.21) for ozanimod 0.92 mg, 0.22 (95% CI, 0.18 to 0.26) for ozanimod 0.46 mg, and 0.28 (95% CI, 0.23 to 0.32) for IFN β-1a. When compared to IFN β-1a, the rate ratio was 0.62 (95% CI, 0.51 to 0.77) with ozanimod 0.92 mg (P<0.0001) and 0.79 (95% CI, 0.65 to 0.96) with ozanimod 0.46 mg (P=0.0167). Secondary: The mean number of new or enlarging T2 lesions over 24 months was 1.84 for ozanimod 0.92 mg, 2.09 for ozanimod 0.46 mg and 3.18 for IFN β-1a. When compared to IFN β-1a rate ratio was 0.58 for ozanimod 0.92 mg (P<0.0001) and 0.66 for ozanimod 0.46 mg (P=0.0001). The mean number of gadolinium-enhancing lesions at month 24 was 0.18 for ozanimod 0.92 mg, 0.20 for ozanimod 0.46 mg and 0.37 for IFN β-1a. When compared to IFN β-1a rate ratio was 047 for ozanimod 0.92 mg (P=0.0006) and 0.53 for ozanimod 0.46 mg (P=0.003). Mean percent change from baseline to month 24 in brain volume was -0.707 for ozanimod 0.92 mg, -0.707 for ozanimod 0.46 mg and -0.937 for IFN β-1a. Although P values are nominal, differences were statistically significant for ozanimod 0.92 mg and 0.46 mg when compared to IFN β-1a (P<0.0001 and P=0.0002, respectively). At month 24, 65.6%, 63.3% and 56.2% of ozanimod 0.92 mg, 0.46 mg and IFN β-1a were free of gadolinium-enhancing lesions. Although P values are nominal, differences were statistically

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				significant for ozanimod 0.92 mg and 0.46 mg when compared to IFN β-1a (P=0.0047 and P=0.0320, respectively). At month 24, 23.8%, 23.5% and 18.4% of ozanimod 0.92 mg, 0.46 mg and IFN β-1a were free of new or enlarging T2 lesions. Although P values are nominal, there was a statistically significant difference for ozanimod 0.92 mg but not ozanimod 0.46 mg when compared to IFN β-1a (P=0.0466 and P=0.0581, respectively). Mean change from baseline in MSFC scores were -0.006, 0.032 and -0.067 for ozanimod 0.92 mg, 0.46 mg and IFN β-1a respectively. Although P values are nominal, there was no statistically significant difference for ozanimod 0.92 mg compared to IFN β-1a (P=0.2480); however, there was a significant difference for ozanimod 0.46 mg when compared to IFN β-1a (P=0.0123). Mean change from baseline in MSQOL-54 physical health composite scores were 0.209, 0.609 and -1.526 for ozanimod 0.92 mg, 0.46 mg and IFN β-1a respectively. Mean change from baseline in MSQOL-54 mental health composite scores were -1.517, -1.182 and -1.831 for ozanimod 0.92 mg, 0.46 mg and IFN β-1a respectively. Of these, there was a nominally significant difference for ozanimod 0.46 mg compared to IFN β-1a for MSQOL-54 physical health score (P=0.0228).
Kappos et al.[77] (2021) OPTIMUM Ponesimod 20 mg QD vs teriflunomide 14 mg QD Dose titration was used for ponesimod over 14 days to the	AC, DB, PG, MC, RCT Patients 18 to 55 years of age with a diagnosis of RMS with active disease (1 relapse in the past year, or ≥2 relapse in the past two years with ≥1 gadolinium-enhancing lesion),	N=1,133 Active treatment: 108 weeks End of study 108 weeks + 30 days	Primary: ARR at the end of study (after all enrolled subjects treated for one year) Secondary: Change from baseline to week 108 in FSIQ–RMS, CUALs from baseline to week	Primary: There were 242 confirmed relapses in the ponesimod group compared to 344 relapses in the teriflunomide group during the study. This represented an ARR of 0.202 for ponesimod ad 0.290 for teriflunomide (relative reduction, 30.5%; P=0.0003) Secondary: The least-square mean changes in FSIQ-RMS score from baseline to week 108 was 0.01 for ponesimod and 3.56 for teriflunomide, representing a treatment difference of -3.57 in favor of ponesimod (95% CI, -5.83 to -1.32; P=0.002).

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maintenance dose of 20 mg QD.	and a baseline EDSS score ≤5.5		108, and time to CDA from baseline to end of study	The mean number of CUALs from baseline to week 108 was 1.405 for ponesimod and 3.164 for teriflunomide (rate ratio, 0.444; 95% CI, 0.364 to 0.542; P<0.001). Similar results were observed for new or enlarging T2 hyperintense lesions per year (1.40 for ponesimod and 3.16 for teriflunomide; P<0.0001) as well as T1 Gd-enhancing lesions per MRI (0.18 for ponesimod and 0.43 for teriflunomide; P<0.0001). There were no significant differences in the time to CDA between groups. The risk of 12-week CDA was 10.1% for ponesimod and 12.4% for teriflunomide (HR, 0.84; 95% CI, 0.58 to 1.18; P=0.29). Similar results were observed for 24-week CDA (HR, 0.84; 95% CI, 0.57 to 1.24; P=0.37).
Kappos et al.[78] (2018) EXPAND Siponimod 2 mg QD vs placebo Treatment with siponimod was titrated from 0.25 to 2 mg from day one to six. Retitration was required for interruptions in therapy ≥4 consecutive days.	DB, PG, PG, RCT Adult patients (18 to 60 years of age) with a diagnosis of SPMS, EDSS score of 3.0 to 6.5 at screening, a history of RRMS, documented EDSS progression in the past two years before the study and no evidence of relapse in the three months before randomization	N=1,651 3 months (up to 36 months followed by open label extension up to seven years)	Primary: CDP at three months (EDSS increase of ≥1.0 or ≥0.5 increase if baseline score was 5.5 to 6.5) Secondary: CDP at three months (T25FW worsening of 20% from baseline), change from baseline in T2 lesion volume, CDP (EDSS) at six months, ARR, time to first relapse, proportion of relapse-free patients, change in score on the patient-reported MSWS-12, number	Primary: There was confirmed disability progress at three months in 26% (288/1,096) of siponimod-treated patients and 32% (173/545) of placebo-treated patients. This represented a statistically significant difference in favor of siponimod (HR, 0.79; 95% CI, 0.65 to 0.95; P=0.013). Secondary: There was confirmed disability progression on T25FW (≥20% from baseline) at three months in 40% (432/1,087) of siponimod-treated patients and 41% (225/543) of placebo-treated patients. There was no significant difference between groups (HR, 0.94; 95% CI, 0.80 to 1.10; P=0.44). Change from baseline to 12 months in the adjusted mean for total volume of T2-weighted images (mm^3) was 204.9 in siponimod-treated patients and 818.0 in placebo-treated patients, representing a between group difference of -613.1 (P<0.001). Change from baseline to 24 months was 162.9 in siponimod-treated patients and 940.4 in placebo-treated patients, representing a between group difference of -777.5 (P<0.001). There was confirmed disability progress on EDSS at six months in 20% (218/1,096) of siponimod-treated patients and 26% (139/545) of placebo-treated patients. This represented a nominally significant

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			of new or enlarging T2 lesions, number of T1 gadolinium-enhancing lesions, and percentage change in brain volume from baseline	difference in favor of siponimod (HR, 0.74; 95% CI, 0.60 to 0.92; P=0.0058). The annualized relapse rate was 0.07 (95% CI, 0.06 to 0.09) for the siponimod group and 0.16 (95% CI, 0.12 to 0.21) for the placebo group. This represented a nominally significant difference in favor of siponimod (RR, 0.45; 95% CI, 0.34 to 0.59; P<0.001). The endpoint for time to first confirmed relapse was not clearly defined, and no results were included for the proportion of relapse-free patients. Results for time to first confirmed relapse was presented as a proportion of patients rather than a time. A nominally significant difference in favor of siponimod was reported (HR, 0.54; 95% CI, 0.41 to 0.70; P<0.0001). These results may actually represent the between group difference for proportion of relapse-free patients. Adjusted mean change from baseline to 12 months in the MSWS-12 score was 1.53 in siponimod-treated patients and 3.36 in placebo-treated patients, representing a between group difference of -1.83 (P=0.076). Change from baseline to 24 months was 4.16 in siponimod-treated patients and 5.38 in placebo-treated patients, representing a between group difference of -1.23 (P=0.37). Adjusted mean number of new or enlarging lesions on T2-weighted images over all visits was 0.70 for the siponimod group and 3.60 in the placebo group, representing a nominally significant difference in favor of placebo (RR, 0.19; 95% CI, 0.16 to 0.24; P<0.0001). Adjusted mean number of gadolinium-enhancing lesions on lesions on T1-weighted MRI per scan from baseline up to and including month 24 was 0.08 in the siponimod group and 0.60 in the placebo group, representing a nominally significant difference in favor of siponimod (RR, 0.14; 95% CI, 0.10 to 0.19; P<0.001). Adjusted mean change from baseline to 12 months in percent brain volume was -0.28% in siponimod-treated patients and -0.46% in placebo-treated patients, representing a between group difference of

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				0.18% (P<0.0001). Mean change from baseline to 24 months was -0.71% in siponimod-treated patients and -0.84% in placebo-treated patients, representing a between group difference of 0.13% (P=0.020). Differences were nominally significant in favor of siponimod.
O'Connor et al.[79] (2011) TEMSO Teriflunomide 7 mg QD vs teriflunomide 14 mg QD vs placebo	DB, MC, PC, PG, RCT Patients aged 18 to 55 years of age who met McDonald criteria for MS diagnosis and had relapsing clinical course with or without progression, EDSS score ≤5.5 and 1 relapse in previous year or 2 relapses in previous 2 years	N=1,088 108 weeks	Primary: ARR Secondary: Disability progression, change in total MRI lesion volume from baseline	Primary: ARR was significantly reduced in both teriflunomide 7 mg (0.37; CI, 0.32 to 0.43) and 14 mg groups (0.37; CI, 0.31 to 0.44) compared to placebo (0.54; CI 0.47 to 0.62; P<0.001 for both). This represented a RRR of 16.7% and 31.2%, respectively. Secondary: The percentage of patients with confirmed progression of disability in the 14 mg group (20.2%; CI, 15.6 to 24.7) was marginally lower than the placebo group (27.3%; CI, 22.3 to 32.3; P=0.03). The percentage of patients with confirmed progression of disability was not significantly different than placebo in the 7 mg group. The changes in total MRI brain lesion volume from baseline were reduced in both the 7 mg group (1.31±6.80 mL) and the 14 mg group (0.72±7.59 mL) compared to the placebo group (2.21±7.00 mL; P=0.03 and P<0.001, respectively).
O'Connor et al.[80] (2016) TEMSO Extension Teriflunomide 7 mg QD vs placebo/teriflunomide 7 mg QD vs teriflunomide 14 mg QD	DB, ES, MC Patients who completed TEMSO entered the long-term extension and patients originally receiving placebo were re-randomized to teriflunomide 7 mg or 14 mg, while patients receiving active treatment	N=742 Up to 9 years	Primary: Long-term safety Secondary: Long-term efficacy	Primary: Over the extension, approximately 90% of patients reported at least one adverse event. The majority (~80%) of patients who entered the extension experienced an adverse event in extension year one. The most commonly reported adverse events in the extension were nasopharyngitis, headache, and alanine aminotransferase (ALT) increase. Serious adverse events were evenly distributed across groups, with no evidence of a dose effect. Adverse events leading to discontinuation were reported in 82 patients (11% of the study population) without a dose effect. The most common reason for discontinuation was confirmed ALT increase, which was required by protocol for ALT elevations >3x upper limit of normal confirmed by a repeated measurement. Other adverse events leading to discontinuation were relatively infrequent. Generally, for each

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo/teriflunomide 14 mg QD	continued on the original dose			individual adverse event, the number of episodes per patient was low (≤2.0) and similar across teriflunomide groups. Secondary: There was a noticeable drop in ARR for the group of patients who received placebo in the core study as they switched to teriflunomide in the extension. ARRs declined over the extension and were numerically lower at the cutoff date than at the end of the core study in all treatment groups. The ARR for the combined core plus extension study periods was lower in patients who received teriflunomide throughout compared with those who began teriflunomide 7 mg after 108 weeks of placebo treatment (14-mg/14-mg group, p=0.003; 7-mg/7-mg group, P=0.022). There was a similar (albeit nonsignificant) effect for patients who received teriflunomide throughout compared with the placebo/14-mg group. Regardless of their dose allocation, ≥55% of patients did not experience a relapse in the extension. Disability remained stable in all treatment groups (median EDSS score ≤2.5; probability of 12-week disability progression ≤0.48).
Freedman et al.[81] (2012) Teriflunomide 7 mg vs teriflunomide 14 mg vs placebo All patients received IFNβ (Avonex® [IFNβ-1a] 30 µg IM QW or Rebif® [IFNβ-1a] 22 µg or 44 µg SC TIW or	DB, MC, PC, RCT, ES Patients aged 18 to 55 years who met McDonald criteria for MS diagnosis and had relapsing clinical course with or without progression, EDSS score ≤5.5 and had received a stable dose of IFNβ for 26 weeks before screening	N=118 24 weeks N=86 24 week extension	Primary: Safety and tolerability Secondary: ARR, total number T1-gadolinium-enhancing lesions, total T1-gadolinium-enhancing lesion volume per MRI scan	Primary: The overall incidence of patients experiencing at least one TEAE was similar across all groups (placebo: 85.4%; teriflunomide 7 mg: 89.2%; teriflunomide 14 mg: 84.2%). TEAEs occurring more frequently in the teriflunomide groups (incidence ≥10%) in any group were increased ALT/AST, decreased white blood cells counts, nasopharyngitis, fatigue, nausea and hypertension. The number of patients experiencing serious TEAEs during the initial 24 week study was similar across groups (placebo: 1; 7 mg: 2; 14 mg: 0), but the incidence was slightly higher in the 7 mg group during the 24 week extension study (placebo: 4.9%; 7 mg: 10.8%; 14 mg: 2.6%). Discontinuation due to TEAEs was low and similar across all groups. No deaths occurred during 48 weeks. Secondary: ARRs at 24 weeks and 48 weeks were not significantly different between groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Betaseron® [IFNβ-1b] 0.25 mg SC QOD)	After initial randomization and treatment for 24 weeks, patients could enter the 24 week blinded extension study in which patients remained on their initial treatment regimen			At baseline, 21.7% of patients had at least one T1-gadolinium-enhancing lesion. The total number of T1-gadolinium-enhancing lesions per MRI scan during the initial 24 week study was decreased in the teriflunomide groups, corresponding to a RRR compared to placebo of 82.6% (P=0.0009) for 7 mg and 84.4% (P=0.0001) for 14 mg. These RRRs were maintained at 48 weeks. Total T1-gadolinium-enhancing lesion volume per MRI scan was reduced in the teriflunomide groups, but only the 14 mg group reached a significant RRR at 24 weeks (7 mg: 67.6%, P=0.19; 14 mg: 64.7%, P=0.007). These reductions were maintained at 48 weeks.
Confavreux et al.[82] (2012) Teriflunomide 7 mg vs teriflunomide14 mg	ES, OL Patients aged 18 to 65 years with RRMS, a EDSS ≤6 and at least two clinical relapses in the previous three years and one during the preceding year	N=147 0.05 to 8.5 years	Primary: Long-term safety Secondary: Relapses, EDSS, T2 lesion volume, cerebral volume	Primary: The most commonly reported treatment emergent adverse events included infections, hepatic disorders, gastrointestinal disorders, neurological disorders, psychiatric disorders and hematologic disorders. The incidence of serious adverse events was slightly higher in the 7 mg group (35.8%) than the 14 mg group (28.8%) and included increased hepatic enzymes, loss of consciousness, neutropenia, pneumonia, MS relapse and breast cancer (No P values reported). The proportion of patients who discontinued treatment to due to an adverse event was 13.6% in both the 7 and 14 mg groups. One death due to a sudden cardiac disorder was reported in a patient who had been taking teriflunomide 14 mg for 4.8 years. This death was not directly attributed to the study drug. Secondary: The AARs decreased over time in the 7 and 14 mg groups and were 0.279 and 0.200 overall, respectively. The mean change (SD) in EDSS from baseline were 0.50 (1.29) and 0.34 (1.20), respectively (No P values reported). Mean cerebral volume decreased slightly more in the 7 mg group than in the 14 mg group at the end of the study. Mean (SD) percentage change from baseline in T2 volume was 62.66 (84.84)% and 72.28 (99.13)% in the 7 mg and 14 mg groups, respectively No P values reported).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Fox et al.[83] (2012) CONFIRM Dimethyl fumarate 240 mg BID vs dimethyl fumarate 240 mg TID vs GA 20 mg QD vs placebo The glatiramer acetate group was not an active comparator, but used as a referenced group. Patients receiving glatiramer were not blinded to treatment regimen.	DB, MC, PC, RCT Patients aged 18 to 55 years with a diagnosis of RRMS, an EDSS score of 0 to 5, and at least one clinically documented relapse in the previous 12 months or at least one gadolinium-enhancing lesion 0 to 6 weeks before randomization	N=1,430 96 weeks	Primary: ARR over two years Secondary: Number of new or enlarging hyperintense T2 lesions, number of new hypointense T1 lesions, proportion of patients with a relapse, time to disability progression	Primary: The ARR in patients receiving dimethyl fumarate twice daily and three times daily was 0.22 and 0.20, respectively. This corresponded to a reduction relative to placebo of 44% and 51% (P<0.001 for both). GAr was associated with a relative ARR reduction of 29% compared to placebo (P=0.001). Secondary: Dimethyl fumarate twice daily, three times daily and GA reduced the number of T2 lesions by 71%, 73% and 54%, respectively (all P<0.001 compared to placebo). The number of T1 lesions was reduced by 57% (P<0.001), 65% (P<0.001) and 41% (P=0.002) relative to placebo, respectively. Compared to placebo, dimethyl fumarate twice daily, three times daily and GA significantly reduced the risk of relapse by 34% (P=0.002), 45% (P<0.001) and 29% (P<0.01), respectively. However, disability progression was not significantly reduced in any group compared to placebo. Post hoc analysis directly comparing dimethyl fumarate twice daily and three times daily to glatiramer determined that a comparison of ARR resulted in P values of 0.10 and 0.02, respectively favoring dimethyl fumarate. The overall incidence of adverse events, serious adverse events and adverse events leading to discontinuation was similar in all groups. The most common adverse events reported in patients receiving dimethyl fumarate were flushing, gastrointestinal events, upper respiratory tract infections and erythema.
Castelli-Haley et al.[84] (2008) GA SC vs	CE, RETRO Patients (mean age 43) diagnosed with MS, with a procedure code, or	N=845 (ITT); N=410 (continuous use)	Primary: Costs (direct medical costs, including inpatient, outpatient and prescription drug	Primary: Compared to IFNβ-1a therapy, patients in the ITT cohort receiving GA experienced a significantly lower two-year relapse rate (5.92 vs 10.89%; P=0.0305).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
IFNβ-1a (Rebif®) SC Doses not reported for either treatment arm.	outpatient prescription for GA or IFNβ-1a, and insurance coverage starting at least six months before and extending through 24 months after the index date; in addition, a continuous use cohort could not have used other disease-modifying therapy within the study period and were required to have received the study medication within 28 days of study end	24 months	cost) and relapse rate (defined as hospitalization with an MS diagnosis or a seven-day steroid therapy) Secondary: Not reported	Compared to IFNβ-1a therapy, patients in the continuous use cohort receiving GA experienced a significantly lower two-year relapse rate (1.94 vs 9.09%; P=0.0049). Compared to IFNβ-1a therapy, patients in the ITT cohort receiving GA had significantly lower two-year estimated direct medical expenses ($41,786 vs $49,030; P=0.0002). Compared to IFNβ-1a therapy, patients in the continuous use cohort receiving GA had significantly lower two-year estimated direct medical expenses ($45,213 vs $57,311; P=0.0001). Secondary: Not reported
Cadavid et al.[85] (2009) BECOME GA 20 mg SC daily vs IFNβ-1b (Betaseron®) 0.25 mg SC every other day	DB, MC, OL, PG, RCT Treatment-naïve patients with RRMS or clinically isolated syndrome suggestive of MS	N=75 24 months	Primary: Number of combined active lesions per patient per scan during year one, combined active lesions includes all enhancing lesions and nonenhancing new T2/fluid-attenuated inversion recovery lesions Secondary:	Primary: The median number of combined active lesions per patient per scan during year one was not significantly different between patients receiving treatment with GA or IFNβ-1b (0.58 vs 0.63, respectively; P=0.58). Moreover, the number of patients who were active-lesion-free during the first year was similar among GA and IFNβ-1b-treated patients (19 vs 26%, respectively; P=0.59). Secondary: Over 24 months, the number of new lesions per patient per month was lower with GA compared to IFNβ-1b, but did not reach statistical significance (0.23 vs 0.46; P=0.13). The total number of relapses between GA and IFNβ-1b over two years was similar between treatments (23 vs 25, respectively; P value

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Number of new lesions and clinical relapses over two years	not reported). Both treatments were similar in regards to their effect on ARR (P=0.68).
Mikol et al.[86] (2008) REGARD GA 20 mg SC daily vs IFNβ-1a (Rebif®) 44 µg SC three times weekly	MC, OL, PG, RCT Patients between 18 and 60 years of age, naïve to both study drugs, diagnosed with RRMS with the McDonald criteria, an EDSS score 0 to 5.5, ≥1 attack within past 12 months and clinically stable or neurologically improving during the four weeks before study onset	N=764 96 weeks	Primary: Time to first relapse (defined as new or worsening neurological symptoms, without fever, lasting at least 48 hours and accompanied by a change in KFS score) Secondary: Proportion of patients relapse-free over study period, relapse rate, number of active T2 lesions (defined as new or enlarging per patient per scan over 96 weeks), mean number of gadolinium-enhancing lesions/patient/scan, change in the volume of gadolinium-enhancing lesions, change in T2 volume, combined unique active	Primary: There was no significant difference in the time to first relapse between the IFNβ-1a and GA groups (HR, 0.94; 95% CI, 0.74 to 1.21; P=0.64). Secondary: There was no significant difference between treatment groups in the proportion of patients who were free from relapse over study period (P=0.96). There was no statistically significant difference between treatment groups in the ARR over the study period (P=0.828). There were no differences between treatment groups in the number of active T2 lesions (new or enlarging) per patient per scan over 96 weeks of therapy (P=0.18). No significant difference was reported between treatment groups in the mean change in T2 lesion volume over 96 weeks of therapy (P=0.26). Patients randomized to IFNβ-1a experienced a significantly lower number of gadolinium-enhancing lesions per patient per scan compared to the GA-treated group (0.24 vs 0.41; P=0.0002). Over the 96 weeks of therapy, a significantly greater number of patients randomized to IFNβ-1a were free of gadolinium-enhancing lesions compared to the GA-treated groups (81 vs 67%; P=0.0005). There were no significant difference between the groups in the mean change in gadolinium-enhancing lesion volume over 96 weeks of therapy (P=0.42). Patients randomized to IFNβ-1a experienced a significantly lower number of combined unique active lesions per patient per scan compared to the GA-treated group (0.91 vs 1.22; P=0.01). There were no significant differences between treatment groups in the number of new T1 hypointense lesions per patient per scan over 96

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			lesions, new T1 hypointensities, T1 hypointense lesion volume, brain volume, disability progression, adverse effects	weeks of therapy (P=0.15). No differences were reported between treatment groups in the mean change in new T1 hypointense lesion volume over 96 weeks of therapy (P=0.29). There was a significant reduction in brain volume among patients randomized to IFNβ-1a compared to the GA-treated group (P=0.018). There was no significant difference between the IFNβ-1a and GA groups in the proportion of patients with a six-month confirmed EDSS progression (11.7 vs 8.7%; P=0.117). Patients randomized to IFNβ-1a and GA experienced 632 and 618 treatment-related adverse effects, respectively (P value not reported). Treatment-related adverse events occurring significantly more often in the IFNβ-1a group than in the GA group included influenza-like illness, headache, myalgia and increased ALT (P<0.05). Treatment-related adverse events occurring significantly more often in the GA group than in the IFNβ-1a group included pruritus, swelling, induration at the injection site, dyspnea and post-injection systemic reactions (P<0.05).
Flechter et al.[87] (2002) GA 20 mg SC daily vs GA 20 mg SC every other day vs IFNβ-1b (Betaseron®) 0.25 mg SC every other day	OL, PRO Patients 18 years of age and older with clinically definite MS and ≥2 exacerbations within the previous two years	N=58 2 years	Primary: Relapse rate, change in EDSS score and adverse effects Secondary: Not reported	Primary: At one and two years of follow-up, the relapse rate decreased significantly in all three treatment groups compared to baseline (P<0.05). While there were no significant changes in the EDSS scores from baseline at two years in the IFNβ-1b group (P=0.30), patients receiving GA daily or every other day experienced significantly higher (worsening) EDSS scores from baseline (P=0.007, P=0.04, respectively). There was no statistically significant difference in adverse events among the three treatment groups (P=NS). IFNβ-1b groups reported the following adverse effects: flu-like symptoms, increased spasticity, injection-site reactions and systemic reactions.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The treatment group receiving GA daily experienced the following adverse effects: flu-like symptoms, injection-site reactions, systemic reaction, lymphadenopathy and lipodystrophy. Side effects were generally reported within the first six months of therapy and resolved with continued therapy. Secondary: Not reported
Khan et al.[88] (2001) GA 20 mg SC daily vs IFNβ-1b (Betaseron®) 0.25 mg SC every other day vs IFNβ-1a (Avonex®) 30 µg IM once-weekly vs no treatment	MC, OL, PRO Patients with RRMS, ≥1 relapses in past two years and EDSS score ≤4	N=156 12 months	Primary: Relapse rate Secondary: Changes in EDSS scores, relapse rate during each half of study, proportion of relapse-free patients and proportion of relapse-free patients during each half of the study	Primary: Relapse rates were 0.97, 0.85, 0.61 and 0.62 for patients receiving no treatment, IFNβ-1a, IFNβ-1b and GA, respectively. Reductions in the relapse rate compared to no treatment was only significant with IFNβ-1b (P<0.002) and GA (P<0.003) groups. Secondary: Mean EDSS scores were significantly reduced with IFNβ-1b (P<0.01) and GA (P<0.001) compared to no treatment. There were no significant reductions in relapse rates in the first half of the study and only GA-treated patients displayed a significant reduction in the second half (P=0.004). The proportions of relapse-free patients were 15, 20, 39 and 38% in the no treatment, IFNβ-1a, IFNβ-1b and GA groups, respectively. The differences between the IFNβ-1b and GA groups were statistically significant compared to the placebo group (P=0.037 and P=0.038, respectively). There was no significant difference between IFNβ-1a and placebo (P=NS). Of the 156 patients, 33 patients elected no treatment, 40 patients elected IFNβ-1a, 41 patients elected IFNβ-1b and 42 patients elected GA.
Khan et al.[89] (2001) GA 20 mg SC daily	MC, OL, PRO 18 months follow up study in patients	N=156 18 months	Primary: Relapse rate Secondary:	Primary: Relapse rates were 1.02, 0.81, 0.55 and 0.49 in the no treatment, IFNβ-1a, IFNβ-1b and GA groups, respectively. Reduction in the relapse rate compared to receiving no treatment was statistically

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs IFNβ-1b (Betaseron®) 0.25 mg SC every other day vs IFNβ-1a (Avonex®) 30 µg IM once-weekly vs no treatment	with RRMS and ≥1 relapse in the past two years and an EDSS score ≤4		Change in EDSS scores, proportion of relapse-free patients	significant only in the IFNβ-1b and GA (P=0.001 for both comparisons) groups. Secondary: Mean EDSS scores were significantly reduced only in the IFNβ-1b (P<0.01) and GA (P=0.003) groups compared to the no treatment group. The proportions of relapse-free patients were 6.7, 11.8, 32.4 and 33.3% in the no treatment, IFNβ-1a, IFNβ-1b and GA groups, respectively. A significantly greater proportion of patients in the IFNβ-1b and GA groups were relapse-free over 18 months of follow-up compared to patients receiving no treatment group (P=0.05). There was no significant difference in the proportion of relapse-free patients between IFNβ-1a and patients receiving no treatment (P>0.999).
O'Connor et al.[90] (2009) BEYOND GA 20 mg SC daily vs IFNβ-1b (Betaseron®) 0.25 mg SC every other day vs IFNβ-1b (Betaseron®) 0.50 mg SC every other day	DB, MC, PG, PRO, RCT Patients 18 to 55 years of age with RRMS, EDSS score 0 to 5.5 and ≥1 relapse in the past year	N=2,244 24 months	Primary: Relapse risk Secondary: Progression on EDSS scale and change in T1-hypointense lesion volume	Primary: There were no differences in ARR between IFNβ-1b 0.25 and 0.50 mg (0.36 vs 0.33, respectively; P=0.10). In addition, no significant reductions in ARR were reported between GA and either dose of IFNβ-1b (0.34 vs 0.36 and 0.33 for the GA and the 0.25 and 0.50 mg doses of IFNβ-1b, respectively; P=0.42 and P=0.79). Secondary: The rate of progression on the EDSS scale was not significantly different between the IFNβ-1b groups and the GA group (21 to 27% across groups; P=0.55 to 0.71). Similarly, there were no differences in T1 hypointense lesion volume among treatment groups after two years compared to baseline values (P=0.18 to 0.68).
Carra et al.[91] (2008) GA 20 mg SC weekly for three years, subsequently switched to IFNβ or mitoxantrone therapy for additional three years	MC, OS, PRO Patients 18 years of age or older with RRMS, an EDSS disability score <6	N=114 3-year, before switch period; 3-year, after	Primary: ARR over the three-year post-switch treatment period Secondary:	Primary: The ARR was reduced by 77% (from 0.63 to 0.14) among patients who switched from IFNβ to GA therapy (P value not reported). The ARR was reduced by 71% (from 0.53 to 0.15) among patients who switched from IFNβ to mitoxantrone therapy (P value not reported).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs IFNβ-1b (Betaseron®) 0.25 mg SC every other day for three years, subsequently switched to GA or mitoxantrone therapy for additional three years vs IFNβ-1a (Rebif®) 22 µg SC three times weekly for three years, subsequently switched to GA, IFNβ-1a 44 µg SC, IFNβ-1b, or mitoxantrone therapy for additional three years vs IFNβ-1a (Rebif®) 44 µg SC three times weekly for three years, subsequently switched to IFNβ-1b, GA or mitoxantrone therapy for additional three years vs IFNβ-1a (Avonex®) 30 µg IM once-weekly for three years, subsequently switched to IFNβ-1b, IFNβ-1a 44 µg SC, GA or mitoxantrone therapy for additional three years vs	and ≥1 relapse in the previous year	switch period	The proportion of patients relapse-free during the three-year post-switch treatment period and mean change in EDSS score over six years	The ARR was reduced by 67% (from 0.52 to 0.17) among patients who switched from IFNβ to GA therapy (P value not reported). The smallest reduction (57%, from 0.37 to 0.16) in the ARR was observed in patients switched between different IFNβ preparations (P value not reported). The ARR was reduced by 75% (from 0.8 to 0.2) in the reference group over six years of therapy (P value not reported). Secondary: The proportion of relapse-free patients increased from 55 to 68% after switching from one IFNβ preparation to another (P value not reported). The proportion of relapse-free patients increased from 16 to 68% after switching from IFNβ to GA therapy due to inadequate efficacy (P value not reported). The proportion of relapse-free patients increased from 71 to 80% after switching from IFNβ to GA therapy due to adverse events (P value not reported). The proportion of relapse-free patients increased from 33 to 81% after switching from IFNβ to mitoxantrone therapy (P value not reported). The proportion of relapse-free patients increased from 27 to 63% after switching from GA to IFNβ therapy due to inadequate efficacy (P value not reported). The proportion of relapse-free patients decreased from 75 to 50% after switching from GA to IFNβ therapy due to adverse events (P value not reported). There was no evidence of disability progression as evidenced by a lack of statistically significant change in EDSS scores among patients switching from IFNβ to GA due to inadequate efficacy or those switching from IFNβ to mitoxantrone (P>0.05). However, patients switching from one IFNβ to another or GA to IFNβ demonstrated a statistically significant disability progression (P<0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
IFNβ or GA therapy for six years (reference cohort)				The change in EDSS scores was significantly higher among patients switching from GA to IFNβ compared to those switching from IFNβ to GA therapy (P=0.0035), suggesting a higher rate of disability progression in the latter group. There was no statistically significant change from baseline in EDSS score in the reference group six months after therapy initiation (P value not reported).
Haas et al.[92] (2005) GA 20 mg SC weekly vs IFNβ-1b (Betaseron®) 0.25 mg SC every other day vs IFNβ-1a (Rebif®) 22 µg SC three times weekly vs IFNβ-1a (Avonex®) 30 µg IM once-weekly	OL, RETRO Patients with RRMS who have had one to three exacerbations within previous year and an EDSS score ≤3.5	N=308 24 months	Primary: Relapse rate Secondary: Number of relapse-free patients, mean EDSS change and progression rate	Primary: The relapse rates decreased significantly for all drugs (P<0.05), with an ARR of 0.80, 0.69, 0.66 and 0.36 for IFNβ-1a 30 µg IM, IFNβ-1b, IFNβ-1a 22 µg SC and GA, respectively. There were no significant differences between the groups at six months, but the decline in relapse rate at 24 months was highest with GA (0.81; P<0.001). Secondary: The percentage of relapse-free patients at 24 months was 35.4, 45.5, 45.8 and 58.2% for IFNβ-1a 30 µg IM, IFNβ-1b, IFNβ-1a 22 µg SC and GA, respectively (P=NS). There were no significant differences in EDSS between groups (P=NS). The progression index declined in all treatment groups (P values were not reported). The discontinuation rate between six and 24 months was highest for IFNβ-1a 30 µg IM and lowest for GA (33 vs 9%; P<0.001).
Lublin et al.[93] (2013) IFNβ-1a (Avonex®) 30 µg IM once-weekly + GA 20 mg SC daily vs	DB, MC, PC, Phase III, RCT Patients between the ages of 18 and 60 years with EDSS score of 0 to 5.5 and diagnosis of RRMS by Poser	N=1,008 36 months	Primary: Reduction in ARR as measured by protocol-defined exacerbations Secondary: Time to confirmed disability, MSFC	Primary: ARR of IFNβ-1a + GA combination treatment group was similar to the ARR of GA + placebo treatment group (P=0.27). GA + placebo treatment group was significantly better than IFNβ-1a + placebo treatment group, reducing the risk of exacerbation by 31% (P=0.027) and the IFNβ-1a + GA combination treatment group was significantly better than IFNβ-1a + placebo treatment group, reducing the risk of exacerbation by 25% (P=0.022).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
IFNβ-1a (Avonex®) 30 µg IM once-weekly + placebo SC daily vs GA 20 mg SC daily + placebo IM once-weekly	or McDonald criteria, with at least 2 exacerbations in the prior 3 years with no prior history of seizure activity		score, MRI metrics, safety	There was no difference between the three treatment groups in time to first exacerbation (P=0.19). There was no difference between the groups in proportion of patients with relapses (IFNβ-1a + placebo vs GA + placebo, P=0.14; IFNβ-1a + GA vs IFNβ-1a + placebo, P=0.19; IFNβ-1a + GA vs GA + placebo, P=0.21). Secondary: There was no difference between the three treatment groups showing 6-month confirmed progression of EDSS with 23.9%, 21.6%, and 24.8% of patients with EDSS progression in the IFNβ-1a + GA, IFNβ-1a + placebo, and GA + placebo treatment groups, respectively. There was no difference between the three treatment groups in the MSFC score over 36 months with all groups showing small increases. Change in a composite score constructed from 4 MRI measures, Z4, from baseline to month 36 did not differ between the IFNβ-1a + placebo and GA + placebo groups (P=0.52) or IFNβ-1a + GA and IFNβ-1a + placebo groups (P=0.23). Similarly, there were no differences between the groups at months 6, 12 and 24. The treatment groups were all effective in reducing MRI-defined disease activity measured by enhanced lesion numbers within 6 months of their initiation. The IFNβ-1a + GA combination treatment group reduced enhancement numbers more than IFNβ-1a + placebo group (P=0.01) when adjusted for baseline age and number of enhancements. There was no difference in the change in the number of enhancements from months 0 to 36 between IFNβ-1a + placebo and GA + placebo groups (P=0.82). The combination therapy with IFNβ-1a + GA did not result in any additional safety issues with the exception of the usual adverse events that were seen with the single agents. There were three deaths in the core study one in the extension study.
Koch-Henriksen et al.[94] (2006)	MC, OL, RCT	N=421	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
IFNβ-1b (Betaseron®) 0.25 mg SC every other day vs IFNβ-1a (Rebif®) 22 µg SC once-weekly	Patients with RMSS who have had ≥2 relapses within two years and an EDSS score ≤5.5	24 months	ARR, time to first relapse and NAb formation Secondary: Time to sustained progression	The ARR, time to first relapse and NAb formation were similar between patients taking either IFNβ therapy (P=NS). Secondary: There was no difference in the time to sustained progression between treatment arms (P=NS). Other: Side effects (15%) were the most frequent cause of withdrawal in the IFNβ-1b group and treatment failure was the most frequent cause of withdrawal in the IFNβ-1a group.
Baum et al.[95] (2007) BRIGHT IFNβ-1b (Betaseron®) 0.25 mg SC every other day vs IFNβ-1a (Rebif®) 44 µg SC three times weekly	I, MC, OS, PRO Patients, mean age 36 years with RRMS and treated with either one of the study regimens	N=445 15 consecutive injections (follow-up period, four to five weeks)	Primary: The proportion of patients pain-free during all injections (immediately, 30 minutes and 60 minutes post-injection) Secondary: Proportion of injections that were pain free per patient, the mean visual analog scale per patient, impact of injection site pain on comfort and satisfaction with treatment	Primary: A significantly greater proportion of patients receiving IFNβ-1b compared to IFNβ-1a were free from pain immediately, 30 minutes and 60 minutes after injection (P<0.0001 at all time points). Secondary: The proportion of pain-free injections per patient was significantly greater with IFNβ-1b compared to IFNβ-1a immediately, 30 minutes and 60 minutes after injection (P<0.0001 at all time points). Mean visual analog scale scores per patient were significantly lower with IFNβ-1b compared to IFNβ-1a immediately, 30 minutes and 60 minutes after injection (P<0.0001 at all time points). Injection site reactions occurred in significantly fewer patients treated with IFNβ-1b compared to IFNβ-1a (P<0.05). A significantly greater proportion of patients treated with IFNβ-1a compared to IFNβ-1b reported that pain after injection negatively impacted their satisfaction with treatment (35.9 vs 23.1%; P=0.006). Adverse effects were reported by 33.3% of patients treated with IFNβ-1b compared to 32.4% of patients receiving IFNβ-1a therapy (P value not reported).
Barbero et al.[96] (2006)	MC, PG, PRO, RCT	N=188	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
INCOMIN IFNβ-1b (Betaseron®) 0.25 mg SC every other day vs IFNβ-1a (Avonex®) 30 µg IM once-weekly	IFNβ-naïve patients with RRMS, ≥2 exacerbations in prior two years and EDSS scores 1 to 3.5	2 years	Proportion of patients with ≥1 active MRI lesion Secondary: Total area/volume of brain lesions or burden of disease, correlation between primary outcome and NAb status	Significantly fewer patients had ≥1 active lesion in the IFNβ-1b arm compared to the IFNβ-1a arm (17 vs 34%; P<0.014). Secondary: The mean T2 burden of disease showed a progressive decrease from baseline in patients treated with IFNβ-1b and a progressive increase in patients treated with IFNβ-1a (P<0.001). The development of NAbs did not appear to have any impact on changes in MRI activity associated with IFNβ-1b treatment during the entire study period (P=NS).
Durelli et al.[97] (2002) INCOMIN IFNβ-1b (Betaseron®) 0.25 mg SC every other day vs IFNβ-1a (Avonex®) 30 µg IM once-weekly	MC, PG, PRO, RCT IFNβ-naïve patients with RRMS and ≥2 exacerbations in prior two years and EDSS scores 1 to 3.5	N=188 2 years	Primary: Proportion of patients free from relapses Secondary: ARR, annualized treated relapse rate, proportion of patients free from sustained and confirmed progression in disability, EDSS score and time to sustained and confirmed progression in disability	Primary: Fifty-one percent of patients taking IFNβ-1b remained relapse-free compared to 36% of patients taking IFNβ-1a who remained relapse-free (P=0.03). Secondary: IFNβ-1b treatment resulted in fewer relapses per patient (0.5 vs 0.7; P=0.03), fewer treated relapses (0.38 vs 0.50; P=0.09), lower EDSS scores (2.1 vs 2.5; P=0.004), lower proportion of patients with progression in EDSS score of one point sustained for six months and confirmed at end of study (13 vs 30%; P=0.005) and longer time to sustained and confirmed disability progression (P<0.01) than IFNβ-1a treatment. Most adverse events (flu-like syndrome, fever, fatigue and increased liver enzymes) declined following six months of treatment. The frequency of adverse events was similar between groups. Local skin reactions and NAbs were more common in patients treated with IFNβ-1b compared to patients treated with IFNβ-1a (P values not reported). NAb were reduced during the second year of treatment and did not appear to have any correlation with relapse rate.
Minagara et al.[98] (2008) Murray[99]	DB, MC, OS, PRO, RETRO	N=136	Primary:	Primary: There was no significant difference between the groups in the change in brain parenchymal fraction (P value not reported).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2004) PROOF IFNβ-1a (Rebif®) 44 µg SC three times weekly vs IFNβ-1a (Avonex®) 30 µg IM once-weekly	Patients between 18 and 50 years of age with RRMS and an EDSS score 0 to 5.5, at least two documented relapses during the three years before study onset, receiving IFNβ-1a 30 µg IM once-weekly or IFNβ-1a 44 µg SC three times weekly for at least 12 months and up to 24 months before enrollment	12 to 24 months (RETRO phase) 6 month (PRO phase)	Change in brain parenchymal fraction Secondary: Proportion of patients who experienced relapses at six months, ARR, change in EDSS, NAb formation and adverse effects	Secondary: There was no significant difference between the treatment groups in the rate of relapse (P value not reported). There was no significant difference between the groups in the change in EDSS scores, suggesting similar sustained disability progression in both the IM IFNβ-1a and IFNβ-1a 44 µg SC groups (25.8 vs 26.7%; P value not reported). More patients in the IFNβ-1a 44 µg SC group developed NAbs compared to patients in the IM IFNβ-1a group (19 vs 0%; P value not reported). More patients positive for NAbs compared to those negative for NAbs had disability progression (40.0 vs 27.8%; P>0.05), new or enlarging T2 lesions (63.6 vs 40.7%; P=0.003) and gadolinium-enhancing lesions after 12 to 24 months of therapy (36.4 vs 15.0%; P=0.001). While general tolerability was comparable between the study drugs, IFNβ-1a 44 µg SC was associated with a greater incidence of injection-site reactions compared to the IM formulation (6.0 vs 2.9%; P value not reported).
Panitch et al.[100] (2002) EVIDENCE IFNβ-1a (Rebif®) 44 µg SC three times weekly vs IFNβ-1a (Avonex®) 30 µg IM once-weekly	MC, PG, RCT IFNβ-naïve patients with RRMS, ≥2 exacerbations in prior two years and EDSS score 0 to 5.5	N=677 48 weeks	Primary: Proportion of patients who were relapse-free at 24 weeks Secondary: Relapse rate, time to first relapse and number of active lesions per patient per scan on MRI	Primary: More patients in the IFNβ-1a 44 µg SC treatment group compared to the IFNβ-1a 30 µg IM group remained relapse free at 24 (75 vs 63%; P=0.0005) and 48 weeks (62 vs 52%; P=0.009). Secondary: The time to first relapse was significantly prolonged in the IFNβ-1a 44 µg SC group compared to the IFNβ-1a 30 µg IM group (P=0.003). Patients receiving IFNβ-1a 44 µg SC compared to IFNβ-1a 30 µg IM had significantly fewer active MRI lesions (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Injection-site reactions, asymptomatic abnormalities of liver enzymes, and altered leukocyte counts were more frequent with IFNβ-1a 44 µg SC compared to IFNβ-1a 30 µg IM (83 vs 28%; P<0.001, 18 vs 9%; P<0.002 and 11 vs 5%; P<0.003), respectively. NAbs developed in 25% of the IFNβ-1a 44 µg SC group compared to 2% of the IFNβ-1a 30 µg IM group (P<0.001).
Panitch et al.[101] (2005) EVIDENCE IFNβ-1a (Rebif®) 44 µg SC three times weekly vs IFNβ-1a (Avonex®) 30 µg IM once-weekly	MC, PG, RCT A 64-week follow-up of the EVIDENCE trial; IFNβ-naïve patients with RRMS, ≥2 exacerbations in prior two years and an EDSS score 0 to 5.5	N=677 64 weeks	Primary: Proportion of patients who were relapse-free at 24 weeks Secondary: Relapse rate, time to first and second relapse, number of T2 active lesions per patient per scan, percentage of active scans per patient and proportion of patients with no active lesions	Primary: At study endpoint, 56% of patients in the IFNβ-1a 44 µg SC group and 48% of patients in the IFNβ-1a 30 µg IM group remained relapse-free (P=0.023). Secondary: In the IFNβ-1a 44 µg SC group compared to the IFNβ-1a 30 µg IM group, there was a 17% reduction in relapse rate, a delayed time to first relapse (HR, 0.70), and a 32% reduction in steroid use to treat relapses (P value not reported). Patients in the IFNβ-1a 44 µg SC group had decreased MRI activity with reductions in T2 active lesions and a lower proportion of active scans and increases in patients with no active scans compared to patients in the IFNβ-1a 30 µg IM treatment group (P<0.001, for all comparisons). The presence of NAbs was associated with reduced efficacy for MRI measures and fewer IFNβ-related adverse effects, but did not have a significant impact on relapse measures.
Schwid et al.[102] (2005) EVIDENCE IFNβ-1a (Rebif®) 44 µg SC three times weekly vs	ES, MC, PG, RCT An eight-month extension of the EVIDENCE trial; IFNβ-naïve patients with RRMS, ≥2 exacerbations in prior two years and	N=677 80 weeks	Primary: Change in relapse rate Secondary: Change in the number of T2 active lesions per patient per scan, proportion of T2 active scans per	Primary: The relapse rate decreased from 0.64 to 0.32 for patients changing therapy (P<0.001) and from 0.46 to 0.34 for patients continuing therapy (P=0.03). The reduction in relapse rate was greater among patients switching to a higher dose and frequency IFNβ regimen (P=0.047). Secondary: Patients converting to the higher dose and frequency IFNβ regimen had fewer active lesions on T2-weighted MRI (P=0.02), fewer active scans (P=0.01) and no significant changes in the proportion of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
IFNβ-1a (Avonex®) 30 µg IM once-weekly increased to 44 µg SC three times weekly Patients initially randomized to 30 µg IM once-weekly were allowed to switch to 44 µg SC three times a week after 48 weeks of therapy while patients initially randomized to 44 µg SC three times a week could withdraw from the study or continue on the regimen for an additional eight months.	an EDSS score 0 to 5.5		patient and proportion of patients without T2 active scans	patients without active scans (P=NS). There were no significant changes in the continuing therapy group (P=NS). Seventy-three percent of the 306 patients receiving IFNβ-1a 30 µg IM switched to the IFNβ-1a 44 µg SC treatment and 91% of patients continued IFNβ-1a 44 µg SC therapy. Patients converting to the increased dose and frequency regimen experienced a higher incidence of adverse effects.
Schwid et al.[103] (2007) EVIDENCE IFNβ-1a (Rebif®) 44 µg SC three times weekly vs IFNβ-1a (Avonex®) 30 µg IM once-weekly, increased to 44 µg SC three times weekly Patients initially randomized to 30 µg IM once-weekly were allowed to switch to 44 µg SC three times a week after 48 weeks of therapy while patients initially randomized to 44 µg SC three times a week could withdraw from the study or continue on the regimen for an additional eight months.	AB, I, MC, PG, RCT, XO Full results of the EVIDENCE trial; IFNβ-naïve patients, between 18 and 55 years of age, with RRMS, ≥2 exacerbations in prior two years and an EDSS score 0 to 5.5	N=677 80 weeks	Primary: Proportion of patients free of relapses Secondary: Time to first relapse, ARR, number of steroid courses, number of T2 active lesions per patient per scan, percentage of active scans per patient, proportion of patients with no active scans, adverse events and NAbs detected	Primary: A significantly greater proportion of patients randomized to receive IFNβ-1a 44 µg SC remained free from relapses during the comparative phase of the study, compared to patients receiving IFNβ-1a 30 µg IM once-weekly (56 vs 48%; OR, 1.5; 95% CI, 1.1 to 2.0; P=0.023). Secondary: Compared to patients in the IFNβ-1a 30 µg IM group, patients in the high-dose IFNβ-1a 44 µg SC group experienced a 30% reduction in the time to first relapse (HR, 0.70; P=0.002) during the comparative phase of the study. Compared to patients in the IFNβ-1a 30 µg IM group, patients in the high-dose, IFNβ-1a 44 µg SC group experienced a 17% reduction in ARR (P=0.033) during the comparative phase of the study. A 50% reduction in the mean ARR occurred among patients who switched from IFNβ-1a 30 µg IM to IFNβ-1a 44 µg SC (P<0.001) during the XO phase of the study.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				A 26% reduction in the mean ARR occurred among patients who continued to receive IFNβ-1a 44 µg SC (P=0.028) during the XO phase of the study. A significantly lower number of steroid courses per patient per year were used in the high-dose IFNβ-1a 44 µg SC group compared to the IFNβ-1a 30 µg IM group (0.19 vs 0.28; P=0.009) during the comparative phase of the study. Patients in the IFNβ-1a 44 µg SC group had a significantly fewer mean number of T2-active lesions compared to patients in the IFNβ-1a 30 µg IM group (0.9 vs 1.4; P<0.001) during the comparative phase of the study. A significant reduction in the mean number of T2-active lesions occurred among patients who converted from IFNβ-1a 30 µg IM to IFNβ-1a 44 µg SC during the XO phase of the study (P=0.022). Patients in the IFNβ-1a 44 µg SC group had a significantly lower percentage of T2-active scans per patient compared to patients in the IFNβ-1a 30 µg IM group (27 vs 44%; P<0.001) during the comparative phase of the study. Patients who converted from IFNβ-1a 30 µg IM to IFNβ-1a 44 µg SC experienced a statistically significant reduction in the percentage of T2-active scans per patient during the XO phase of the study (P<0.001). A significantly greater percentage of patients randomized to the IFNβ-1a 44 µg SC group did not have a T2-active scan compared to patients in the IFNβ-1a 30 µg IM group (58 vs 38%; OR, 2.4; 95% CI, 1.7 to 3.3; P<0.001) during the comparative phase of the study. Converting from IFNβ-1a 30 µg IM to IFNβ-1a 44 µg SC was not correlated with a significant change in the percentage of patients with no T2-active scans (P=0.803).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Patients who continued IFNβ-1a 44 µg SC therapy from the start of the study did not have significant changes in any of the MRI measures (P value not reported). Injection-site reactions were significantly more common in patients receiving IFNβ-1a 44 µg SC compared to patients receiving IFNβ-1a 30 µg IM (85 vs 33%; P<0.001). Flu-like symptoms were significantly more common in patients receiving IFNβ-1a 30 µg IM than in patients receiving IFNβ-1a 44 µg SC (53 vs 45%; P=0.031). Abnormal liver function test results were significantly more common in patients receiving IFNβ-1a 44 µg SC than in patients receiving IFNβ-1a 30 µg IM (18 vs 10%; P=0.003). Most liver enzyme elevations resolved with continued therapy. Abnormal WBC counts were significantly more common in patients receiving IFNβ-1a 44 µg SC compared to patients receiving IFNβ-1a 30 µg IM (14 vs 5%; P<0.001). WBC counts normalized in most patients with continued therapy. The development of NAbs occurred in a significantly greater percentage of patients receiving IFNβ-1a 44 µg SC compared to patients receiving IFNβ-1a 30 µg IM (26 vs 3%; P<0.001). However, relapse rate was not affected by the NAb status (P=0.203).
Traboulsee et al.[104] (2008) EVIDENCE IFNβ-1a (Rebif®) 44 µg SC three times weekly vs IFNβ-1a (Avonex®) 30 µg IM once-weekly, increased to 44 µg SC three times weekly	PH This was a PH analysis of the EVIDENCE study; patients were included if had received at least one dose of the study drug and had an evaluable T2-weighted MRI scan obtained at	N=533 48 weeks	Primary: Percentage change in T2 burden of disease from baseline to week-48 Secondary: Absolute change in burden of disease, percentage and absolute change in burden of disease when stratified by	Primary: Median percentage decreases in burden of disease were greater in the IFNβ-1a 44 µg SC group compared to the IFNβ-1a 30 µg IM group (-6.7 vs -0.6%; P value not reported). The adjusted mean treatment difference in percentage change in burden of disease from baseline to week-48 showed a significant treatment benefit for patients treated with IFNβ-1a 44 µg SC compared to patients treated with IFNβ-1a 30 µg IM (-4.6%; SE, 2.6%; P=0.002). Secondary: A greater median absolute reduction from baseline in BOD was observed in the IFNβ-1a 44 µg SC group compared to IFNβ-1a 30 µg IM (-189.5 vs -19.0; P value not reported).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	baseline and week-48		NAb status from baseline to week-48	Among patients randomized to IFNβ-1a 44 µg SC, median percentage decreases in burden of disease were smaller in patients positive for NAbs compared to those with a negative NAb status (-0.8 vs -8.0; P value not reported). Among patients randomized to IFNβ-1a 44 µg SC, absolute decreases in burden of disease were smaller in patients positive for NAbs compared to those with a negative NAb status (-46.2 vs -254.6; P value not reported). The adjusted mean treatment difference in percentage change in burden of disease from baseline to week-48 showed a significant treatment benefit for NAb negative patients treated with IFNβ-1a 44 µg SC compared to IFNβ-1a 30 µg IM treated patients (-6.6%; SE, 2.8%; P<0.0001). The adjusted mean treatment difference in percentage change in burden of disease from baseline to week-48 showed comparable treatment benefit for NAb positive patients treated with IFNβ-1a 44 µg SC compared to IFNβ-1a 30 µg IM treated patients (-0.5%; SE, 3.9%; P=0.583).
Etemadifar et al.[105] (2006) IFNβ-1b (Betaseron®) 0.25 mg SC every other day vs IFNβ-1a (Rebif®) 44 µg SC three times weekly vs IFNβ-1a (Avonex®) 30 µg IM once-weekly	MC, RCT, SB Patients with RRMS with ≥2 relapses in past two years and EDSS score ≤5	N=90 24 months	Primary: Number of relapses, proportion of relapse-free patients and EDSS scores Secondary: Not reported	Primary: Mean relapse rates were reduced from 2.0 to 1.2, 2.4 to 0.6 and 2.2 to 0.7 episodes (P<0.001 for each) for the IFNβ-1a 30 µg IM, IFNβ-1a 44 µg SC, and IFNβ-1b groups, respectively. The proportions of relapse-free patients were 20, 43 and 57% for IFNβ-1a 30 µg IM, IFNβ-1a 44 µg SC, and IFNβ-1b, respectively. The mean number of relapses were lower with IFNβ-1a 44 µg SC and IFNβ-1b compared to IFNβ-1a 30 µg IM treatment (P<0.05). EDSS scores decreased by 0.3 in the IFNβ-1a 44 µg SC group (P<0.05) and 0.7 in the IFNβ-1b group (P<0.001) while the IFNβ-1a 30 µg IM group remained stable. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Rio et al.[106] (2005) IFNβ-1b (Betaseron®) 0.25 mg SC every other day vs IFNβ-1a (Rebif®) 22 µg SC three times weekly vs IFNβ-1a (Avonex®) 30 µg IM once-weekly	OL, OS, PM Patients with RRMS with ≥2 relapses in the previous two years and an EDSS score 0 to 5.5	N=495 Up to 8 years	Primary: Proportion of relapse-free patients, proportion of patients with confirmed and sustained disability progression, ARR, proportion of decrease in relapse rate, proportion of patients reaching EDSS of six and number of patients who discontinued treatment due to inefficacy Secondary: Not reported	Primary: At two years 59, 59 and 50% of patients were relapse-free in the IFNβ-1a 30 µg IM, IFNβ-1a 22 µg SC, and IFNβ-1b groups, respectively. At four years 52, 39 and 35% of patients were relapse-free in the IFNβ-1a 30 µg IM, IFNβ-1a 22 µg SC and IFNβ-1b groups, respectively. Each group showed a significant reduction in relapse rate (P<0.0001). The number of relapses decreased with treatment at two years from 2.24 to 0.80 for IFNβ-1a 30 µg IM, from 2.51 to 0.64 for IFNβ-1a 22 µg SC and from 2.86 to 0.87 for IFNβ-1b. The relapse rates decreased at four years (from 1.07 to 0.33 for IFNβ-1a 30 µg IM, 1.21 to 0.41 for IFNβ-1a 22 µg SC, and from 1.36 to 0.38 for IFNβ-1b; P<0.0001 for all comparisons). The proportions of patients with confirmed and sustained disability at two and four years respectively, were 17 and 23% for IFNβ-1a 30 µg IM, 19 and 35% for IFNβ-1a 22 µg SC, and 10 and 24% for IFNβ-1b. There were no significant differences between the treatment groups (P=NS). Thirteen percent of patients had an EDSS ≥6 following four years of therapy, but there were no significant differences between groups (P=NS). The proportions of patients discontinuing treatment due to lack of efficacy were 8% for IFNβ-1a 30 µg IM, 3% for IFNβ-1a 22 µg SC and 10% for IFNβ-1b (P values not reported). Patients selecting therapy with IFNβ-1a 30 µg IM were older than those selecting IFNβ-1a 22 µg SC. Patients selecting IFNβ-1b had greater disease activity and disability at baseline compared to the other treatments. Secondary: Not reported
Trojano et al.[107] (2003) IFNβ-1b (Betaseron®) 0.25 mg SC every other day	MC, OL, OS, PM Patients with RRMS	N=1,033 24 months	Primary: Proportion of relapse-free patients and number of patients with ≥1	Primary: The proportions of patients who were relapse free in each group were similar (54% with IFNβ-1a 30 µg IM, 49% with IFNβ-1a 22 µg SC and 54% with IFNβ-1b at 12 months (P value not reported). The

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs IFNβ-1a (Rebif®) 22 µg SC three times weekly vs IFNβ-1a (Avonex®) 30 µg IM once-weekly			point progression in EDSS Secondary: Changes from baseline in ARR and EDSS score	proportions of patients who remained relapse free at 24 months were 33% with IFNβ-1a 30 µg IM and 38% with IFNβ-1b (P=NS). The number of patients experiencing ≥1 point progression in EDSS was 3% with IFNβ-1a 30 µg IM, 5% with IFNβ-1a 22 µg SC and 4% with IFNβ-1b at 12 months (P=NS). The number of patients with ≥1 point progression in EDSS at 24 months was 7% with IFNβ-1a 30 µg IM and 11% with IFNβ-1b (P=NS). Secondary: Relapse rates were 0.71 with IFNβ-1a 30 µg IM and 0.65 with IFNβ-1b (P=0.16). Mean changes in EDSS score were similar among the groups (P=NS).
Trojano et al.[108] (2007) IFNβ-1b (Betaseron®) 0.25 mg SC every other day vs IFNβ-1a (Rebif®) 22 µg SC three times weekly vs IFNβ-1a (Rebif®) 44 µg SC three times weekly vs IFNβ-1a (Avonex®) 30 µg IM once-weekly vs no treatment	OS Patients with RRMS	N=1,504 7 years	Primary: Incidence of SPMS Secondary: EDSS score of four and an EDSS score of six	Primary: Patients treated with IFNβ patients showed a reduction in the incidence of SPMS compared to untreated patients (P<0.0001) in terms of time from first visit (HR, 0.38) and current age (HR, 0.36). Secondary: There was a significant difference in favor of IFNβ-treated patients for EDSS score of four (P<0.02) and EDSS score of six (P≤0.03).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Limmroth et al.[109] (2007) QUASIMS IFNβ-1b (Betaseron®) 0.25 mg SC every other day vs IFNβ-1a (Rebif®) 22 µg SC three times weekly vs IFNβ-1a (Rebif®) 44 µg SC three times weekly vs IFNβ-1a (Avonex®) 30 µg IM once-weekly	MC, OS Patients 18 to 65 years of age with RRMS and uninterrupted ≥2 year history of therapy with one of the study regimens	N=4,754 ≥2 years	Primary: Change from baseline EDSS score, percentage of progression-free patients (defined as <1 point increase in EDSS score over two years of therapy), percentage of relapse-free patients, ARR and reasons for therapy change Secondary: Not reported	Primary: There were no differences in the change from baseline EDSS scores among patients who received IFNβ-1a 30 µg IM, IFNβ-1b, IFNβ-1a 22 µg SC and IFNβ-1a 44 µg SC regimens over two years of therapy (0.17 vs 0.25 vs 0.20 vs 0.35, respectively; P value not reported). The percentage of progression-free patients was significantly lower in the IFNβ-1a 44 µg SC group compared to the IFNβ-1a 30 µg IM group (P<0.001) and IFNβ-1a 22 µg SC group (P=0.001). The percentage of progression-free patients was significantly lower in the IFNβ-1b group compared to the IFNβ-1a 30 µg IM group (P=0.001). The percentage of relapse-free patients was significantly lower in the IFNβ-1a 44 µg SC group compared to the IFNβ-1a 30 µg IM group (34.6 vs 48.5%; P=0.002) and IFNβ-1b group (34.6 vs 45.7%; P=0.007). The percentage of relapse-free patients was significantly lower in the IFNβ-1a 22 µg SC group compared to the IFNβ-1a 30 µg IM group (39.8 vs 48.5%; P=0.005). There were no significant differences in ARR over two years among treatment-naïve patients who received IFNβ-1a 30 µg IM, IFNβ-1b, IFNβ-1a 22 µg SC and IFNβ-1a 44 µg SC regimens (0.51 vs 0.52 vs 0.53 vs 0.63, respectively; P=NS). The most common reason for therapy change was a perceived lack of efficacy (7.1%). A significantly greater percentage of patients changed therapy due to perceived lack of efficacy in the IFNβ-1a 22 µg SC group compared to either IFNβ-1a 30 µg IM (P=0.0027) or IFNβ-1b group (P<0.0001). Therapy change due to injection-site reactions was significantly less frequent among patients receiving IFNβ-1a 30 µg IM compared to IFNβ-1b (P<0.0001) and IFNβ-1a 22 µg SC groups (P=0.0001). In addition, a significantly greater percentage of patients in the IFNβ-1b

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				group changed therapy due to flu-like symptoms compared to patients in the IFNβ-1a 22 µg SC group (1.2 vs 0.2 %; P=0.0038). Secondary: Not reported
Hauser et al.[110] (2017) OPERA I and OPERA II Ocrelizumab 600 mg IV infusion every 24 weeks (initial dose given as 300 mg IV on day 1 and 14) vs interferon β-1a (Rebif®) 44 µg SC three times weekly Each patient received a matching IV or SC placebo, as appropriate. All patients received IV methylprednisolone 100 mg before infusion. Optional prophylaxis with analgesics or antipyretics and antihistamine was recommended before infusion.	AC, DB, DD, MC, RCT Patients 18 to 55 years of age with a diagnosis of MS (according to 2005 revised McDonald criteria), EDSS score of 0 to 5.5 at screening, at least two documented clinical relapses within the previous two years (or one clinical relapse with the year before screening), MRI showing abnormalities consistent with MS, no neurologic worsening for at least 30 days before screening and baseline	N=1,656 (821 and 835 for OPERA I and II, respectively) 96 weeks	Primary: ARR by 96 weeks Secondary: The proportion of patients with disability progression confirmed at 12 weeks through week 96 (pooled); the total (cumulative) mean number of gadolinium-enhancing lesions identified on T1-weighted MRI of the brain at weeks 24, 48, and 96; the total number of new or newly enlarged hyperintense lesions on T2-weighted MRI of the brain at weeks 24, 48, and 96; the proportion of patients with disability improvement confirmed at 12	Primary: The ARR at 96 weeks in OPERA I was 0.16 for ocrelizumab and 0.29 for interferon β-1a (rate ratio, 0.54; 95% CI, 0.40 to 0.72; P<0.001). The annualized relapse rate at 96 weeks in OPERA II was 0.16 for ocrelizumab and 0.29 for interferon β-1a (rate ratio, 0.53; 95% CI, 0.40 to 0.71; P<0.001). Secondary: The pooled proportion of patients with disability progression at 12 weeks, defined as an increase from the baseline EDSS score of at least 1.0 point (or 0.5 points if the baseline EDSS score was >5.5) that was sustained for at least 12 weeks, was 9.1% for ocrelizumab and 13.9% for interferon β-1a (HR, 0.60; 95% CI, 0.45 to 0.81; P<0.001). The pooled proportion of disability improvement confirmed at 12 weeks, defined as a reduction from the baseline EDSS score of at least 1.0 point (or 0.5 points if the baseline EDSS score was >5.5) that was sustained for at least 12 weeks in patients with a baseline EDSS score of at least 2.0, was 20.7% for ocrelizumab and 15.6% for interferon β-1a (P=0.02). The pooled proportion of patients with disability progression at 24 weeks was 6.9% for ocrelizumab and 10.5% for interferon β-1a (HR, 0.60; 95% CI, 0.43 to 0.84; P=0.003). The change in the MSFC score from baseline to week 96 in was 0.21 for ocrelizumab and 0.17 for placebo (P=0.33) in OPERA I and 0.28 for ocrelizumab and 0.17 for interferon β-1a (P=0.004) in OPERA II. The change in adjusted mean SF-36 physical component summary score from baseline to week 96 in OPERA I was 0.04 for ocrelizumab and -0.66 for interferon β-1a (P=0.22). In OPERA II, the change in

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			weeks through week 96 (pooled); the rate of disability progression confirmed at 24 weeks through week 96 (pooled); the total number of new hypointense lesions on T1-weighted MRI of the brain at weeks 24, 48, and 96; the change in the MSFC score from baseline to week 96; the percentage change in brain volume from week 24 to week 96; the change in the physical-component summary score of the Medical Outcomes Study SF-36 from baseline to week 96; the proportion of patients with a baseline EDSS score of at least 2.0 who had no evidence of disease activity; immunogenicity of ocrelizumab; safety	adjusted mean SF-36 physical component scores was 0.33 for ocrelizumab and -0.83 for interferon β-1a (P=0.04).† The proportion of patients with a baseline EDSS of 2.0 who had no evidence of disease activity (defined as no relapse, no disability progression confirmed at 12 weeks or at 24 weeks, no new or newly enlarged lesions on T2-weighted MRI, and no gadolinium-enhancing lesions on T1-weighted MRI) by week 96 was 47.9% for ocrelizumab and 29.2% for interferon β-1a (P<0.001) in OPERA I and 47.5% for ocrelizumab and 25.1% for interferon β-1a (P<0.001) in OPERA II.† The mean number per scan of new gadolinium-enhancing lesions on T1-weighted MRI by week 96 was 0.02 for ocrelizumab and 0.29 for interferon β-1a (rate ratio, 0.06; 95% CI, 0.03 to 0.10; P<0.001) in OPERA I and 0.02 for ocrelizumab and 0.42 for interferon β-1a (rate ratio, 0.05; 95% CI, 0.03 to 0.09; P<0.001) in OPERA II. The mean number per scan of new or newly enlarged hyperintense lesions on T2-weighted MRI by week 96 was 0.32 for ocrelizumab and 1.41 for interferon β-1a (rate ratio, 0.23; 95% CI, 0.17 to 0.30; P<0.001) in OPERA I and 0.33 for ocrelizumab and 1.90 for interferon β-1a (rate ratio, 0.17; 95% CI, 0.13 to 0.23; P<0.001) in OPERA II. The mean number per scan of new hyperintense lesions on T1-weighted MRI by week 96 was 0.42 for ocrelizumab and 0.98 for interferon β-1a (rate ratio, 0.43; 95% CI, 0.33 to 0.56; P<0.001) in OPERA I and 0.45 for ocrelizumab and 1.26 for interferon β-1a (rate ratio, 0.36; 95% CI, 0.27 to 0.47; P<0.001) in OPERA II. Mean percentage change in brain-volume from week 24 to 96 was -0.57 for ocrelizumab and -0.74 for interferon β-1a (P=0.004) in OPERA I and -0.64 for ocrelizumab and -0.75 for interferon β-1a (P=0.09) in OPERA II.† The proportion of patients that reported any adverse event in OPERA I and II, was 80.1% and 86.3% for ocrelizumab and 80.9% and 86.3%

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			profile of ocrelizumab	for interferon β-1a, respectively. Serious adverse events in OPERA I and II were reported in 6.9% and 7.0% of patients treated with ocrelizumab, respectively and 7.8% and 9.6% of patients treated with interferon β-1a, respectively. In pooled data, infection occurred in 483 patients (58.5%) for ocrelizumab and 441 patients (53.4%) for interferon β-1a. In pooled data, neoplasm occurred in four patients (0.5%) for ocrelizumab and two patients (0.2%) for interferon β-1a. †Nominal P values reported but are non-confirmatory (i.e., descriptive only) as a consequence of the failure in the statistical hierarchical testing procedure.
Vermersch et al.[111] (2014) TENERE Teriflunomide 7 mg vs teriflunomide 14 mg vs Rebif® (IFNβ-1a) SC titrated to 8.8 µg for 2 weeks, 22 µg for 2 weeks then 44 µg; those who could not tolerate 44 µg were reduced to 22 µg	DB, MC, PG, RCT Patients aged 18 years or older who met McDonald criteria for MS diagnosis and had relapsing clinical course, EDSS score of 5.5 or lower and no systemic corticosteroid use in 2 weeks prior to randomization	N=324 48 weeks	Primary: Time to failure Secondary: Safety and tolerability of teriflunomide, ARR, fatigue impact scale, global satisfaction score	Primary: Time to failure was not significantly different between groups (Rebif®: 42.3%; teriflunomide 7 mg: 48.6%, P=0.52; teriflunomide 14 mg: 37.8%, P=0.60). Secondary: The overall incidence of patients experiencing at least one TEAE was similar across all groups. The most common, potentially teriflunomide-related TEAEs were nasopharyngitis, diarrhea, alopecia, paresthesia and back pain and the most common potentially Rebif®-related TEAEs were headache, influenza-like illness and increased ALT. ARR was marginally lower in the Rebif® group (0.216) than the 7 mg group (0.410; P=0.03) and was not significantly different from the 14 mg group (0.259; P=0.59). The increase from baseline in fatigue impact score was marginally lower in the Rebif® group (9.10) than the 7 mg group (0.97; P=0.03) and not statistically different than the 14 mg group (4.10; P=0.18). Patients in the Rebif® group expressed marginally lower global satisfaction scores (60.98) than patients in the 7 mg and 14 mg groups (68.29 and 68.82; P=0.02 for both).

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Calabresi et al.[112] (2014) FREEDOMS II Fingolimod 0.5 mg QD vs fingolimod 1.25 mg QD vs placebo QD (all patients assigned to fingolimod 1.25 mg were switched to the 0.5 mg dose in a blinded manner after a review of data from other phase III trials and recommendation from the data and safety monitoring board, but were analyzed as being in the 1.25 mg group in the primary outcome analysis)	DB, MC, PC, PG, RCT Patients 18 to 55 years of age with RRMS who had one or more confirmed relapses during the preceding year (or two or more confirmed relapses during the previous two years), had EDSS score of 0 to 5.5, and had no relapse or steroid treatment within 30 days before randomization (previously treated patients were eligible if interferon β or glatiramer acetate therapy was stopped at least three months before randomization and natalizumab treatment at least six months before randomization)	N=1,083 24 months	Primary: Annualized relapse rate at month 24 Secondary: Percentage brain volume change from baseline; time-to-disability-progression confirmed at three months	Primary: Patients given fingolimod had lower aggregate annualized relapse rates (over 24 months) than those given placebo (rate ratio, 0.5; 95% CI, 0.39 to 0.65; P<0·0001), corresponding to relative reductions in relapse rates compared to placebo of 50% in the 1.25 mg group and 48% in the 0.5 mg group (rate ratio, 0.52; 95% CI, 0.40 to 0.66; P<0.0001). Secondary: The mean percentage brain volume change from baseline was lower with both doses of fingolimod than it was with placebo at month 24 and the estimated treatment difference was statistically significant (1.25 mg dose, P<0.0001; 0.5 mg dose, P<0.0002. In general, patients given placebo had increased brain volume loss compared with those given fingolimod at months 6, 12, and 24. There was no statistically significant effect of fingolimod on time to disability progression confirmed at three months (1.25 mg dose, P=0.056; 0.5 mg dose, P=0.320) or six months (1.25 mg dose, P=0.113; 0.5 mg dose, P=0.101). The time to first confirmed relapse was delayed in both fingolimod treatment groups versus placebo (1.25 mg dose, HR, 0.50; 95% CI, 0.38 to 0.64; P<0.0001 and for the 0.5 mg dose, HR, 0.52; 95% CI, 0.40 to 0.67, P<0.0001), and more fingolimod-treated patients were relapse-free at the end of month 24. At month 24, patients given fingolimod had an improved median MSFC score compared with those given placebo.
Confavreux et al.[113] (2014)	DB, MC, PC, RCT	N=1,169	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
TOWER Teriflunomide 7 mg QD vs teriflunomide 14 mg QD vs placebo QD	Patients 18 to 55 years of age with relapsing multiple sclerosis who had one or more relapse in the previous 12 months or two or more in the previous 24 months but no relapse in the previous 30 days and an EDSS score of 5.5 or less.	48 weeks	Annualized relapse rate Secondary: Time to sustained accumulation of disability	The annualized relapse rate was higher in patients assigned to placebo (0.50, 95% CI, 0.43 to 0·58) than in those assigned to teriflunomide 14 mg (0.32, 95% CI, 0.27 to 0.38; P=0·0001) or teriflunomide 7 mg (0.39, 95% CI, 0.33 to 0.46; P=0.0183). Secondary: Compared with placebo, teriflunomide 14 mg reduced the risk of sustained accumulation of disability (HR, 0.68; 95% CI, 0.47 to 1.00, log-rank P=0.0442); however, teriflunomide 7 mg had no effect on sustained accumulation of disability (HR, 0.95; 95% CI, 0.68 to 1.35, log-rank P=0.7620).
Lublin et al.[114] (2013) ComiRX Interferon-β-1a (Avonex®) 30 µg IM weekly + glatiramer acetate (Copaxone®) 20 mg SQ QD vs interferon-β-1a (Avonex®) 30 µg IM weekly + placebo SQ QD vs glatiramer acetate (Copaxone®) 20 mg SQ QD + placebo IM weekly	DB, MC, PC, RCT Patients 18 to 60 years of age with an EDSS score of 0 to 5.5 and diagnosed with RRMS with at least two exacerbations in the prior three years, where one exacerbation could be an MRI change	N=1,008 3 years	Primary: Annualized relapse rate (only including protocol-defined relapses) Secondary: Confirmed progression of expanded disability status scale and change in a composite score constructed from four MRI measures	Primary: Annualized relapse rate of the combination group at 36 months was not significantly improved to the better of the 2 single-agent arms when adjusting for baseline age (P=0.27). Glatiramer acetate provided a significant reduction of risk of exacerbation compared to interferon by 31%, and the combination group provided a significant reduction of risk of exacerbation than interferon by 25% (P=0.027 and P=0.022 respectively). The results were similar combining protocol-defined exacerbation and with non-protocol defined exacerbations, a less stringent definition for exacerbation. Secondary: There were no differences between groups for the proportions showing six-month confirmed progression of EDSS, with progression observed in 22 to 25% of the participants. There was no difference in the m score between groups, with all groups showing small increases, primarily driven by the Paced Auditory Serial Addition Test. The 9-hole peg test and 25-foot timed walk were minimally worse after 36 months. The primary MRI outcome, change in the Z4 composite from baseline to month 36, did not differ between the interferon and glatiramer groups (P=0.52) or between the nominal monotherapy winner

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				interferon and the combination (P=0.23), adjusted for baseline Z4 and age. Similarly, analyses at months six, 12, and 24 demonstrated no significant differences between the treatment arms.
Coles et al.[115] (2012) IFNβ-1a 44 µg SC three times weekly vs alemtuzumab 12 mg treatment regimen	AC, MC, RCT, rater-masked Patients 18 to 55 years of age with relapsing remitting MS with a maximum disease duration of 10 years, at least two attacks in the prior two years, at least one relapse while on interferon β or glatiramer after at least six months of treatment, EDSS scores of 5.0 or less, as well as cranial and spinal MRI lesions fulfilling protocol-defined criteria.	N=667 2 years	Primary: Relapse rate and time to six month sustained accumulation of disability based on EDSS and MSFC Secondary: Change in T2-hyperintense lesion volume and safety endpoints	Primary: Alemtuzumab reduced the rate of relapse compared with IFNβ-1a (P<0.0001). Of the 426 patients treated with alemtuzumab, 147 patients experienced a relapse event (0.26 annualized relapse rate) compared with 102 of the 202 patients treated with IFNβ-1a (0.52 annualized relapse rate). Alemtuzumab reduced risk of sustained accumulation of disability compared with IFNβ-1a (P<0.0084). Of the 426 patients treated with alemtuzumab, 54 patients sustained confirmed disability accumulation (13% relapse rate) compared with 40 of the 202 patients treated with IFNβ-1a (20% relapse rate). Mean disability improved from baseline by -0.17 EDSS points after treatment with alemtuzumab (P=0.004) compared with a 0.24 EDSS point deterioration for IFNβ-1a (P=0.0064), resulting in a net benefit of treatment with alemtuzumab of 0.41 EDSS points (P<0.0001). MSFC scored improved from baseline by 0.08 after treatment with alemtuzumab and worsened on IFNβ-1a by -0.04, which was not noted to be a statistically significant difference (P=0.002). Secondary: There was no significant difference in the change in T2 lesion volume between the treatment groups. There was a -1.3% and -1.2% change in T2 lesion volume from baseline through year two for the alemtuzumab and IFNβ-1a treatment groups, respectively. Of the 435 patients in the alemtuzumab treatment group, 393 patients (90%) had infusion-associated reactions, 334 patients (77%) had infections, 69 patients (16%) had thyroid disorders and three (1%) had immune thrombocytopenia. Of the 202 patients randomized to the IFNβ-1a group, 134 patients (66%) had infections.
Cohen et al.[116] (2012)	AC, MC, RCT, rater-masked	N=581 2 years	Primary: Relapse rate and time to six month	Primary: Alemtuzumab reduced the rate of relapse compared with IFNβ-1a (P<0.0001). Of the 376 patients treated with alemtuzumab, 82

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
IFNβ-1a 44 µg SC three times weekly vs alemtuzumab 12 mg treatment regimen	Patients 18 to 50 years of age with previously untreated relapsing remitting MS with a maximum disease duration of up to five years, at least two relapses in the previous two years, at least once relapse in the prior one year, EDSS scores of 3.0 or lower and cranial abnormalities on MRI attributable to MS		sustained accumulation of disability Secondary: Proportion of relapse-free patients, change in EDSS, percentage change in T2-hyperintense lesion volume, change in MSFC and safety endpoints	patients experienced a relapse event (0.18 annualized relapse rate) compared with 75 of the 187 patients treated with IFNβ-1a (0.39 annualized relapse rate). A greater number of alemtuzumab-treated patients (77.6%), compared to IFNβ-1a-treated patients (58.7%), remained relapse free during the study (P<0.0001). Rates of sustained accumulation of disability did not differ between the treatment groups (P=0.22). Of the 376 patients treated with alemtuzumab, 30 patients sustained confirmed disability accumulation (8%) compared with 20 of the 202 patients treated with IFNβ-1a (11%). Secondary: Mean disability improved from baseline by 0.14 EDSS points in both the alemtuzumab and IFNβ-1a treatment groups (P=0.97). The difference in MSFC change between the treatment groups over 24 months was not statistically significant (P=0.01). There was a 0.15 mean change in MSFC score from baseline for the alemtuzumab treatment group and a 0.07 mean change in MSFC score from baseline for the IFNβ-1a treatment group. Decreases in T2-hyperintense lesions volume did not differ between the treatment groups over the 24 month time period (P=0.31). Compared with the IFNβ-1a treatment group (58% developed new or enlarging T2-hyperintense lesions), patients in the alemtuzumab treatment group (48% developed new or enlarging T2-hyperintense lesions) had a reduced proportion of new or enlarging T2-hyperintense lesions (P=0.04) Of the 376 patients in the alemtuzumab treatment group, 338 patients (90%) had infusion-associated reactions and 12 patients (3%) had serious infusions reactions. Infections occurred in 67% of patients treated with alemtuzumab compared 45% of patients treated with IFNβ-1a. Thyroid-related disorders occurred in in 18% of patients treated with alemtuzumab compared 6% of patients treated with IFNβ-1a. Blood and lymphatic system disorders occurred in 18% of

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				patients treated with alemtuzumab compared 19% of patients treated with IFNβ-1a. Two patients (1%) in the alemtuzumab treatment group developed thyroid papillary carcinoma. In the alemtuzumab treatment group, 98 serious adverse events occurred per year compared to 33 events per year in the IFNβ-1a treatment group.
Coles et al.[117] (2008) IFNβ-1a 44 μg SC three times weekly vs alemtuzumab 12 mg treatment regimen vs alemtuzumab 24 mg treatment regimen	AC, DB, MC, RCT Patients with previously untreated relapsing remitting MS with an onset of symptoms no more than 36 months before the time of screening, at least two clinical episodes during the previous two years, a score of 3 or less on the EDSS and once or more enhancing lesions as seen on cranial MRI scans	N=334 36 months	Primary: Time to sustained accumulation of disability and the rate of relapse Secondary: Proportion of patients who did not have a relapse, changes in lesion burden, brain volume and safety endpoints	Primary: As compared with the IFNβ-1a treatment group, the alemtuzumab treatment groups reduced the risk of sustained disability by 71% (P<0.001): 75% risk reduction in the 12-mg group and 67% risk reduction in the 24-mg group. In both alemtuzumab treatment groups, the mean disability score on the EDSS improved by 0.39 point at 36 months: 0.32 points for the 12-mg dose (P=0.006) and 0.45 point for the 24-mg dose (P=0.001). The mean disability score worsened by 0.38 point among patients receiving IFNβ-1a, representing a net advantage of 0.77 points among patients receiving alemtuzumab (P<0.001). As compared with the IFNβ-1a treatment group, the alemtuzumab treatment groups had a reduced rated of relapse by 74% (P<0.001): 69% reduction in the 12-mg group and 79% reduction in the 24-mg group. The annualized relapse rate at 36 months was 0.36 for the IFNβ-1a group and 0.10 for the alemtuzumab treatment groups: 0.11 for the 12-mg group and the 0.08 for the 24-mg group. Secondary: The proportion of patients who remained relapse-free at 36 months was 52% for IFNβ-1a and 80% for the alemtuzumab treatment group: 77% for the 12-mg group and 84% for the 24-mg group (P<0.001). From baseline to month 36, there was a reduction in the volume of lesions, as seen on T2-weighted MRI, in all three study groups including a -13.3, -18.2 and -13.5 median change in lesion load on T2-weighted MRI for the IFNβ-1a, alemtuzumab 12-mg and alemtuzumab 24-mg treatment groups, respectively (P=0.005).

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				The reduction in brain volume between baseline and month 36 was significantly less among patients receiving alemtuzumab than among those receiving IFNβ-1a (-0.5% and -1.8, respectively; P=0.05). Of the 216 patients in the alemtuzumab treatment groups, 213 patients (98.6%) had infusion-associated reactions and 3 patients (1.4%) had serious infusions reactions. Infections occurred in 65.7% of patients treated with alemtuzumab compared 46.7% of patients treated with IFNβ-1a. Thyroid-related disorders occurred in in 22.7% of patients treated with alemtuzumab compared 2.8% of patients treated with IFNβ-1a. Immune thrombocytopenic purpura occurred in 2.8% of patients treated with alemtuzumab compared 0.9% of patients treated with IFNβ-1a. Three patients (1.4%) in the alemtuzumab treatment group developed malignancies compared to one patient (0.9%) in the IFNβ-1a treatment group. Two patients (0.9%) in the alemtuzumab treatment group died compared to zero patients in the IFNβ-1a treatment group.
Planche et al.[118] (2017) Natalizumab 300 mg IV every 4 weeks	MC, OL Patients were ≥18 years of age with a diagnosis of RRMS for >6 months and <10 years with no relapse within 1 month before enrollment and an EDSS score <7.0	N=48 36 months	Primary: Health-related quality of life (HRQoL), ARR Secondary: Not reported	Primary: The global HRQoL was significantly increased from baseline six months after initiation of natalizumab (58.8 vs 68.7; P=0.001). The improvement was maintained at 12 months (P<0.001), 18 months (P=0.024) and 16 months (P=0.011). The ARR decreased from 1.3±0.5 before treatment to 0.6±0.7 during the first 18 month of natalizumab and 0.2±0.4 between months 18 to 36 (P<0.001). Secondary: Not reported
Calabresi et al.[119] (2014) ADVANCE Peginterferon β-1a 125 µg SC every two weeks vs	DB, MC, PC, PG, RCT Patients 18 to 65 years of age with a diagnosis of RRMS, a score of zero to five on the	N=1,012 48 weeks	Primary: Annualized relapse rate at week 48 Secondary: Number of new or newly enlarging hyperintense	Primary: Relapses were significantly less frequent in patients taking Peginterferon β-1a than in those taking placebo. At week 48, the adjusted annualized relapse rate was 0.397 relapses per patient-year (95% CI, 0.328 to 0.481) in the placebo group, 0.256 (95 % CI, 0.206 to 0.318) in the every two weeks group, and 0.288 (95% CI, 0.234 to 0.355) in the every four weeks group. The rate ratio for peginterferon every two weeks compared to placebo was 0.644 (95% CI, 0.500 to

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Peginterferon β-1a 125 µg SC every four weeks vs placebo	EDSS, two clinically documented relapses in the previous three years, with one having occurred within 12 months prior to randomization		lesions on T2-weighted images, proportion of patients who relapsed, and proportion of patients with disability progression at 48 weeks	0.831; P=0.0007) and the rate ratio for peginterferon every four weeks compared to placebo was 0.725 (95% CI, 0.565 to 0.930; P=0·0114. Hazard ratios show significant reductions in risk of relapse after treatment with study drug relative to placebo. When placebo is compared to the every two weeks group the HR was 0.61 (95% CI, 0.47 to 0.80; P=0.0003) and when compared to the every four weeks group the HR was 0.74 (95% CI, 0.57 to 0.95; P=0.02). Secondary: The proportion of patients who had had 12 weeks of sustained disability progression at 48 weeks was 0.105 in the placebo group and 0.068 in both intervention groups. Hazard ratios show that peginterferon β-1a significantly reduced the risk of progression of disability (HR, 0.62; 95% CI, 0.40 to 0.97; P=0.0383). Patients treated with peginterferon β-1a had fewer new or newly enlarging hyperintense lesions on T2-weighted images at 48 weeks than did patients in the placebo group; these lesions were also significantly smaller for those patients taking study drug compared to those taking placebo (P<0·0001). Patients in the every two weeks group had significantly fewer and smaller new T1 hypointense and gadolinium-enhancing lesions, and significantly fewer new active lesions, compared to patients in the placebo group (all P<0·0001). Patients in the every four weeks group had fewer new active lesions and smaller T2 and gadolinium-enhancing lesions compared to those in the placebo group (P<0·0001). There were fewer T1 hypointense and gadolinium-enhancing lesions, with peginterferon β-1a every four weeks compared to placebo, but differences were not statistically significant (P values not reported). There was no significant difference for whole brain volume between groups. Mean percentage decrease in magnetization transfer ratio was significantly lower for patients in the every two weeks group, compared to those in the placebo group (P=0·0438); however, there was no statistically significant difference when comparing those

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				treated to peginterferon every four weeks with those treated with placebo (P=0·6873). The adverse events that were >2% more common in the peginterferon β-1a groups than in the placebo group were injection-site reactions, influenza-like illness, pyrexia, and headache. The most commonly reported treatment-related adverse events were injection-site reactions, influenza-like illness, and headache. The incidence of adverse events that led to discontinuation of study treatment was higher in the intervention groups than the placebo group (P values not reported). A greater proportion of patients in the intervention groups had reductions of hematological parameters and increased liver enzymes compared to patients in the placebo group; however, most were not clinically significant and did not result in discontinuation of treatment. The incidence of serious adverse events was similar in each group.
Arnold et al.[120] (2017) Peginterferon β-1a 125 µg SC every two weeks vs Peginterferon β-1a 125 µg SC every four weeks Patients in the ADVANCE trial who had received placebo were randomized to one of the two treatment groups above.	DB, ES, MC Patients had completed the 48-week ADVANCE trial	N=1,189 2 years	Primary: Number and volume of T1-hypointense; number of new active; whole brain volume; magnetization transfer ratio (MTR) in normal-appearing brain tissue (NABT); proportion of patient with no evidence of disease activity (NEDA) Secondary: Not reported	Primary: Patients who received peginterferon beta-1a every two weeks had a 58% reduction in T1 lesion formation (p<0.0001) compared to 52% with delayed treatment or peginterferon beta-1a every four weeks (P<0.0001). Patients in the peginterferon beta-1a every two weeks group also had, a 65% reduction (P<0.0001) in new active lesions from baseline to Week 96 compared to a 55% reduction in those who received peginterferon beta-1a every four weeks (P<0.0001). During the first year of the study, whole brain volume decreased from baseline to a greater extent with peginterferon beta-1a every two weeks than with delayed treatment (P<0.01 at Weeks 24 and 48); however, the changes were small (<1%) and by Week 96, the reduction versus baseline was numerically smallest in the peginterferon beta-1a every two weeks group. During the period from Week 24 to 96, reduction in whole brain volume was significantly smaller with both peginterferon beta-1a every two weeks and peginterferon beta-1a every four weeks compared with delayed treatment

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				All groups had reductions in MTR or NABT. MTR of NABT had decreased by a mean of 0.12% in the peginterferon beta-1a every two weeks group, compared with 0.39% in the delayed treatment group (P=0.05) at week 48. A significantly higher proportion of patients in the peginterferon beta-1a every 2 weeks group met overall-NEDA criteria compared with the delayed treatment group (36.7% vs 15.8% respectively) (OR 3.09; P< 0.0001). The proportion of patients in the peginterferon beta-1a every two weeks group met overall-NEDA criteria was also significantly higher than in the peginterferon beta-1a every four weeks group (36.7% vs 23.0% respectively) (OR, 1.94; P<0.0001). Secondary: Not reported
Coyle et al.[121] (2017) Teri-PRO Teriflunomide 7 mg or 14 mg once daily	OL, MC, PRO, phase IV Patients were ≥18 years of age and had a diagnosis of RRMS	N=1,000 48 weeks	Primary: Treatment Satisfaction Questionnaire for Medication Secondary: Changes from baseline to Week 48 on the following patient reported outcomes scales: Patient-Determined Disease Steps (PDDS); Multiple Sclerosis Performance Scale (MSPS); Multiple Sclerosis International Quality of Life	Primary: Satisfaction scores ranged from 66.3 to 90.4 across all TSQM domains. For patients who had received a different disease modifying therapy prior to initiation of teriflunomide statistically significant improvement in responses were observed in all domains (P<0.0001). Secondary: The MSPS score remained stable from 12.2 (95% CI, 11.8 to 12.7) at baseline to 11.9 (95% CI, 11.4 to 12.4) at week 48. Mean EDSS and PDDS scores remained stable from baseline to week 48. The MusiQoL total score increased 67.7 (95% CI, 66.7 to 68.6) to 69.2 (95% CI, 68.1 to 70.2) at Week 48 (P=0.0029). The Stern Leisure Scale increased from 7.30 (95% CI 7.16 to 7.44) at baseline to 7.4 (95% CI, 7.24 to 7.56) at Week 48. Most patients remained free from treated relapse over the course of the study. The Kaplan–Meier estimate of proportion of patients

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			(MusiQoL); Stern Leisure Activity Scale; me to first treated relapse, and annualized rate of treated relapse	having a treated relapse at Week 48 was 15.5% (95% CI, 13.2 to 17.9%). The annualized treated relapse rate was low at 0.200 (95% CI, 0.169 to 0.230).
Steinman et al.[122] (2022) ULTIMATE I and ULTIMATE II Ublituximab IV (150 mg on day 1, followed by 450 mg on day 15 and at weeks 24, 48, and 72) and oral placebo vs Oral teriflunomide (14 mg once daily) and IV placebo	DB, DD, MC, RCT Patients 18 to 55 years of age with relapsing multiple sclerosis (meeting 2010 revised McDonald criteria); at least two relapses in the previous 2 years, or one relapse or at least one gadolinium-enhancing lesion or both in the year before screening; brain MRI with abnormalities consistent with multiple sclerosis; a score on the EDSS of 0 to 5.5 at screening (scores range from 0 to 10.0, with higher scores indicating greater disability); and neurologic stability for at least 30 days before	N=549 (I) N=545 (II) 96 weeks	Primary: ARR Secondary: Six hierarchically ordered secondary end points: the total number of gadolinium-enhancing lesions per T1-weighted MRI scan by week 96; the total number of new or enlarging hyperintense lesions per T2-weighted MRI scan by week 96; worsening of disability confirmed at 12 weeks (pooled across the two trials); the number of participants with no evidence of disease activity from week 24 to week 96; the number of participants who had impaired status	Primary: In the ULTIMATE I trial, the ARR was 0.08 with ublituximab and 0.19 with teriflunomide (rate ratio, 0.41; 95% CI, 0.27 to 0.62; P<0.001); in the ULTIMATE II trial, the ARR was 0.09 and 0.18, respectively (rate ratio, 0.51; 95% CI, 0.33 to 0.78; P=0.002). Secondary: The mean number of gadolinium-enhancing lesions was 0.02 in the ublituximab group and 0.49 in the teriflunomide group (rate ratio, 0.03; 95% CI, 0.02 to 0.06; P<0.001) in the ULTIMATE I trial and 0.01 and 0.25, respectively (rate ratio, 0.04; 95% CI, 0.02 to 0.06; P<0.001), in the ULTIMATE II trial. In the pooled analysis of the two trials, 5.2% of the participants in the ublituximab group and 5.9% in the teriflunomide group had worsening of disability at 12 weeks (hazard ratio, 0.84; 95% CI, 0.50 to 1.41; P=0.51). Infusion-related reactions occurred in 47.7% of the participants in the ublituximab group. Serious infections occurred in 5.0% in the ublituximab group and in 2.9% in the teriflunomide group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	screening and the baseline assessment		according to the Symbol Digit Modalities Test; and the percentage change in brain volume from baseline to week 96	
Primary Progressive Multiple Sclerosis				
Montalban et al.[123] ORATORIO trial Ocrelizumab 600 mg IV infusion (given as two 300 mg IV infusions 14 days apart) every 24 weeks vs placebo All patients received IV methylprednisolone 100 mg before infusion. Optional prophylaxis with analgesics or antipyretics and antihistamine was recommended before infusion.	DB, PC, MC, RCT Patients 18 to 55 years of age with a diagnosis of PPMS (according to 2005 revised McDonald criteria), EDSS of 3.0 to 6.5 at screening, Functional System Scale pyramidal functions component score of at least 2, duration of MS <15 years (if EDSS >5.0 at screening) or <10 years (if EDSS ≤5.0 at screening), and a documented history of or the presence at screening of an elevated IgG index or at least one IgG oligoclonal band detected in the CSF	N=732 120 weeks	Primary: Percentage of patients with disability progression confirmed at 12 weeks Secondary: Percentage of patients with progression confirmed at 24 weeks, change in performance on the timed 25-foot walk from baseline to week 120, change in total volume of brain lesions on T2-weighted MRI from baseline to week 120, change in brain volume from week 24 to week 120 and change in the Physical Component Summary score	Primary: The percentage of patients with disability progression confirmed at 12 weeks (defined as an increase in EDSS of at least 1.0 from baseline sustained for at least 12 weeks) was 32.9% with ocrelizumab and with 39.3% with placebo (HR, 0.76; 95% CI, 0.59 to 0.98; P=0.03) representing a RRR of 24%. Secondary: The percentage of patients with disability progression confirmed at 24 weeks was 29.6% with ocrelizumab and 35.7% with placebo (HR, 0.75; 95% CI, 0.58 to 0.98; P=0.04) representing a RRR of 25%. The mean change from baseline to week 120 in performance on the timed 25-foot walk (defined as an increase in time to perform ≥20%) was 38.9% with ocrelizumab and 55.1% with placebo (RR, 29.3%; 95% CI, –1.6 to 51.5; P=0.04), which did not show a statistically significant difference. The adjusted geometric mean percent change in total volume of brain lesions on T2-weighted MRI from baseline to week 120 was -3.37 for ocrelizumab and 7.43 for placebo (HR, 0.90; 95% CI, 0.88 to 0.92; P<0.001). The mean percent change in brain volume from week 24 to week 120 -0.90 for ocrelizumab and -1.09 for placebo (RR, 17.5%; 95% CI, 3.2 to 29.3; P=0.02).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			from the SF-36 version 2 from baseline to week 120, safety	The adjusted mean change in SF-36 Physical Component Summary score from baseline to week 120 was -0.73 for ocrelizumab and -1.11 for placebo (HR, 0.38; 95% CI, -1.05 to 1.80; P=0.60). The percentage of patients who had at least one adverse event was 95.1% with ocrelizumab and 90.0% with placebo. Serious adverse events were reported among 20.4% of those who received ocrelizumab and 22.2% of those who received placebo. Adverse events that led to discontinuation of the trial agent occurred among 4.1% of patients who received ocrelizumab and 3.3% of patients who received placebo. Infusion reaction occurred in 39.9% of patients receiving ocrelizumab compared with 25.5% of patients receiving placebo. Two patients withdrew due to infusions reaction to ocrelizumab. Infusion-related reactions decreased in both rate and severity with subsequent administration; none were fatal or life-threatening. The percentage of patients reporting any infection was 71.4% in the ocrelizumab group and 69.9% in the placebo group. Upper respiratory tract infections were higher in the ocrelizumab group than in the placebo group (10.9% vs. 5.9%). Serious infections were similar in the two groups (6.2% with ocrelizumab and 5.9% with placebo). Neoplasms were reported in 2.3% (11/486) of patients in the ocrelizumab group and in 0.8% (2/239) of patients in the placebo group.
Other				
Comi et al.[124] (2009) PRECISE GA 20 mg SC daily vs placebo	DB, DD, MC, PG, PRO, RCT Patients aged 18 to 45 years of age, with one unifocal neurological event in the previous 90 days, and	N=481 Up to 36 months	Primary: Time to conversion to clinically definite MS Secondary: Number of new T2 lesions detected at last scan, T2 lesion	Primary: There was a 45% reduction in the risk of conversion to clinically definite MS associated with GA compared to placebo (HR, 0.55; 95% CI, 0.40 to 0.77; P=0.0005). In addition, the time for 25% of patients to convert to clinically definite MS was significantly longer with GA compared to placebo (722 vs 336 days; P=0.0041). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	positive brain MRI (defined as at least two cerebral lesions on the T2-weighted images at least 6 mm in diameter)		volume at last scan, percent change in brain volume (atrophy) and proportion of patients converting to clinically definite MS	The new number of new T2 lesions on MRI at the last visit was significantly reduced in patients treated with GA compared to patients randomized to placebo (0.7 vs 1.8; P<0.001). In PH analyses of patients completing two years of treatment without conversion to clinically definite MS, the cumulative number of new T2 lesions was reduced by 43% (RR, 0.57; 95% CI, 0.45 to 0.72; P<0.0001) of the MRI activity during the first year and by 52% (RR, 0.48; 95% CI, 0.3 to 0.61; P<0.0001) during the entire two years with GA compared to placebo. The reduction in the number of new T2 lesions corresponded with a reduction in lesion volume for patients treated with GA compared to patients randomized to placebo (geometric means ratio, 0.75; 95% CI, 0.64 to 0.87; P=0.0002). Fewer patients who were treated with GA experienced a second attack and converted to clinically definite MS compared to patients randomized to placebo (24.7 vs 42.9%; P<0.0001).
Clerico et al.[125] (2008) IFNβ-1b (Betaseron®) 0.25 mg SC every other day vs IFNβ-1a (Rebif®) 22 µg SC weekly vs IFNβ-1a (Avonex®) 30 µg IM once-weekly vs	MA DB, PC, RCTs of patients with clinically isolated syndrome treated with either IFNβ or GA therapy	N=1,160 (3 studies) 2 to 3 years	Primary: The proportion of patients who converted to clinically definite MS Secondary: Side effects/adverse events	Primary: The proportion of patients converting to clinically definite MS was significantly lower in the IFNβ group compared to the placebo-treated group both at one year (OR, 0.53; 95% CI, 0.40 to 0.71; P<0.0001) and two years of follow-up (OR, 0.52; 95% CI, 0.38 to 0.70; P<0.0001). Secondary: Flu-like syndrome and injection site reactions occurred more frequently in patients receiving IFNβ compared to placebo: flu-like syndrome and injection-site reactions (P<0.00001). There was no significant difference in the incidence of serious adverse events between the two groups (P value not reported).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo				
Bell et al.[126] (2007) GA 20 mg SC daily vs IFNβ-1b (Betaseron®) 0.25 mg SC every other day vs IFN-1a (Rebif®) 22 to 44 µg SC three times weekly vs AA IFNβ-1a (Avonex®) 30 µg IM once-weekly vs symptomatic management	CE Patients diagnosed with RRMS in the United States	N=3,151 Up to 10 years	Primary: Incremental cost per QALY gained, cost per year spent in EDSS 0 to 5.5, cost per relapse-free year, cost per life-year gained Secondary: Not reported	Primary: The incremental cost per QALY gained was $258,465, $337,968, $416,301, and $310,691 for GA, IFNβ-1a 30 µg IM, IFNβ-1a 22 to 44 µg SC and IFNβ-1b 0.25 mg, respectively, compared to symptomatic management. The incremental cost per year spent in EDSS 0 to 5.5 was $21,667, $28,293, $41,008, and $27,860 for GA, IFNβ-1a 30 µg IM, IFNβ-1a 22 to 44 µg SC and IFNβ-1b 0.25 mg, respectively, compared to symptomatic management. The incremental cost per relapse-free year was $17,599, $24,327, $32,207, and $23,065 for GA, IFNβ-1a 30 µg IM, IFNβ-1a 22 to 44 µg SC and IFNβ-1b 0.25 mg, respectively, compared to symptomatic management. The incremental cost per life-year gained was $2,076,622, $2,588,087, $3,378,626, and $2,452,616 for GA, IFNβ-1a 30 µg IM, IFNβ-1a 22 to 44 µg SC and IFNβ-1b 0.25 mg, respectively, compared to symptomatic management. Consequently, compared to symptomatic management alone, GA was found to be the most CE immunomodulatory therapy option for MS. Secondary: Not reported
Prosser et al.[127] (2004) GA vs IFNβ-1b (Betaseron®) vs	CE Hypothetical cohorts of patients with non-primary progressive MS	N=not reported 10 years	Primary: Gain in quality-adjusted life expectancy, incremental CE ratios in dollars per QALY gained Secondary: Not reported	Primary: Ten-year therapy with IFNβ-1a was associated with the largest gain in quality-adjusted life expectancy (QALY, 7.955) with an incremental CE ratio of $2,200,000/QALY for women and $1,800,000/QALY for men, compared to no treatment. For five-year treatment duration, no treatment strategy was associated with more quality-adjusted life years compared to alternative treatments. CE ratios were similar across all treatment groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
IFNβ-1a (Avonex®) vs no treatment Details of the clinical studies, including medication doses, used for the CE were not reported.				Secondary: Not reported
Noyes et al.[128] (2011) GA 20 mg SC daily vs IFNβ-1b (Betaseron®) 0.25 mg SC every other day vs IFN-1a (Rebif®) 22 to 44 µg SC three times weekly vs IFNβ-1a (Avonex®) 30 µg IM once-weekly vs symptomatic management	CE Patients diagnosed with RRMS and SPMS in the United States	N=1,121 10-year simulated disease progression cohort	Primary: Net gain in quality-adjusted life expectancy, incremental CE ratios in dollars per QALY gained Secondary: Not reported	Primary: The net gain in QALYs after 10 years of treatment with disease modifying therapy compared to supportive treatment was 0.192, 0.173, 0.082 and 0.126 years for IFNβ-1a 30 µg IM, IFNβ-1b 0.25 mg, IFNβ-1a 22 to 44 µg SC and GA, respectively. The CE of all disease modifying treatments exceeded $900,000/QALY. IM IFNβ-1a 30 µg was associated with the lowest incremental cost per QALY at $901,319. The incremental cost/QALY for IFNβ-1b 0.25 mg and IFNβ-1a 22 to 44 µg SC were similar, costing $1,123,162 and $1,487,306, respectively. Treatment with GA was calculated to cost $2,178,555 per QALY. Investigators reported that disease modifying therapies were associated with reduced costs/QALY and were more likely to become CE when drug costs were reduced and treatment was initiated earlier in the disease. Secondary: Not reported

Drug regimen abbreviations: BID=twice daily, GA=glatiramer acetate, IFNβ=interferon beta, IM=intramuscularly, IV=intravenous, QD=once daily, SC=subcutaneously, TID=three times daily
Study abbreviations: AAR=absolute risk reduction, AB=assessor-blind, AC=active control, CE=cost-effectiveness study, CI=confidence interval, DB=double blind, DD=double dummy, ES=extension study, HR=hazard ratio, I=international, ITT=intention-to-treat, MA=meta-analysis, MC=multi-center, NS=not significant, OL=open-label, OR=odds ratio, OS=observational study, PC=placebo-

controlled, PG=parallel-group, PH=post-hoc analysis, PM=post-marketing, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, RR=relative risk, RRR=relative risk reduction, SB=single-blind, SE=standard error, SR=systematic review, XO=crossover
Miscellaneous abbreviations: ALT=alanine aminotransferase, ARR=annualized relapse rate, ATRS=Adductor Tone Rating Scale, EDSS=expanded disability status scale, GA=glatiramer acetate, GPS=global pain score, IFN=interferon, KFS=Kurtzke functional score, MAS=Modified Ashworth Scale, MRI=magnetic resonance imaging, MS=multiple Sclerosis, MSFC=multiple sclerosis functional composite, MSIS-29=multiple Sclerosis Impact Scale-29, NAb=neutralizing antibody, PBVC=percent brain volume change, PSFS=Penn Spasm Frequency Scale, QALY=quality-adjusted life years, RRMS=relapsing-remitting MS, SPMS=secondary progressive MS, TEAE=treatment emergent adverse event, WBC=white blood cell, 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 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 12. Relative Cost of the Immunomodulatory Agents used to treat Multiple Sclerosis

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Alemtuzumab	injection	Lemtrada®	$$$$$	N/A
Dimethyl fumarate	delayed-release capsule	Tecfidera®*	$$$$$	$$$
Diroximel fumarate	delayed-release capsule	Vumerity DR®	$$$$$	N/A
Fingolimod	capsule, orally disintegrating tablet	Gilenya®*, Tascenso® ODT	$$$$$	$$$$$
Glatiramer acetate	injection	Copaxone®*, Glatopa®†	$$$$$	$$$$$
Interferon β-1a	injection	Avonex®, Avonex Pen®, Rebif®, Rebif Rebidose®	$$$$$	N/A
Interferon β-1b	injection	Betaseron®, Extavia®	$$$$$	N/A
Monomethyl fumarate	delayed-release capsule	Bafiertam DR®	$$$$$	N/A
Natalizumab	injection	Tysabri®	$$$$$	N/A
Ocrelizumab	injection	Ocrevus®	$$$$$	N/A
Ofatumumab	injection	Kesimpta®	$$$$$	N/A
Ozanimod	capsule	Zeposia®	$$$$$	N/A
Peginterferon β-1a	injection	Plegridy®	$$$$$	N/A

Ponesimod	tablet	Ponvory®	$$$$$	N/A
Siponimod	tablet	Mayzent®	$$$$$	N/A
Teriflunomide	tablet	Aubagio®*	$$$$$	$$$$
Ublituximab	injection	Briumvi®	$$$$$	N/A

N/A=Not available
*Generic available in at least one dosage form or strength.
†Glatopa® is a generic equivalent of Copaxone®.

X. Conclusions

Several immunomodulatory agents are Food and Drug Administration (FDA)-approved for the treatment of adult patients with relapsing forms of multiple sclerosis (MS), including both injectable product sand oral products.[1-23] Of note, ocrelizumab (Ocrevus®) is also FDA-approved for the treatment of primary progressive MS.[13]

Current clinical guidelines generally recommend the immunomodulatory agents as first line agents.[26,29-31] All available agents have been shown to decrease MRI lesion activity, prevent relapses, delay disease progression, and ultimately reduce disability from MS.[32-128] The goals of MS therapy include slowing disease progression, reducing relapse rate and preventing or postponing long-term disability. Guidelines from the American Academy of Neurology (AAN) and the MS Coalition recommend patient specific factors guide therapy.[29,31] Specifically, the AAN guideline recommends alemtuzumab, fingolimod, or natalizumab for patients with highly-active RRMS.[29] Guidance from the Association of British Neurologists categorize therapies for relapsing remitting MS into two groups including agents of moderate efficacy (β-interferons, glatiramer acetate, teriflunomide, dimethyl fumarate, and fingolimod) and agents of high efficacy (alemtuzumab and natalizumab). They recommend starting with a moderate efficacy therapy given the improved safety profile.[26] Clinical guidelines do not currently recommend therapy for individuals with PPMS, though it should be noted that at the time the draft guidelines were published, the FDA had not issued a decision on ocrelizumab.[26,29-31] Guidelines have not been updated to incorporate specific recommendations for the newly approved agents. Guidelines recommend the use of alemtuzumab in highly active MS; however, because of its safety profile, the use of alemtuzumab should generally be reserved for patients who have had an inadequate response to two or more drugs indicated for the treatment of MS.[1]

There are head-to-head trials comparing newer immunomodulatory agent to one of the interferons. The TRANSFORM trial compared fingolimod to IFN β-1a 30 mcg IM every week.[48] Fingolimod had significantly lower annualized relapse rate (ARR) (P<0.001), but there were no differences in disability progression. In the TENERE trial, the ARR for teriflunomide 7 mg was significantly higher than that of teriflunomide 14 mg and interferon β-1a 44 mcg three times a week.[111] Despite the higher relapse rates, patients rated teriflunomide better on the Treatment Satisfaction Questionnaire for Medication domains of Global Satisfaction, Convenience, and Side Effects. The OPERA I and II studies demonstrated a statistically significant decrease in ARR with ocrelizumab as compared to interferon β-1a[110] In the CONFIRM trial, there were no significant differences between dimethyl fumarate and glatiramer acetate for ARR, though both were more effective than placebo.[83] There were no significant differences between any of the groups in confirmed disability progression sustained for 12 weeks.

The ORATORIO trial evaluated ocrelizumab compared to placebo for the treatment of primary progressive MS. In this trial ocrelizumab demonstrated a statistically significant reduction in the percentage of patients who experienced confirmed disability progression (P=0.03).[123] Ocrelizumab is the only agent within this class that is FDA-approved for the treatment of primary progressive MS.[13]

The efficacy of Briumvi® (ublituximab) in RMS was demonstrated in two randomized, double-blind, double-dummy, parallel group, active comparator-controlled clinical trials of identical design, ULTIMATE I and ULTIMATE II. Patients were randomized 1:1 to receive ublituximab 450 mg intravenously (IV) every 24 weeks (with initial treatment given as 150 mg IV on day 1 and 450 mg IV on day 14) with oral placebo administered daily, or Aubagio® (teriflunomide) 14 mg given orally daily with IV placebo administered on the same schedule as ublituximab. The primary end point for ULTIMATE I and ULTIMATE II was the annualized relapse rate (ARR). In ULTIMATE I, the ARR at 96 weeks was 0.08 in the ublituximab group and 0.19 in the teriflunomide group (P<0.001). In ULTIMATE II, the ARR at 96 weeks was 0.09 in the ublituximab group and 0.18 in the teriflunomide group (P=0.002). In a pooled analysis of the two trials, 5.2% of the participants in the ublituximab

group and 5.9% in the teriflunomide group had worsening of disability at 12 weeks (P=0.51). Infusion-related reactions occurred in 47.7% of the participants in the ublituximab group. Serious infections occurred in 5.0% in the ublituximab group and in 2.9% in the teriflunomide group.[122]

The most frequently reported adverse events associated with IFNβ therapy are influenza-type symptoms, injection site reactions, headache, nausea, and musculoskeletal pain. Rare cases of hepatic toxicity have occurred in patients who were treated with IFN therapy.[22-23] Therapy with IFNβ should be used cautiously in patients with depression or other mood disorders. Patients receiving glatiramer acetate therapy may experience a transient, self-limiting, post-injection systemic reaction (flushing, chest pain, palpitations, anxiety, dyspnea, throat constriction, and/or urticaria) immediately following drug administration.[6,7] Ocrelizumab may cause infusion reactions and has been associated with an increased risk of infections and malignancies.[13] Similarly, ofatumumab and ublituximab have also been associated with an increased risk of infections as has been observed with other anti-CD20 B-cell depleting therapies.[14,21] Fingolimod has been associated with cardiac-related death and thus requires cardiac monitoring. It is contraindicated in patients with certain pre-existing cardiovascular conditions.[4] There are now four S1P modulators available that have differing affinities to the S1P receptor subtypes. Ponesimod, siponimod and ozanimod bind to S1P-3 with very low affinity, although some binding does still occur and thus potential for cardiac adverse events continue to exist.[22,23] Teriflunomide has boxed warnings regarding hepatotoxicity and its risk of teratogenicity.[20] Dimethyl fumarate appears to have the most mild side effect profile with its most common adverse events being flushing and gastrointestinal effects.[2] There are now multiple fumarate therapies available, and diroximel fumarate has been shown to have less gastrointestinal side effects than dimethyl fumarate.[40] Natalizumab increases the risk of progressive multifocal leukoencephalopathy (PML). When initiating and continuing treatment with natalizumab, physicians should consider whether the expected benefit is sufficient to offset this risk. Natalizumab is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the TOUCH® Prescribing Program because of the risk of PML.[12,24] Because of the risks of autoimmune conditions, stroke, and increased risk of malignancies, alemtuzumab is also available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the LEMTRADA REMS Program.[1] Because of its safety profile, the use of alemtuzumab should generally be reserved for patients who have had an inadequate response to two or more drugs indicated for the treatment of MS.[1]

There is insufficient evidence to support that one brand immunomodulatory agent used to treat multiple sclerosis is safer or more efficacious than another within its given indication, with the exception of safety concerns associated with alemtuzumab use. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process. Because of its safety profile, the use of alemtuzumab should generally be reserved for patients who have had an inadequate response to two or more drugs indicated for the treatment of MS.

Therefore, all brand immunomodulatory agent used to treat multiple sclerosis, with the exception of alemtuzumab, within the class reviewed are comparable to each other and to the generic products in the class (if applicable) within their given indications and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand immunomodulatory agent used to treat multiple sclerosis 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.

Alemtuzumab should not be placed in preferred status regardless of cost.

XII. References

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2. Tecfidera® [package insert]. Cambridge (MA): Biogen Idec Inc.; 2023 Feb.
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4. Gilenya® [package insert]. East Hanover (NJ): Novartis Pharmaceuticals Corporation; 2023 Aug.
5. Tascenso ODT® [package insert]. Cambridge (UK): Cycle Pharmaceuticals Ltd; 2023 Aug.
6. Copaxone® [package insert]. Overland Park (KS): Teva Neuroscience, Inc.; 2023 Jan.
7. Glatopa® [package insert]. Princeton (NJ): Sandoz, Inc.; 2023 Mar.
8. Betaseron® [package insert]. Whippany (NJ): Bayer Healthcare Pharmaceuticals. Inc.; 2023 Jul.
9. Extavia® [package insert]. East Hanover (NJ): Novartis Pharmaceuticals; 2023 Jul.
10. Rebif® [package insert]. Rockland (MA): EMD Serono, Inc; 2023 Jul.
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12. Tysabri® [package insert]. Cambridge (MA): Biogen Idec Inc.; 2023 Apr.
13. Ocrevus® [package insert]. South San Francisco (CA): Genentech Inc.; 2023 Aug.
14. Kesimpta® [package insert]. East Hanover (NJ): Novartis Pharmaceuticals; 2022 Sep.
15. Zeposia® [package insert]. Summit (NJ): Celgene Corporation; 2023 Aug.
16. Plegridy® [package insert]. Cambridge (MA): Biogen Idec Inc.; 2023 Jul.
17. Ponvory® [package insert]. Titusville (NJ): Janssen Pharmaceuticals, Inc.; 2023 Aug.
18. Mayzent® [package insert]. East Hanover (NJ): Novartis Pharmaceuticals Corporation; 2023 Aug.
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I. Overview

Gout is an inflammatory disease that occurs as a response to the presence of monosodium urate crystals in joints, bones, and soft tissues.[1] Clinical manifestations include acute arthritis, chronic arthritis, and tophi.[1] Risk factors include male gender, advanced age, ethnicity, obesity, consumption of alcohol, soda, and fruit juice, diets high in meat, seafood, and high-fructose foods, hypertension, use of a thiazide or loop diuretic, chronic kidney disease, postmenopausal and organ transplant recipient status, and use of certain medications.[1,2] Hyperuricemia, frequently defined as a serum urate level >6.8 mg/dL, is a necessary predisposing factor for gout; however, not all individuals with hyperuricemia will develop gout.[1] Hyperuricemia can be caused by impairment of renal and gut urate excretion and overproduction of urate.[1]

There are multiple guidelines that have been published describing best practices for the treatment of gout. The recommendations for management of this condition include both nonpharmacologic and pharmacologic approaches. Nonpharmacologic management focuses on lifestyle changes, including diet, exercise, and weight loss as appropriate. Pharmacologic therapies focus on urate-lowering strategies for both treatment of acute symptoms and the prevention of attacks and anti-inflammatory drugs used in the setting of acute attacks.[2-4]

The antigout agents are urate-lowering therapies with a variety of indications as it relates to gout and hyperuricemia. Allopurinol is approved by the Food and Drug Administration (FDA) for the management of primary or secondary gout as well as management of calcium oxalate calculi in certain patients, and hyperuricemia in patients receiving chemotherapy.[5,10] Colchicine is FDA-approved for treatment and prophylaxis of gout flares and treatment of familial Mediterranean fever.[6] Probenecid is approved for the treatment of hyperuricemia in gout and as adjuvant therapy with certain antibiotics.[10] Febuxostat, pegloticase, and probenecid-colchicine are only FDA-approved for indications directly related to the treatment of gout.[8-11]

The antigout agents that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. All of these products are currently available in a generic formulation, with the exception of pegloticase. This class was last reviewed in November 2021.

Table 1. Antigout Agents Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Single Entity Agents			
Allopurinol	injection, tablet	Aloprim®*	allopurinol
Colchicine	capsule, oral solution, tablet	Colcrys®*, Gloperba®, Mitigare®*	colchicine tablets
Febuxostat	tablet	Uloric®*	febuxostat
Pegloticase	injection	Krystexxa®	none
Probenecid	tablet*	N/A	probenecid
Combination Products			
Probenecid and colchicine	tablet*	N/A	probenecid and colchicine

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

II. Evidence-Based Medicine and Current Treatment Guidelines

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

Table 2. Treatment Guidelines for Antigout Agents

Clinical Guideline	Recommendation(s)

American College of Rheumatology: **Guidelines for Management of Gout. (2020)**[2]	<u>Indications for pharmacologic urate-lowering therapy</u>
	• Initiating therapy is strongly recommended for gout patients with any of the following:
	  o ≥1 subcutaneous tophi
	  o Evidence of radiographic damage (any modality) attributable to gout
	  o Frequent attacks (≥2 flares per year)
	• Initiating therapy is conditionally recommended for patients who have previously experienced >1 flare but have infrequent flares (<2/year).
	• Initiating therapy is conditionally recommended *against* in patients with gout experiencing their first gout flare.
	  o However, initiating therapy is conditionally recommended for patients with comorbid moderate-to-severe chronic kidney disease (CKD; stage ≥3), serum urate concentration >9 mg/dl, or urolithiasis.
	• Initiating therapy is conditionally recommended *against* in patients with asymptomatic hyperuricemia.
	
	<u>Recommendations for choice of urate-lowering therapy in patients with gout</u>
	• Treatment with allopurinol as the preferred first-line agents is strongly recommended for all patients, including those with moderate-to-severe CKD (stage ≥3).
	• The choice of either allopurinol or febuxostat over probenecid is strongly recommended for patients with moderate-to-severe CKD (stage ≥3).
	• The choice of pegloticase as a first-line therapy is strongly recommended *against*.
	• Starting treatment with low-dose allopurinol (≤100 mg/day and lower in patients with CKD and febuxostat (≤40 mg/day) with subsequent dose titration over starting at a higher dose is strongly recommended.
	• Starting treatment with low-dose probenecid (500 mg once to twice daily) with subsequent dose titration over starting at a higher dose is conditionally recommended.
	• Administering concomitant antiinflammatory prophylaxis therapy (e.g., colchicine, NSAIDs, prednisone/prednisolone) over no antiinflammatory prophylaxis therapy is strongly recommended.
	• Continuing concomitant antiinflammatory prophylaxis therapy for three to six months over <3 months, with ongoing evaluation and continued prophylaxis as needed if the patient continues to experience gout flares, is strongly recommended.
	
	<u>Timing of urate-lowering therapy initiation</u>
	• When the decision is made that urate-lowering therapy is indicated when the patient is experiencing a gout flare, starting therapy during the gout flare over starting after the gout flare has resolved is conditionally recommended.
	• A treat-to-target management strategy that includes urate-lowering therapy dose titration and subsequent dosing guided by serial serum urate measurements to achieve a target serum urate is strongly recommended.
	• Achieving and maintaining a serum urate target of <6 mg/dl is strongly recommended.
	• Delivery of an augmented protocol of urate-lowering therapy dose management by nonphysician providers to optimize the treat-to-target strategy that includes patient education, shared decision-making, and treat-to-target protocol is conditionally recommended for all patients receiving urate-lowering therapy.
	• Continuing urate-lowering therapy indefinitely over stopping therapy is conditionally recommended.
	
	<u>Specific recommendations for the use of allopurinol</u>

Clinical Guideline	Recommendation(s)
	• Testing for the HLA–B*5801 allele prior to starting allopurinol is conditionally recommended for patients of Southeast Asian descent (e.g., Han Chinese, Korean, Thai) and for African American patients, over not testing for the HLA–B*5801 allele. • Universal testing for the HLA–B*5801 allele prior to starting allopurinol is conditionally recommended *against* in patients of other ethnic or racial backgrounds. • The starting dose should be no greater than 100 mg/day. <u>Specific recommendations for the use of febuxostat</u> • Switching to an alternative oral urate-lowering therapy agent, if available and consistent with other recommendations in this guideline, is conditionally recommended for patients taking febuxostat with a history of CVD or a new CVD-related event. <u>Specific recommendations for the use of uricosuric therapy</u> • Checking urinary uric acid is conditionally recommended *against* for patients considered for or receiving uricosuric treatment. • Alkalinizing the urine is conditionally recommended *against* for patients receiving uricosuric treatment. <u>When to consider switching to a new urate-lowering therapy strategy</u> • Switching to a second xanthase oxidase inhibitor over adding a uricosuric agent is conditionally recommended for patients taking their first xanthase oxidase inhibitor, who have persistently high serum urate concentrations (>6 mg/dl) despite maximum-tolerated or FDA-indicated xanthase oxidase inhibitor dose, and who have continued frequent gout flares (>2 flares/year) OR who have nonresolving subcutaneous tophi. • Switching to pegloticase over continuing current urate-lowering therapy is strongly recommended for patients with gout for whom xanthase oxidase inhibitor treatment, uricosurics, and other interventions have failed to achieve the serum urate target, and who continue to have frequent gout flares (≥2 flares/year) OR who have nonresolving subcutaneous tophi. • Switching to pegloticase over continuing current urate-lowering therapy is strongly recommended *against* for patients with gout for whom xanthase oxidase inhibitor treatment, uricosurics, and other interventions have failed to achieve the serum urate target, but who have infrequent gout flares (<2 flares/year) AND no tophi. <u>Gout flare management</u> • Using colchicine, NSAIDs, or glucocorticoids as appropriate first-line therapy for gout flares over IL-1 inhibitors or adrenocorticotropic hormone (ACTH) is strongly recommended for patients experiencing a gout flare. • Given similar efficacy and a lower risk of adverse effects, low-dose colchicine over high-dose colchicine is strongly recommended when colchicine is the chosen agent. • Using topical ice as an adjuvant treatment over no adjuvant treatment is conditionally recommended for patients experiencing a gout flare. • Using an IL-1 inhibitor over no therapy (beyond supportive/analgesic treatment) is conditionally recommended for patients experiencing a gout flare for whom the above antiinflammatory therapies are either ineffective, poorly tolerated, or contraindicated. • Treatment with glucocorticoids (intramuscular, intravenous, or intraarticular) over IL-1 inhibitors or ACTH is strongly recommended for patients who are unable to take oral medications.

Clinical Guideline	Recommendation(s)
British Society for Rheumatology: **Guideline for the Management of Gout (2017)[3]**	Recommendations for management of acute attacks • Patients should be educated to treat attacks as soon as they start. • During attacks the affected joints should be rested, elevated, and kept in a cool environment. • Nonsteroidal antiinflammatory drugs (NSAIDs) at the maximum daily dose or colchicine 0.5 mg once or twice daily is recommended as first-line therapy for the treatment of acute gout attacks. • In acute monoarticular gout attacks, joint aspiration and injection of a corticosteroid are suggested and may be the treatment of choice in patients with acute illness and co-morbidity. • In patients who are unable to tolerate NSAIDs or colchicine and are not candidates for intra-articular injection, a short course of oral corticosteroid or a single injection of an intramuscular corticosteroid is recommended as an alternative. This is also appropriate for oligo- or polyarticular attacks of gout. • Combination therapy is recommended in patients with inadequate response to monotherapy. • Interleukin-1 (IL-1) inhibitors may be considered in patients who have previously not responded adequately to standard treatment of acute gout. Recommendations for optimal use of urate-lowering therapies • Urate-lowering therapies should be discussed with patients following diagnosis and they should be involved in the decision of when to initiate therapy. • Urate-lowering therapy should be offered to all patients with a diagnosis of gout and particularly advised in patients with the following: o Recurring attacks (≥2 attacks in 12 months) o Tophi o Chronic gouty arthritis o Joint damage o Renal impairment o A history of urolithiasis o Diuretic therapy use o Primary gout starting at a young age • It is recommended that initiation of urate-lowering therapy is delayed until inflammation settles because discussion of therapy is better when patients are not in pain. • The aim of urate-lowering therapy is to reach and maintain a target serum urate of at least 300 µmol/L. • A less stringent target of less than 360 µmol/L can be implemented for patients who have had successful treatment for years, when tophi have resolved, and the patient remains free of symptoms. • Allopurinol is recommended as first-line urate-lowering therapy. o It is recommended to start allopurinol therapy at a low dose of 50 to 100 mg daily and then increase the dose in 100 mg increments approximately every four weeks until the serum urate target has been achieved o The suggested maximum dose is 900 mg. o In patients with renal impairment, smaller increments of 50 mg should be used and the maximum dose should be lower, but target urate levels should be the same. • Febuxostat is recommended as an alternative second-line xanthine oxidase inhibitor for patients who cannot tolerated allopurinol or whose renal impairment prevents allopurinol dose escalation sufficient to achieve the therapeutic target. o The recommended starting dose is 80 mg daily and, if necessary, increase to 120 mg after four weeks in order to achieve serum urate target.

Clinical Guideline	Recommendation(s)

	• Uricosuric agents are recommended in patients who are resistant to, or intolerant of, xanthine oxidase inhibitors.
	  o Preferred uricosuric agents:
	  ▪ Sulfinpyrazone (200 to 800 mg/day)
	  ▪ Probenecid (500 to 2,000 mg/day) in patients with normal or mildly impaired renal function
	  ▪ Benzbromarone (50 to 200 mg/day) in patients with mildly to moderately impaired renal function
	• Losartan and fenofibrate are not recommended as a primary urate-lowering therapy but do have some uricosuric effect.
	• In patients who do not achieve serum urate targets with monotherapy, the use of a uricosuric and a xanthine oxidase inhibitor in combination.
	• Colchicine 0.5 mg once or twice daily should be considered as prophylaxis against acute attacks resulting from initiation or up-titration of any urate lowering therapy and continued for up to six months.
	• In patients who cannot tolerate colchicine, a low-dose NSAID or cyclooxygenase 2 (COX-2) inhibitors, with gastroprotection, can be used as an alternative.

European League Against Rheumatism: **Updated EULAR evidence-based recommendations for the management of gout (2016)**[4]	<u>Overarching principles</u>
	• All patients diagnosed with gout should be educated about the disease, effective treatments, associated comorbidities and the principles of managing acute attacks and importance of lowering of serum uric acid level below a target goal.
	• Every patient with gout should receive advice regarding lifestyle including weight loss, avoidance of alcohol and sugar-sweetened drinks, heavy meals and excessive intake of meat and seafood. Low-fat dairy products should be encouraged. Regular exercise should be advised.
	• Every person with gout should be systematically screened for associated comorbidities and cardiovascular risk factors.
	<u>Recommendations for the treatment of gout</u>
	• Treatment of acute flares of gout should be started at the first signs of a flare. The choice of medication should be based on patient specific factors such as contraindications, past experiences, time of treatment initiation, and number of joints affected.
	• The recommended first-line options for acute flare are:
	  o Colchicine at a loading dose of 1 mg followed one hour later by 0.5 mg on day one (within 12 hours of flare onset)
	  o Nonsteroidal antiinflammatory drugs (NSAIDs) (plus a proton pump inhibitor if appropriate)
	  o Oral corticosteroids at 30 to 35 mg/day of equivalent prednisolone for three to five days
	  o Articular aspiration and injection of corticosteroids
	• Colchicine and NSAIDs should be avoided in patients with severe renal impairment.
	• Colchicine should not be given to patients receiving strong P-glycoprotein and/or CYP3A4 inhibitors such as cyclosporin or clarithromycin.
	• In patients with frequent flares and contraindications to colchicine, NSAIDs and corticosteroids (oral and injectable), interleukin-1 (IL-1) blockers should be considered for treating flares.
	• Prophylaxis is recommended during the first six months of urate-lowering therapy. The recommended drug for prophylactic treatment is colchicine, 0.5 to 1 mg/day, with dose reductions in patients with renal impairment. If colchicine is not tolerated or is contraindicated, prophylaxis with NSAIDs at a low dosage, should be considered.
	• Urate-lowering therapy should be considered in all patients diagnosed with gout.
	• Urate-lowering therapy is indicated in patens with recurrent flares (≥2 per year), tophi, urate arthropathy and/or renal stones.

Clinical Guideline	Recommendation(s)
	• Initiation of urate-lowering therapy is recommended close to the time of first diagnosis in patients presenting at a young age (<40 years of age), or with a very high serum uric acid level (>8 mg/dL) and/or comorbidities such as, renal impairment, hypertension, ischemic heart disease, heart failure. • It is recommended to maintain serum uric acid levels at <6 mg/dL. • Urate-lowering therapies should be started at a low dose and titrated up until target serum uric acid levels are achieved. • In patients with normal kidney function, allopurinol is recommended as first-line therapy at a starting dose of 100 mg/day, increased at 100 mg increments every two to four weeks until the serum uric acid target is met. • In patients unable to tolerate allopurinol or who have inadequate response, switching to febuxostat or a uricosuric therapy is recommended. • It is recommended that the maximum dose of allopurinol be adjusted in patients with impaired renal function. If target serum uric acid levels are not reached the patients should be switched to febuxostat or given benzbromarone with or without allopurinol. • Pegloticase is indicated in patients with crystal-proven severe debilitating chronic tophaceous gout and poor quality of life, in whom the serum uric acid target cannot be reached with any other available drug at the maximal dosage (including combinations). • When gout occurs in a patient receiving loop or thiazide diuretics, substitute the diuretic if possible; for hypertension, consider losartan or calcium channel blockers; for hyperlipidemia, consider a statin or fenofibrate.

European League Against Rheumatism: **EULAR recommendations for the management of familial Mediterranean fever (2016)**[12]	<u>Recommendations for the management of familial Mediterranean fever (FMF)</u>
	• The goal of treatment is to obtain control of unprovoked attacks and minimize subclinical inflammation between attacks.
	• It is recommended to initiate treatment with colchicine as soon as the diagnosis of FMF is made.
	• The recommended colchicine starting dose is as follows:
	  ○ For children <5 years of age: 0.5 mg per day
	  ○ For children five to 10 years of age: 0.5 to 1.0 mg per day
	  ○ For adults and children >10 years of age: 1.0 to 1.5 mg per day
	• It is recommended that colchicine be dosed once or twice daily dependent on patient tolerance and compliance.
	• In patient with adverse effects it is recommended to initiate treatment of colchicine at 0.5 mg per day and increase gradually by 0.5 mg in divided daily doses.
	• In patients with persistent attacks or subclinical inflammation the dose of colchicine should be increased by 0.5 mg per day up to a maximum of 2 mg per day in children and 3 mg per day in adults.
	• Compliant patients at the maximum tolerated dose of colchicine for at least six months who do not have adequate response should be considered for treatment with a biologic, such as an interleukin-1 (IL-1) inhibitor.
	• In FMF patients with amyloid A (AA) amyloidosis treatment should be intensified to the maximum tolerated dose of colchicine and supplemented with biologics as required.
	• Temporarily increasing the dose of colchicine during periods of physical or emotional stress can be considered.
	• It is recommended that patients' response, toxicity, and compliance be monitored every six months.
	• In patients with FMF treated with colchicine, liver enzymes should be monitored regularly. If liver enzymes are elevated greater than twofold the upper limit of normal it is recommended that the dose of colchicine be reduced.
	• Patients with decreased renal function should be monitored for signs of colchicine toxicity and the dose should be reduced.

Clinical Guideline	Recommendation(s)

	• It is recommended that the potential risk of toxicity with colchicine be taken seriously and be prevented. The following scenarios may potentially lead to colchicine toxicity:
	  ○ Exceeding the maximum dose
	  ○ Liver or renal failure
	  ○ Concomitant administration of other drugs including macrolides, ketoconazole, ritonavir, verapamil, ciclosporin, statins or other drugs metabolized by cytochrome 3A4
	• During attacks it is recommended that patients continue taking their usual dose of colchicine and use nonsteroidal anti-inflammatory drugs (NSAIDs).
	• It is recommended that colchicine not be discontinued during conception, pregnancy or lactation. Men do not need to stop colchicine during conception except in cases of azoospermia or oligospermia proven to be related to colchicine.
	• FMF patients with chronic arthritis may need additional medication such as disease modifying antirheumatic drugs, intra-articular steroid injections or biologics.
	• In patients with FMF and protracted febrile myalgia, glucocorticoids lead to the resolution of symptoms; NSAID and IL-1 blockade might also be a treatment option. NSAIDs are suggested for the treatment of exertional leg pain.
	• A dose reduction in colchicine may be considered in patients who are stable with no attacks for more than five years.

National Comprehensive Cancer Network: **Supportive Care Tumor Lysis Syndrome (2023)**[13]	Treatment of tumor lysis syndrome (TLS)
	• TLS is best managed if it is anticipated and treatment is initiated prior to starting chemotherapy.
	• The three key elements of treatment are:
	  ○ Vigorous hydration
	  ○ Management of hyperuricemia
	  ○ Frequent monitoring of electrolytes and aggressive correction
	• First-line and at retreatment for hyperuricemia:
	  ○ Glucose-6-phosphate dehydrogenase (G6PD) testing is required prior to use of rasburicase. Rasburicase is contraindicated in patients with a history consistent with G6PD. In these patients, rasburicase should be substituted with allopurinol.
	  ○ Low-risk disease: Allopurinol or febuxostat beginning two to three days prior to chemotherapy and continued for ten to fourteen days.
	  ○ Intermediate-risk disease: Allopurinol or febuxostat OR Rasburicase if renal dysfunction and uric acid, potassium, and/or phosphate >ULN.
	  ○ High-risk disease: Rasburicase.
	  ○ Rasburicase 3 to 6 mg (one dose is usually adequate, redosing should be individualized) is indicated for patients with any of the following:
	  ▪ Urgent need to initiate therapy in a high-bulk patient
	  ▪ Situations where adequate hydration may be difficult or impossible
	  ▪ Acute renal failure
	  ○ If TLS is not treated its progression may lead to acute kidney failure, cardiac arrythmias, seizures, loss of muscle control and death.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the antigout agents are noted in Table 3.

Table 3. FDA-Approved Indications for the Antigout Agents[5-11]

Indications	Single Entity Agents					Combination Products
	Allopurinol	Colchicine	Febuxostat	Pegloticase	Probenecid	Colchicine and Probenecid
Gout/ Hyperuricemia						
Chronic management of hyperuricemia in adult patients with gout who have an inadequate response to a maximally titrated dose of allopurinol, who are intolerant to allopurinol, or for whom treatment with allopurinol is not advisable			✔			
Management of patients with signs and symptoms of primary or secondary gout (acute attacks, tophi, joint destruction, uric acid lithiasis, and/or nephropathy)	✔					
Management of patients with recurrent calcium oxalate calculi whose daily uric acid excretion exceeds 800 mg/day in male patients and 750 mg/day in female patients	✔					
Prophylaxis of gout flares		✔				
Treatment of chronic gout in adult patients refractory to conventional therapy				✔		
Treatment of chronic gouty arthritis when complicated by frequent, recurrent acute attacks of gout						✔
Treatment of gout flares		✔ (tablets only)				
Treatment of hyperuricemia associated with gout and gouty arthritis					✔	
Miscellaneous						
Adjuvant therapy with penicillin or with ampicillin, methicillin, oxacillin, cloxacillin, or nafcillin, for elevation and prolongation of plasma levels by whatever route the antibiotic is given					✔	
Management of patients with leukemia, lymphoma, and malignancies who are receiving cancer therapy which causes elevations of serum and urinary uric acid levels	✔					
Treatment of Familial Mediterranean Fever		✔ (tablets only)				

IV. Pharmacokinetics

The pharmacokinetic parameters of the antigout agents are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Antigout Agents[5-11]

Generic Name(s)	Bioavailability (%)	Time to Peak Concentration (hours)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Single Entity Agents					
Allopurinol	80 to 90 IV: 100	1.5 IV: 0.5	Liver (70)	Feces (20) Renal (80)	1 to 2 IV: 1 to 1.2
Colchicine	45	1 to 2	Liver	Bile (% not reported) Feces (extensive, % not reported) Renal (40 to 65)	26.6 to 31.2
Febuxostat	75 to 85	0.5 to 1.5	Liver (extensive)	Feces (45) Renal (49)	5 to 9.4
Pegloticase	100	18.25	Not reported	Not reported	Not reported
Probenecid	90	1 to 5	Liver (extensive)	Renal (75 to 88)	3 to 17
Combination Products					
Probenecid and colchicine	Probenecid: 90 Colchicine: 45	Probenecid: 1 to 5 Colchicine: 1 to 2	Probenecid: Liver (extensive) Colchicine: Liver	Probenecid: Renal (75 to 88) Colchicine: Bile (% not reported) Feces (extensive, % not reported) Renal (40 to 65)	Probenecid: 3 to 17 Colchicine: 26.6 to 31.2

V. Drug Interactions

Significant drug interactions with the antigout agents are listed in Table 5.

Table 5. Significant Drug Interactions with the Antigout Agents[11]

Generic Name(s)	Interaction	Mechanism
Allopurinol	Azathioprine	Concomitant use of allopurinol and azathioprine may result in azathioprine toxicity. Consider reducing the dose of azathioprine and monitoring closely when coadministered.
Allopurinol	Capecitabine	Concomitant use of allopurinol and capecitabine may result in decreased efficacy of capecitabine. Consider avoiding the use of allopurinol during treatment with capecitabine.
Allopurinol	Captopril	Concomitant use of allopurinol and captopril may result in hypersensitivity reactions. Monitor for hypersensitivity reaction when coadministered.
Allopurinol	Coumarin-derivative anticoagulants	Concomitant use of allopurinol and coumarin-derivative anticoagulants may result in increased INR. Consider this interaction when initiating, adjusting, or discontinuing concomitant use and monitor INR closely.
Allopurinol	Didanosine	Concomitant use of allopurinol with didanosine may result in increased concentration serum concentrations of didanosine. The use of allopurinol with didanosine is contraindicated.
Allopurinol	Enalapril	Concomitant use of allopurinol and enalapril may result in hypersensitivity reactions. Monitor for hypersensitivity reaction when coadministered.
Allopurinol	Mercaptopurine	Concomitant use of allopurinol and mercaptopurine may result in increased mercaptopurine toxicity. Consider reducing the dose of mercaptopurine to one-third to one-fourth of the usual dose. Monitor closely and make subsequent dose adjustments on the basis of response to therapy and presence of toxicities.

Generic Name(s)	Interaction	Mechanism
Allopurinol	Pegloticase	Concomitant use of allopurinol and pegloticase may thereby increase the risk of anaphylaxis and infusion reactions. Consider discontinuing treatment with oral urate-lowering drugs before initiating pegloticase therapy, and do not initiate therapy with urate-lowering agents while patients are on pegloticase therapy.
Allopurinol	Tegafur	Concomitant use of allopurinol and tegafur may result in decreased activation of 5-fluorouracil. Consider avoiding the concomitant use of these agents.
Colchicine	Aprepitant	Concomitant use of colchicine and aprepitant may result in increased colchicine plasma concentrations and increased risk of toxicity. Consider adjusting the dose of colchicine when coadministered with aprepitant and monitor closely for colchicine toxicity.
Colchicine	Atorvastatin	Concomitant use of atorvastatin and colchicine may result in increased colchicine exposure and an increased risk of myopathy or rhabdomyolysis. Use caution with the coadministration of atorvastatin and colchicine and consider monitoring the patient for signs and symptoms of myopathy or rhabdomyolysis.
Colchicine	CYP3A4 inhibitors	Concomitant use of colchicine and CYP3A4 inhibitors may result in increased colchicine plasma concentrations and increased risk of toxicity. Coadministration of colchicine and CYP3A4 inhibitors is contraindicated in patients with renal or hepatic impairment. Consider adjusting the dose of colchicine when coadministered with CYP3A4 inhibitors.
Colchicine	Dual CYP3A4 and P-gp inhibitors	Concomitant use of colchicine and dual CYP3A4 and P-gp inhibitors may result in increased colchicine plasma concentrations and increased risk of toxicity. Coadministration of colchicine and dual CYP3A4 and P-gp inhibitors is contraindicated in patients with renal or hepatic impairment. Consider adjusting the dose of colchicine when coadministered with dual CYP3A4 and P-gp inhibitors.
Colchicine	Fenofibrate	Concomitant use of colchicine and fenofibrate may result in an increased risk of myopathy, including rhabdomyolysis. Use caution with the coadministration of fenofibrate and colchicine and consider monitoring the patient for signs and symptoms of myopathy or rhabdomyolysis.
Colchicine	Fluconazole	Concomitant use of colchicine and fluconazole may result in increased colchicine plasma concentrations and increased risk of toxicity. Consider adjusting the dose of colchicine when coadministered with fluconazole and monitor closely for colchicine toxicity.
Colchicine	Gemfibrozil	Concomitant use of colchicine and gemfibrozil may result in an increased risk of myopathy or rhabdomyolysis. Consider monitoring patients for signs and symptoms of myopathy or rhabdomyolysis when coadministered.
Colchicine	Interferon alfa-2A	Concomitant use of colchicine and interferon alfa-2A may result in decreased interferon alfa-2A effectiveness. Consider avoiding coadministration of these agents.
Colchicine	Itraconazole	Concomitant use of colchicine and itraconazole may result in increased colchicine plasma concentrations and increased risk of toxicity. Coadministration of colchicine and itraconazole is not recommended and should be avoided for up to two weeks after itraconazole discontinuation. Coadministration of colchicine and itraconazole is contraindicated in patients with renal or hepatic impairment. Consider adjusting the dose of colchicine when coadministered with itraconazole and monitor closely for signs and symptoms of increased or prolonged effects.

Generic Name(s)	Interaction	Mechanism
Colchicine	Nilotinib	Concomitant use of colchicine and nilotinib may result in increased colchicine plasma concentrations and increased risk of toxicity. Coadministration of colchicine and nilotinib is contraindicated in patients with renal or hepatic impairment. Consider adjusting the dose of colchicine when coadministered with nilotinib and monitor closely for colchicine toxicity.
Colchicine	P-gp inhibitors	Concomitant use of colchicine and dual CYP3A4 and P-gp inhibitors may result in increased colchicine exposure and potential life-threatening toxicity. Coadministration of colchicine and P-gp inhibitors is contraindicated in patients with renal or hepatic impairment. Consider adjusting the dose of colchicine when coadministered with a P-gp inhibitor.
Colchicine	Reserpine	Concomitant use of colchicine and reserpine may result in increased colchicine concentrations and increased risk of toxicity. Coadministration of colchicine and reserpine in patients with renal or hepatic impairment is contraindicated. Consider adjusting the dose of colchicine when coadministered with reserpine.
Colchicine	Select statins	Concomitant use of colchicine and select statins may result in an increased risk of myopathy or rhabdomyolysis. Consider monitoring for signs and symptoms of myopathy or rhabdomyolysis when coadministered.
Colchicine	Tacrolimus	Concomitant use of colchicine and tacrolimus m ay result in increased colchicine plasma concentrations and increased risk of toxicity. Coadministration of colchicine and tacrolimus is contraindicated in patients with renal or hepatic impairment. Consider adjusting the dose of colchicine when coadministered with tacrolimus.
Colchicine	Venetoclax	Concomitant use of colchicine and venetoclax may result in increases exposure of colchicine. Consider administering colchicine at least six hours before venetoclax when coadministered.
Febuxostat	Azathioprine	Concomitant use of febuxostat and azathioprine may result in increased azathioprine plasma concentrations. Coadministration of azathioprine and febuxostat is contraindicated.
Febuxostat	Mercaptopurine	Concomitant use of febuxostat and azathioprine may result in increased azathioprine plasma concentrations. Coadministration of febuxostat and mercaptopurine is contraindicated.
Pegloticase	Probenecid	Concomitant use of pegloticase and probenecid may result in increased risk of anaphylaxis and infusion reactions. Consider discontinuing treatment with oral urate-lowering drugs before initiating pegloticase therapy, and do not initiate therapy with urate-lowering agents while patients are on pegloticase therapy.
Pegloticase	Sulfinpyrazone	Concomitant use of pegloticase and sulfinpyrazone may result in increased risk of anaphylaxis and infusion reactions. Consider discontinuing treatment with oral urate-lowering drugs before initiating pegloticase therapy, and do not initiate therapy with urate-lowering agents while patients are on pegloticase therapy.
Probenecid	Avibactam	Concomitant use of avibactam and probenecid may result in decreased avibactam elimination and increased exposure. Coadministration of avibactam with probenecid is not recommended.
Probenecid	Baricitinib	Concomitant se of baricitinib and probenecid may result in increased baricitinib exposure. Coadministration of baricitinib with probenecid is not recommended.
Probenecid	Cephalexin	Concomitant use of cephalexin and probenecid may result in increased cephalexin exposure. Coadministration of cephalexin and probenecid is not recommended.

Generic Name(s)	Interaction	Mechanism
Probenecid	Citalopram	Concomitant use of citalopram and probenecid may result in increased citalopram exposure and risk of QT interval prolongation. Do not exceed citalopram doses of >20 mg/day when coadministered with probenecid.
Probenecid	Deferiprone	Concomitant use of deferiprone and probenecid may result in reduced deferiprone clearance and increased deferiprone plasma concentrations. When coadministered monitor patients for adverse reactions and consider downward deferiprone dose titrations or interruption of therapy if needed.
Probenecid	Doripenem	Concomitant use of probenecid and doripenem may result in increased plasma concentrations of doripenem. Coadministration of doripenem with probenecid is not recommended.
Probenecid	Indomethacin	Concomitant use of indomethacin and probenecid may result in increased indomethacin plasma concentration. Consider adjusting the dose of indomethacin.
Probenecid	Ketorolac	Concomitant use of probenecid and ketorolac may result in increased ketorolac plasma concentrations and toxicity. Coadministration of these agents is contraindicated.
Probenecid	Methotrexate	Concomitant use of probenecid and methotrexate may result in methotrexate toxicity. Consider monitoring methotrexate serum levels and potentially reducing the dose of methotrexate when coadministered.
Probenecid	Naproxen	Concomitant use of naproxen and probenecid may result in increased naproxen exposure. Consider a dose adjustment of naproxen if coadministered with probenecid.
Probenecid	Zalcitabine	Concomitant use of probenecid and zalcitabine may result in an increased risk of zalcitabine toxicity. Consider reducing the dose of zalcitabine and monitoring for adverse effects of zalcitabine.

CYP3A4=cytochrome P450 3A4, INR=international normalized ratio, P-gp=P-glycoprotein

VI. Adverse Drug Events

The most common adverse drug events reported with the antigout agents are listed in Table 6.

Table 6. Adverse Drug Events (%) Reported with the Antigout Agents[5-11]

Adverse Event(s)	Single Entity Agents					Combination Products
	Allopurinol	Colchicine	Febuxostat	Pegloticase	Probenecid	Colchicine and Probenecid
Cardiovascular						
Cardiorespiratory arrest	<1*					
Chest pain				6		
Congestive heart failure				✔		
Death			✔			
Heart failure	<1*					
Myocardial infarction			✔			
Necrotizing angiitis	<1					
Septic shock	<1*					
Vasculitis	<1					
Ventricular fibrillation	<1†					
Dermatologic						
Alopecia		✔			✔	✔
Dermatitis					✔	✔
Ecchymosis	<1			11		
Eczematoid dermatitis	<1					
Exfoliative dermatitis	<1					

Adverse Event(s)	Single Entity Agents					Combination Products
	Allopurinol	Colchicine	Febuxostat	Pegloticase	Probenecid	Colchicine and Probenecid
Cardiovascular						
Cardiorespiratory arrest	<1*					
Chest pain				6		
Congestive heart failure				✔		
Death			✔			
Heart failure	<1*					
Myocardial infarction			✔			
Necrotizing angiitis	<1					
Septic shock	<1*					
Vasculitis	<1					
Ventricular fibrillation	<1†					
Flushing					✔	✔
Lichen planus	<1					
Maculopapular rash	✔	✔				
Onycholysis	<1					
Purpura	<1	✔				✔
Rash	3	✔	0.5 to 16.			
Stevens-Johnson syndrome	<1		✔		✔	
Toxic epidermal necrolysis	<1		✔			
Vesicular bullous dermatitis	<1					
Gastrointestinal						
Abdominal cramping		✔				
Abdominal pain	<1	✔				✔
Alkaline phosphate increase	✔					
Anorexia					✔	✔
Constipation				6		
Diarrhea	✔	23 to 77	<1			✔
Dyspepsia	✔					
Gastritis	<1					
Lactose intolerance		✔				
Nausea	✔	4 to 17	1.1 to 1.3	12	✔	✔
Sore gums					✔	✔
Vomiting	1.2*	17		5	✔	✔
Genitourinary						
Costovertebral pain					✔	✔
Renal colic					✔	✔
Uric acid stones with or without hematuria					✔	✔
Urinary frequency					✔	✔
Hematologic						
Agranulocytosis	✔	✔				✔
Anemia					✔	✔
Aplastic anemia	✔	✔			✔	✔
Disseminated intravascular coagulation	<1*					
Elevated eosinophil count	✔					
Glucose-6-phosphate dehydrogenase deficiency anemia				✔	✔	✔
Granulocytopenia		✔				
Leukocytosis	✔					
Leukopenia	✔	✔			✔	✔
Pancytopenia		✔				
Myelosuppression	✔	✔				
Neutropenia					✔	

Adverse Event(s)	Single Entity Agents					Combination Products
	Allopurinol	Colchicine	Febuxostat	Pegloticase	Probenecid	Colchicine and Probenecid
Cardiovascular						
Cardiorespiratory arrest	<1*					
Chest pain				6		
Congestive heart failure				✔		
Death			✔			
Heart failure	<1*					
Myocardial infarction			✔			
Necrotizing angiitis	<1					
Septic shock	<1*					
Vasculitis	<1					
Ventricular fibrillation	<1†					
Thrombocytopenia	0.6	✔			✔	
Hepatic						
Abnormal liver function			4.4 to 6.6			
Cholestatic jaundice	<1					
Elevated liver enzymes	✔	✔	✔			
Granulomatous hepatitis	<1					
Hepatic necrosis	<1				✔	✔
Hepatotoxicity	✔					
Hyperbilirubinemia	<1					
Immunologic						
Anaphylaxis				4.8 to 6.5	✔	✔
Antibody development				92		
Fever	<1				✔	✔
Hypersensitivity reactions	✔				✔	✔
Pruritis	<1				✔	✔
Urticaria	<1				✔	✔
Metabolic						
Acute attacks of gout	✔	4	✔	41 to 81		
Precipitation of acute gouty arthritis					✔	✔
Musculoskeletal						
Arthralgia	<1		0.7 to 1.1			
Elevated CPK		✔				
Muscle pain		✔				
Muscle weakness		✔				✔
Myopathy	<1	✔				
Myositis			✔			
Myotonia		✔				
Rhabdomyolysis		✔	✔			
Neurologic						
Cerebrovascular accident	<1*		✔			
Dizziness			✔		✔	✔
Fatigue		1 to 4				
Headache	<1	1 to 2			✔	✔
Neuritis	✔					
Paresthesia	✔					
Peripheral neuritis		✔				✔
Peripheral neuropathy	<1					
Seizure	<1*					
Sensory motor neuropathy		✔				
Somnolence	<1					
Taste loss/perversion	<1					
Renal						
Nephrotic syndrome					✔	✔
Renal failure	1.2					
Uremia	<1					

Adverse Event(s)	Single Entity Agents					Combination Products
	Allopurinol	Colchicine	Febuxostat	Pegloticase	Probenecid	Colchicine and Probenecid
Cardiovascular						
Cardiorespiratory arrest	<1*					
Chest pain				6		
Congestive heart failure				✔		
Death			✔			
Heart failure	<1*					
Myocardial infarction			✔			
Necrotizing angiitis	<1					
Septic shock	<1*					
Vasculitis	<1					
Ventricular fibrillation	<1†					
Reproductive						
Azoospermia		✔				
Oligospermia		✔				
Respiratory						
Acute respiratory distress syndrome	<1*					
Epistaxis	✔					
Nasopharyngitis				7		
Pharyngolaryngeal pain		3				
Respiratory failure	<1*					
Miscellaneous						
Infusion reaction				26		

* Intravenous only.
✔ Percent not specified.

Table 7. Boxed Warning for Febuxostat[8]

WARNING
WARNING: CARDIOVASCULAR DEATH • Gout patients with established cardiovascular (CV) disease treated with febuxostat had a higher rate of CV death compared to those treated with allopurinol in a CV outcomes study. • Consider the risks and benefits of febuxostat when deciding to prescribe or continue patients on febuxostat. Febuxostat should only be used in patients who have an inadequate response to a maximally titrated dose of allopurinol, who are intolerant to allopurinol, or for whom treatment with allopurinol is not advisable.

Table 8. Boxed Warning for Pegloticase[9]

WARNING
WARNING: ANAPHYLAXIS AND INFUSION REACTIONS; G6PD DEFICIENCY ASSOCIATED HEMOLYSIS AND METHEMOGLOBINEMIA • Anaphylaxis and infusion reactions have been reported to occur during and after administration of pegloticase. • Anaphylaxis may occur with any infusion, including a first infusion, and generally manifests within 2 hours of the infusion. However, delayed-type hypersensitivity reactions have also been reported. • Pegloticase should be administered in healthcare settings and by healthcare providers prepared to manage anaphylaxis and infusion reactions. • Patients should be pre-medicated with antihistamines and corticosteroids. • Patients should be closely monitored for an appropriate period of time for anaphylaxis after administration of pegloticase. • Monitor serum uric acid levels prior to infusions and consider discontinuing treatment if levels increase to above 6 mg/dL, particularly when 2 consecutive levels above 6 mg/dL are observed.

- Screen patients at risk for G6PD deficiency prior to starting pegloticase. Hemolysis and methemoglobinemia have been reported with pegloticase in patients with G6PD deficiency. Do not administer pegloticase to patients with G6PD deficiency.

VII. Dosing and Administration

The usual dosing regimens for the antigout agents are listed in Table 7.

Table 9. Usual Dosing Regimens for the Antigout Agents[5-11]

Generic Name (Trade Name)	Adult Dose	Pediatric Dose	Availability
Single Entity Agents			
Allopurinol	Management of patients with signs and symptoms of primary or secondary gout: Tablet: initial, 100 mg/day as a single or divided dose with increases at weekly intervals by 100 mg until serum uric acid <6 mg/dL; maintenance, mild gout: 200 to 300 mg/day as a single or divided dose; maintenance, moderate-severe gout: 400 to 600 mg/day as a single or divided dose; maximum, 800 mg/day Management of patients with leukemia, lymphoma and malignancies who are receiving cancer therapy which causes elevations of serum and urinary uric acid levels: Tablet: 600 to 800 mg/day as a divided dose (BID to TID) for two to three days IV: 200 to 400 mg/m^2/day IV as a single infusion or in equally divided doses at 6, 8, or 12-hour intervals; dosage is dependent on severity of disease; maximum 600 mg/day. Whenever possible, initiate 24 to 48 hours prior to initiation of chemotherapy. Management of patients with recurrent calcium oxalate calculi: Tablet: 200 to 300 mg/day as a single or divided dose (BID to TID)	Management of patients with leukemia, lymphoma and malignancies who are receiving cancer therapy which causes elevations of serum and urinary uric acid levels (children <6 years of age): Tablet: 150 mg/day Management of patients with leukemia, lymphoma and malignancies who are receiving cancer therapy which causes elevations of serum and urinary uric acid levels (children six to 10 years of age): Tablet: 300 mg/day IV: Starting dose, 200 mg/m^2/day IV as a single infusion or in equally divided doses at 6, 8, or 12-hour intervals; dosage is dependent on severity of disease. Whenever possible, initiate 24 to 48 hours prior to initiation of chemotherapy.	Tablet: 100 mg 300 mg Injection: 500 mg intravenous powder for solution
Colchicine	Prophylaxis of gout flares: Tablet, oral solution, capsule: 0.6 mg QD to 0.6 mg BID; maximum, 0.6 mg BID Treatment of gout flares: Tablet: 1.2 mg at the first sign of flare followed by 0.6 mg one hour later	Treatment of Familial Mediterranean Fever (children four to six years of age): Tablet: 0.3 to 1.8 mg/day as a single or divided dose (BID); maximum, 1.8 mg/day	Capsule: 0.6 mg Oral solution: 0.6 mg/5 mL Tablet: 0.6 mg

Generic Name (Trade Name)	Adult Dose	Pediatric Dose	Availability
	Treatment of Familial Mediterranean Fever: Tablet: 1.2 to 2.4 mg/day as a single or divided dose (BID); maximum, 2.4 mg/day	Treatment of Familial Mediterranean Fever (children six to 12 years of age): Tablet: 0.9 to 1.8 mg/day as a single or divided dose (BID); maximum, 1.8 mg/day Treatment of Familial Mediterranean Fever (adolescents >12 years of age): Tablet: 1.2 to 2.4 mg/day as a single or divided dose (BID); maximum, 2.4 mg/day Prophylaxis of gout flares (adolescents >16 years of age): Tablet: 0.6 mg QD to 0.6 mg BID; maximum, 0.6 mg BID	
Febuxostat	Chronic management of hyperuricemia in adult patients with gout who have an inadequate response to a maximally titrated dose of allopurinol, who are intolerant to allopurinol, or for whom treatment with allopurinol is not advisable: Tablet: initial, 40 mg QD; maintenance, 40 to 80 mg QD; maximum, 80 mg QD	Safety and efficacy in children have not been established.	Tablet: 40 mg 80 mg
Pegloticase	Treatment of chronic gout in adult patients refractory to conventional therapy: IV: 8 mg given as an intravenous infusion over no less than 120 minutes every two weeks.	Safety and efficacy in children have not been established.	Injection: 8 mg/1 mL, 2 mL vial
Probenecid	Treatment of hyperuricemia associated with gout and gouty arthritis: Tablet: initial, 250 mg BID for one week; maintenance, 500 mg BID; maximum, 2 g/day Adjuvant therapy for elevation and prolongation of plasma levels by whatever route the antibiotic is given: Tablet: 500 mg QID	Adjuvant therapy for elevation and prolongation of plasma levels by whatever route the antibiotic is given (children two to 14 years of age): Tablet: initial, 25 mg/kg/dose or 0.7 g/m^2/dose as a single dose; maintenance, 40 mg/kg/day or 1.2 g/m^2/day in four divided doses; maximum, 500 mg/single dose	Tablet: 500 mg
Combination Products			
Colchicine-Probenecid	Treatment of chronic gouty arthritis when complicated by frequent, recurrent acute attacks of gout: Tablet: initial, 0.5 mg-0.5 g QD for one week; maintenance, 0.5 mg-0.5 g BID	Safety and efficacy in children have not been established.	Tablet: 0.5 mg-0.5 g

Abbreviations: BID=twice daily, IV=intravenously, QD=once daily, QID=four times daily, TID=three times daily

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the antigout agents are summarized in Table 8.

Table 8. Comparative Clinical Trials with the Antigout Agents

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Familial Mediterranean Fever				
Goldstein et al.[14] (1974) Colchicine 0.6 mg TID vs placebo	DB, PC, RCT, XO Patients with FMF and at least 1 attack/month for ≥1 year without amyloidosis or concurrent disease with no chronic steroid or narcotic use and no evidence of pregnancy	N=15 6 months (XO was done after 90 days of treatment and patients were reexamined at 30-day intervals)	Primary: Patient reported record of attacks Secondary: Not reported	Primary: In the colchicine treatment group eight patients experienced no attacks and two patients had a reduction in frequency from 10 and five attacks to two and three attacks respectively. In the placebo group nine patients reported a total of 59 attacks. One patient did not have an attack during either treatment arm. Overall, 80% of patients did not have attacks while being treated with colchicine compared to 10% of patients while treated with placebo. The decrease in attacks during colchicine therapy compared to placebo was statistically significant (P<0.002). Secondary: Not reported
Polat et al.[15] (2016) FAVOR Colchicine 1 mg QD vs colchicine 0.5 mg BID	MC, non-inferiority, PG, RCT Pediatric patients, 5 to 16 years of age, who weighed between 15 to 30 kg, were newly diagnosed with FMF, who were confirmed by genetic analysis to have compound heterozygous or homozygous mutations and were treatment naive.	N=90 24 weeks	Primary: Efficacy in control of disease symptoms, reduction in disease severity assessed using the modified Mor scoring system, and laboratory findings indicative of inflammation, such as erythrocyte sedimentation rate, C-reactive protein, and serum amyloid A Secondary:	Primary: After colchicine treatment, a significant decrease was observed in both the once daily and twice daily administration groups for clinical findings frequently seen in patients with FMF, such as fever (>38 °C), abdominal pain, arthralgia (P≤0.001 for all findings in the once-daily dosage group, P≤0.001 for the twice-daily dosage group), arthritis (P<0.001 for the once-daily dosage group, P=0.003 for the twice daily dosage group), and chest pain (P<0.001 for the once-daily dosage group, P=0.002 for the twice-daily dosage group). Other clinical findings manifesting during the disease course, such as malaise, confinement to bed during attacks, and headache also decreased significantly after colchicine treatment started (P<0.05 for all findings). Disease severity according to the Mor scoring system decreased from 3.48 at baseline to 2.81 at 24 weeks (P<0.001) in the once daily dosing group and from 3.27 at baseline to 2.76 at 24 weeks (P<0.001) in the twice daily group.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			Safety and tolerability	Erythrocyte sedimentation rate levels decreased from 55.9 to 4.2 (P<0.001) for the once-daily dosage group and from 22.2 to 0 (P=0.042) for the twice-daily dosage group. C-reactive protein decreased from 40.5 to 14.3 (P=0.010) for the once-daily dosage group and decreased from 37.8 to 10.8 (P=0.00) for the twice-daily dosage group. Serum amyloid A levels decreased from 4.86 to 3.28 (P=0.004) in the once-daily dosage group and from 4.70 to 3.28 (P=0.022) in the twice-daily dosage group. Secondary: Anorexia was significantly more frequent in both the once-daily (P=0.006) and twice-daily (P=0.018) dosage groups after treatment. There was no statistically significant difference observed between the groups regarding changes in the number of patients with diarrhea before and after treatment (P=0.403). No significant difference between the once- and twice-daily dosage groups was observed for changes between visits in ALT levels (P=0.838) or AST levels (P=0.573).
Wright et al.[16] (1977) Colchicine 0.6 mg vs placebo Separate courses of both colchicine and placebo were supplied to the patient. The order of therapy was determined by a randomized scheme.	DB, PC, RCT, XO Patients with a history of FMF attacks that were characterized by acute short lived episodes of peritonitis or pleuritis and usually with fever	N=9 10 months	Primary: Patient reported number of attacks aborted with colchicine Secondary: Time interval between attacks, safety	Primary: Five patients completed their treatment assignments and colchicine was effective in aborting the attacks of three patients and was ineffective in two patients. The remaining four patients could not be assessed due to the insufficient number of courses. During the 10 months of the trial, 28 courses of colchicine and 31 courses of placebo were taken during the early stages of FMF attacks. Of the colchicine courses 21 (75%) were followed by attacks that were considered to have been aborted compared to only three (10%) courses with placebo (P value not reported). Secondary: No significant differences were seen in the time interval between attacks after colchicine treatment was compared to placebo. The mean interval between attacks after colchicine treatment was 15.1±1.8 days compared to 20.1±5.0 days in the placebo group (P value not reported). Two patients experienced diarrhea early in the trial and their treatment was reduced. Further adverse events attributed to colchicine did not occur.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Each course consisted of 10 total tablets; six tablets on day 1 and 2 tablets on each of the following 2 days. Patients were told to begin medication at the earliest suspicion that an attack was about to occur.				
Treatment of Gout Flares				
Ahern et al.[17] (1987) Colchicine 1 mg followed by 0.5 mg every 2 hours until complete response or toxicity vs placebo	PC, RCT Patients with joint aspiration proven acute gout	N=45 Patients were assessed every 6 hours for 48 hours	Primary: Percentage of joints with a 50% decrease in baseline pain and clinical score measures Secondary: Safety	Primary: The percentage of joints with a 50% decrease in baseline pain score was 23, 41, 73, and 73% in the colchicine group compared to 9, 9, 32, and 36% in the placebo group for 12, 24, 36 and 48 hours after starting treatment respectively. The difference between the two groups was statistically significant at the 36-hour (P<0.05) and 48-hour (P<0.05) marks. The percentage of joints with a 50% decrease in baseline clinical score were 5, 23, 50, and 64% in the colchicine group compared to 0, 0, 5, and 23% in the placebo group for 12, 24, 36 and 48 hours after starting treatment respectively. The difference between the two groups was statistically significant only at the 36-hour (P<0.01) and 48-hour (P<0.05) marks. Secondary: Diarrhea and/or vomiting occurred in all patients taking colchicine at a median time of 24 hours and at a median total dose of 6.7 mg. Five patients developed nausea while on the placebo (P values not reported).
Terkeltaub et al.[18] (2010) (AGREE)	DB, MC, PC, PG RCT	N=575 24 hours	Primary: The proportion of patients in the high	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Colchicine 1.2 mg followed by 0.6 mg every hour for 6 hours (High-dose) vs colchicine 1.2 mg followed by 0.6 mg in 1 hour followed by placebo doses every hour for 5 hours (Low-dose) vs placebo	Male and postmenopausal female patients ≥18 years of age with a confirmed gout diagnosis who had ≥2 gout flares within the prior 12 months		dose group compared to placebo group who responded to treatment (defined as a having a pretreatment pain score within 12 hours of flare onset and a ≥50% reduction in pain within 24 hours without rescue medication Secondary: The proportion of patients in the low dose group compared to the placebo group who responded (defined above) to treatment, proportion of patients who required rescue medication, safety	In the ITT population (N=184), 32.7% of patients in the high-dose group were responders compared to 15.5% in the placebo group. The difference between these two groups was statistically significant (P=0.034). Secondary: In the ITT population (N=184), 37.8% of patients in the low-dose group were responders compared to 15.5% in the placebo group. The difference between these two groups was statistically significant (P=0.005). In the placebo group 50% of patients required rescue medication within the first 24 hours compared to 34.6% in the high-dose group and 31.1% in the low dose group. The difference between the high-dose group and the placebo group was not statistically significant (P=0.103). The difference between the low-dose group and the placebo group was statistically significant (P=0.027). There were no deaths, serious adverse events, or patient withdrawals due to adverse events. All adverse events in the low-dose group were mild to moderate in intensity, while 19.2% of the high dose group had severe adverse events, all of which were diarrhea. The overall rate for adverse events was 76.9, 36.5, and 27.1% in the high-dose, low-dose and placebo groups respectively. The most common adverse event was diarrhea which occurred in 76.9, 23.0% and 13.6% of patients in the high-dose, low-dose and placebo groups respectively. The difference was statistically significant between the high-dose and low-dose groups (OR, 11.2; 95% CI, 4.8 to 25.9) and the high-dose and placebo groups (OR, 21.3; 95% CI, 7.9 to 56.9). The difference was not statistically significant between the low-dose and placebo groups (OR, 1.9; 95% CI, 0.8 to 25.9) (P values not reported). Nausea occurred in 17.3, 4.1 and 5.1% of patients in the high-dose, low dose and placebo groups respectively. The difference was statistically significant between the high-dose and low-dose groups only (OR, 5.0; 95% CI, 1.3 to 19.3) (P values not reported). Vomiting occurred in 17.3% of patients in the high-dose group compared to 0% in both the low dose and placebo groups; P values not reported.
Prophylaxis of Gout Flares				
Borstad et al.[19] (2004)	DB, PC, PRO, RCT	N=43	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Allopurinol 100 mg QD and colchicine 0.6 mg BID vs allopurinol 100 mg QD and placebo Dose of allopurinol was increased in 100 mg increments until a sUA level <6.5 mg/dL. In the setting of renal insufficiency the dose was escalated in 50 mg increments.	Patients with crystal-proven gouty arthritis who met the criteria for allopurinol administration which was presence of tophi, sUA overproduction, frequent gout attacks (≥3 attacks/year), elevated sUA in the setting of chronic renal insufficiency and nephrolithiasis	6 months	Number of acute gout flares Secondary: Change in sUA level at three months from baseline, number of acute gout flares over time, number of multiple acute gout flares, severity of multiple acute gout flares, average length of acute gout flares, safety	There were a total of 77 acute gout flares. There were 12 flares in the allopurinol and colchicine group and 65 acute gout flares in the allopurinol and placebo group. Acute gout flares occurred in 33% of the allopurinol and colchicine patients compared to 77% of the allopurinol and placebo patients. The difference between the two groups was statistically significant (P=0.008). Secondary: The average baseline sUA level was 9.49 and 9.15 mg/dL in the allopurinol and colchicine group and allopurinol and placebo group respectively. At three months, the average sUA level was 6.35 mg/dL in the allopurinol and colchicine group and 6.21 mg/dL in the allopurinol and placebo group. In patients who experienced acute gout flares the baseline sUA level was 9.15 mg/dL in both groups. The three month average was 6.07 mg/dL in the allopurinol and colchicine group and 6.13 mg/dL in the allopurinol and placebo group. There was no significant difference in the change of sUA levels from baseline to three months in all patients (P=0.552) or for only those patients who had an acute gout flare (P=0.648). Compared to the allopurinol and placebo group, patients in the allopurinol and colchicine group had significantly fewer acute gout flares from zero to three months (P=0.022), from three to six months (P=0.033) and overall (P=0.008). Multiple gout flares occurred in 14% of patients in the allopurinol and colchicine group and in 63% of patients in the allopurinol and placebo group. The difference between the groups was statistically significant (P=0.004). Severity of acute gout flares as measured subjectively by VAS averaged 3.64 in the allopurinol and colchicine group and 5.08 in the allopurinol and placebo group. The difference between the groups was statistically significant (P=0.018).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				The average length of acute gout flares was six days in the allopurinol and colchicine group and 5.56 days in the allopurinol and placebo group. The difference between the groups was not statistically significant (P=0.566). Similar study withdrawal rates were reported in both groups. The allopurinol and colchicine group had a significantly higher rate of diarrhea; however this was never a reason for study withdrawal and responded when the dose was decreased (P values not reported).
Mackenzie et al.[20] (2020) FAST Allopurinol vs febuxostat	Blinded-endpoint, NO, PRO, RCT Patients 60 years or older with gout, already receiving allopurinol, and had at least one additional cardiovascular risk factor	N=6,128 Median follow-up time was 1467 days	Primary: Composite of hospitalization for non-fatal myocardial infarction or biomarker-positive acute coronary syndrome; non-fatal stroke; or cardiovascular death Secondary: Components of the composite outcome	Primary: For incidence of the primary endpoint, on-treatment, febuxostat (172 patients [1.72 events per 100 patient-years]) was non-inferior to allopurinol (241 patients [2.05 events per 100 patient-years]; adjusted HR 0.85; 95% CI, 0.70 to 1.03; P<0.0001). Secondary: In the febuxostat group, 222 (7.2%) of 3063 patients died and 1720 (57.3%) of 3001 in the safety analysis set had at least one serious adverse event (with 23 events in 19 [0.6%] patients related to treatment). In the allopurinol group, 263 (8.6%) of 3065 patients died and 1812 (59.4%) of 3050 had one or more serious adverse events (with five events in five [0.2%] patients related to treatment). Randomized therapy was discontinued in 973 (32.4%) patients in the febuxostat group and 503 (16.5%) patients in the allopurinol group.
Paulus et al.[21] (1974) Colchicine-probenecid 0.5-500 mg TID vs probenecid-placebo 500 mg TID	DB, MC, PC, PG, RCT Male patients with confirmed gout	N=52 6 months	Primary: Gout attack rate Secondary: Gout attack rate in patients with sUA levels <6.5 mg/dL, safety	Primary: The data from 38 members was analyzed. In the colchicine/probenecid group there were a total of 23 acute attacks during a combined 109 months of therapy. In the probenecid/placebo group there were a total of 35 acute attacks during a combined 94 months of therapy. For the colchicine/ probenecid group the rate of attacks per month per patient were 0.19±0.05 compared to 0.48±0.12 attacks per month per patient in the probenecid/placebo group. The difference between the two groups was statistically significant (P<0.05). Secondary: For patients with sUA levels <6.5 mg/dL in the colchicine/probenecid group the rate of attacks per month per patient were 0.13±0.06 compared

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
In the event of an acute gout attack patients were instructed to take additional colchicine, indomethacin or phenylbutazone until the attack subsided.				to 0.49±0.13 attacks per month per patient in the probenecid/placebo group. The difference between the two groups was statistically significant (P<0.05). Adverse events were reported by 15 of the 20 patients in the colchicine/ probenecid group compared to eight of the 18 patients in the probenecid/placebo group. The difference between these two groups was not statistically significant (P>0.05). In the colchicine/probenecid group adverse events included, diarrhea in nine patients, vomiting or anorexia in 11 patients and steadily increasing AST/ALT in one patient. In the probenecid/placebo group, diarrhea was reported in six patients, and nausea, vomiting or anorexia in five patients (P values not reported).
Wortman et al.[22] (2010) Febuxostat 40 mg QD vs febuxostat 80 mg QD vs febuxostat 120 mg QD vs febuxostat 240 mg QD	Post hoc analysis of FACT, APEX and CONFIRMS Adults 18 to 85 years of age with hyperuricemia (sUA level ≥8 mg/dL) and gout, as defined by preliminary criteria of the American College of Rheumatology	N=4,101 FACT: N=760 52 weeks APEX: N=1,072 28 weeks CONFIRMS: N=2,269 24 weeks	Primary: Proportion of patients who required treatment for gout flares, flares rates based on sUA levels <6 mg/dL or ≥6 mg/dL Secondary: Rate of discontinuation of study medication due to gout flares, safety of prophylaxis agents colchicine and naproxen	Primary: In the FACT and APEX trials where prophylaxis was administered for eight weeks the flare rates increased sharply (up to 40%) at the end of gout prophylaxis and then declined gradually. In comparison those patients in the CONFIRMS trial who were treated with six months of prophylaxis had a consistently low rate of gout flares (3 to 5%) at the end of six months of prophylaxis (P values not reported). In the FACT study, patients with a mean post baseline sUA levels <6 mg/dL, had flare rates during the first four weeks, weeks four to eight, eight to 12, and 12 to 16 that were 16, 16, 36, and 28% respectively. In patients with sUA levels ≥6 mg/dL the flare rates during the first four weeks, weeks four to eight, eight to 12, and 12 to 16 were 18, 13, 37, and 27% respectively. However, by the final four weeks the mean rate of gout flares in patients with a mean post baseline sUA level <6 mg/dL was 6% compared to 14% in the patients with a mean post baseline sUA level ≥6. This difference was statistically significant (P<0.05). In the APEX study, during the first 12 weeks of treatment patients with a mean post baseline sUA level <6 mg/dL had numerically higher gout flare

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vs febuxostat 30 mg QD vs allopurinol 300 mg QD vs allopurinol 100 or 300 mg QD (dose depended on renal function) vs allopurinol 300 mg QD (for patients with normal renal function or mild renal impairment; CrCl 60 to 89 mL/minute) or 200 mg QD (for patients with moderate renal impairment; CrCl 30 to 59 mL/minute) vs				rates compared to those with a mean sUA level ≥6 mg/dL (P value not reported). However, this pattern was reversed after weeks 12 and 16 and by the end of the study patients with a mean post baseline sUA level <6 mg/dL had a 13% rate of gout flares compared to a 10% rate of gout flares for patients whose mean post baseline sUA level ≥6 mg/dL, (P value not reported). In the CONFIRMS study patients with a mean post baseline sUA level <6 mg/dL had consistently lower flare rates beginning with 10% during the first four weeks of the study and declined steadily to 3% during the last four weeks. In patients with a mean post baseline sUA level ≥6 mg/dL flare rates during the first four weeks were 11% and they declined to 5% by weeks 24 to 48 (P values not reported). Secondary: In the studies that utilized only eight weeks of prophylaxis 18.7 and 9.3% of patients discontinued the trials prematurely due to gout flares compared to 2.9% of patients in the study that utilized six months of prophylaxis (P values not reported). Pooled rates of overall adverse events in the FACT and APEX study were significantly higher in the patient population that was prophylaxed with colchicine (55.1%) compared to those prophylaxed with naproxen (44.3%). The difference between these two groups was statistically significant (P<0.001). However, in the CONFIRMS study the rate of adverse events was not significantly different between the colchicine (55.1%) and naproxen (54.9%) groups (P value not reported).

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placebo Gout flare prophylaxis was provided with naproxen 250 mg BID or colchicine 0.6 mg QD for first 8 weeks in the FACT and APEX studies and for entire 6 months of the CONFIRMS study.				
Yamanaka et al.[23] (2018) Febuxostat dosed using a stepwise dose increase from 10 to 40 mg/day vs febuxostat 40 mg/day plus colchicine 0.5 mg/day vs febuxostat 40 mg/day	MC, OL, PRO, RCT Males ≥20 years of age with gout who had at least one episode of gouty arthritis within one year before study entry, serum urate >7.0 mg/dL (416.39 µmol/L) and who had not received treatment with any urate-lowering drugs for at least one month prior to entry	N=255 24 weeks total (12-week treatment period followed by 12-week observation period)	Primary: Incidence rate of gouty arthritis during the treatment period Secondary: Number of gout flares per patient during the treatment period, the number of gout flares per patient during the observation period, and the percentage of patients with serum urate ≤6.0 mg/dL in the observation period	Primary: The percent of patients who experienced gouty arthritis during the treatment period was 20.8% of the patients who received stepwise dosing of febuxostat, 18.9% of the patients receiving febuxostat plus colchicine and 36.0% of the patients receiving febuxostat. The overall Pearson $\chi 2$ test determined that for stepwise dosing of febuxostat compared to febuxostat P=0.054. Secondary: During the treatment period, a total of 27 flares were identified in 20 patients (1.35 flares/patient) in the patients who received stepwise dosing of febuxostat, 24 flares in 18 patients (1.33 flares/patient) in the patients receiving febuxostat plus colchicine, and 37 flares in 18 patients (2.06 flares/patient) in the patients receiving febuxostat. The differences between groups were not statistically significant. During the observation period, there were 18 flares in 15 patients (1.20 flares/patient) in the patients who received stepwise dosing of febuxostat, 26 flares in 17 patients (1.53 flares/patient) in the patients receiving febuxostat plus colchicine and eight flares in six patients (1.33 flares/patient) the patients receiving febuxostat. The differences between groups were not statistically significant.

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				A significantly lower percentage of patients reached the target level of serum urate at four weeks (P<0.001) and eight weeks (P<0.001) in the group who received stepwise dosing of febuxostat, compared with the groups who received febuxostat plus colchicine or febuxostat. There was no significant difference among the three treatment groups after 12 weeks.
Sundy et al.[24] (2011) Pegloticase 8 mg every two weeks vs pegloticase 8 mg every four weeks vs placebo All patients also received an oral antihistamine, intravenous corticosteroids, and acetaminophen as prophylaxis for infusion reactions and NSAIDS or colchicine or both as prophylaxis for gout flares beginning at least one week before	DB, PC, RCT Adult patients with symptomatic gout with either ≥ 3 gout flares in the previous 18 months or the presence of ≥ 1 gout tophus or gouty arthritis, with a self-reported contraindication to allopurinol or a medical history of failure to normalize uric acid with at least three months of allopurinol treatment	N=108 6 months	Primary: Proportion of patients who achieved PUA < 6 mg/dL for ≥ 80% of the time during month 3 and month 6 Secondary: Tophus resolution, gout flares, number of tender joints from baseline to final visit, number of swollen joints from baseline to final visit, safety	Primary: In the pegloticase 8 mg every two weeks group, 38% of patients achieved PUA < 6 mg/dL for ≥ 80% of the time during month three and month six (95% CI, 23 to 53; P<0.001). In the pegloticase 8 mg every four weeks group, 49% of patients achieved PUA < 6 mg/dL for ≥ 80% of the time during month three and month six (95% CI, 34 to 64; P<0.001). In the placebo group 0% of patients were able to meet the primary endpoint. Secondary: In the pegloticase 8 mg every two weeks group, 50% of patients achieved complete tophus resolution by month-6 (P=0.040). In the pegloticase 8 mg every four weeks group, 21% of patients achieved complete tophus resolution by month six (P=1.000). In the placebo group 14% of achieved complete tophus resolution. In the pegloticase 8 mg every two weeks group there was a 78.6% incidence of gout flares from months one to three which decreased to 53.1% from months four to six. For months four to six the results were not statistically significant when compared to placebo (P=0.595). In the pegloticase 8 mg every four weeks group there was an 86.0% incidence of gout flares from months one to three which decreased to 52.8% from months four to six. For months four to six the results were not statistically significant when compared to placebo (P=0.599). In the placebo group there was a 47.8% incidence of gout flares from months one to three which increased to 60.9% from months four to six. In the pegloticase 8 mg every two weeks group there was a mean change of -6.2 in the number of tender joints from baseline to final (P=0.220) compared to a mean change of -6.3 in the pegloticase 8 mg every four weeks group (P=0.195). The placebo group had a mean change of -2.9.

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pegloticase treatment				In the pegloticase 8 mg every two weeks group there was a mean change of -5.2 in the number of swollen joints from baseline to final visit (P=0.594) compared to a mean change of -4.7 in the pegloticase 8 mg every four weeks group (P=0.735). The placebo group had a mean change of -4.1. Safety results were pooled for both of the randomized controlled studies. Anaphylaxis occurred in 6.5% of patients in the pegloticase 8 mg every two weeks group and 4.8% in the pegloticase 8 mg every four weeks group compared to 0% in the placebo group. Infusion reactions occurred in 26% of patients in the pegloticase 8 mg every two weeks group, 41% in the pegloticase 8 mg every four weeks group, and 5% of the placebo group. The percentage of patients with any gout flare during the first three months of treatment were 74%, 81% and 51% for pegloticase 8 mg every two weeks, pegloticase 8 mg every four weeks and placebo respectively. The percentage of patients with any gout flare during the subsequent three months of treatment were 41%, 57% and 67% for pegloticase 8 mg every two weeks, pegloticase 8 mg every four weeks and placebo respectively. Also the following AEs occurred in >5% of patients treated with pegloticase: nausea (12% compared to 2% in the placebo group), contusions (11% compared to 5% in the placebo group), nasopharyngitis (7% compared to 2% in the placebo group), constipation (6% compared to 5% in the placebo group), chest pain (6%0 compared to 2% in the placebo group) and vomiting (5% compared to 2% in the placebo group. There were also two cases of CHF exacerbation reported in the pegloticase 8 mg every two weeks group (P values not reported).
Hyperuricemia Due to Chemotherapy				
Goldman et al.[25] (2001) Rasburicase 0.20mg/kg IV QD for 5 to 7 days vs	AC, MC, OL, RCT Pediatric oncology patients with Murphy stage III or IV NHL, or ALL with a peripheral WBC count ≥25,000 µL at presentation or	N=52 14 days (study duration included 5 to 7 days of treatment and a final safety analysis of day 14)	Primary: sUA AUC from the start of the study drug until 96 hours (AUC_{0-96}) Secondary: Percent reduction sUA at four hours after first dose of	Primary: The mean AUC_{0-96} was 128±70 mg/dL (hour) in the rasburicase group compared to 329±129 mg/dL (hour) in the allopurinol group. The difference between the two groups was statistically significant (P<0.0001). Secondary: In the rasburicase group there was an 86% reduction in sUA levels four hours after the first dose compared to only 12% in the allopurinol

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
allopurinol 300 mg/m^2 or 10 mg/kg every 8 hours for 5 to 7 days	any childhood lymphoma or leukemia with a sUA ≥8 mg/dL at the time of study entry; patients must have been scheduled to receive chemotherapy that was not investigational; patients were required to have a minimum life expectancy of 4 weeks and an ECOG score ≤3 or a Karnofsky scale ≥30%		therapy, number of patients who were hyperuricemic at baseline and achieved an sUA level <8 mg/dL, safety	treatment group. The difference between the two groups was statistically significant (P<0.0001). Patients who were hyperuricemic at baseline and were treated with rasburicase all achieved a sUA <8 mg/dL in less than four hours compared to no patients in the allopurinol group (P values not reported). Therapy was discontinued for one patient in the rasburicase group because of hemolysis. No patients experienced anaphylactic events due to rasburicase. There were also no patients with detectable amount of antibodies to rasburicase. Frequent adverse events were common among the study patients including fever, pain and mucositis secondary to their disease and chemotherapy agents. Two patients receiving allopurinol therapy died during the study period. One patient died of pseudomonal sepsis and the other due to an intracerebral hemorrhage (P values note reported).
Cortes et al.[26] (2010) Rasburicase 0.20 mg/kg/day IV on days 1 to 5 vs rasburicase 0.20 mg/kg/day IV on days 1 to 3	AC, MC, OL, PG, RCT Patients ≥18 years of age, with an ECOG score of 0 to 3, life expectancy >3 months, active leukemia/ lymphoma, and at	N=280 1 week	Primary: Rate of plasma uric acid response defined as the percentage of patients achieving or maintaining a plasma uric acid ≤7.5 mg/dL from days three to seven Secondary:	Primary: Plasma uric acid response rates were 87% (95% CI, 80 to 94) in the rasburicase only group, 78% (95% CI, 70% to 87%) in the rasburicase and allopurinol group, and 66% (95% CI, 56 to 76) in the allopurinol only group. The difference between the rasburicase only group and allopurinol only group was statistically significant (P=0.001). The difference between the allopurinol only group and the rasburicase and allopurinol group was not statistically significant (P=0.06). Secondary: In the high TLS risk subpopulation, plasma uric acid response rates were 89% in the rasburicase only group, 79% in the rasburicase and allopurinol

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followed by allopurinol 300 mg QD on day 3 to 5 vs allopurinol 300 mg QD on days 1 to 5 Cytoreductive chemotherapy was initiated within 4 to 24 hours after the first dose of antihyperuricemic treatment.	a high or potential risk for TLS		Plasma uric acid response rates in patients at high risk of TLS or hyperuricemia at baseline, plasma uric acid AUC from day one to seven, time to plasma uric acid control in patients with baseline hyperuricemia, safety	group, and 68% in the allopurinol only group. The difference between the rasburicase only group and allopurinol only group was statistically significant (P=0.001). The difference between the allopurinol only group and the rasburicase and allopurinol group was not statistically significant (P=0.1). In the subpopulation with baseline hyperuricemia, plasma uric acid response rates were 90% in the rasburicase only group, 77% in the rasburicase and allopurinol group, and 53% in the allopurinol only group. The difference between the rasburicase only group and allopurinol only group was statistically significant (P=0.015). The difference between the allopurinol only group and the rasburicase and allopurinol group was not statistically significant (P=0.2). Plasma uric acid AUC from day one to seven was significantly lower in the rasburicase only group and the rasburicase and allopurinol group when compared to the allopurinol only group (P<0.001 for both groups). Median time to plasma uric acid control in patients with baseline hyperuricemia was four hours in the rasburicase only group, and in the rasburicase and allopurinol group and 27 hours in the allopurinol only group (P values not reported). Drug related adverse events were reported in 4% of the rasburicase only group, 5% in the rasburicase and allopurinol group, and 1% in the allopurinol only group. There were no drug-related life-threatening events or deaths. Eight patients discontinued the study due to drug induced adverse event. One patient in the rasburicase only group discontinued therapy because of hyperbilirubinemia and neutropenic sepsis. Five patients in the rasburicase and allopurinol group discontinued due to tachycardia, pulmonary hemorrhage, rasburicase-related hypersensitivity reaction, respiratory failure, and confusional state. Two patients in the allopurinol only group discontinued because of TLS. The most common adverse events across all treatment arms were thrombocytopenia, neutropenia, anemia, pyrexia, peripheral edema, nausea, vomiting and diarrhea. The most common serious adverse events were neutropenia infection (4 to 9%), febrile neutropenia (3 to 6%) and neutropenic sepsis

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				(1 to 5%). Potential hypersensitivity events were reported in 4% of patients in the rasburicase only group and in 1% of patients in the rasburicase and allopurinol group (P values not reported).
Management of Recurrent Calcium Oxalate Calculi				
Kohri et al.[27] (1990) Allopurinol 100 mg TID and trichlormethiazide 2 mg every morning vs allopurinol 100 mg TID	RCT Male patients with idiopathy calcium oxalate or calcium phosphate urinary stones with no history of primary hyper-parathyroidism, renal tubular acidosis or urinary obstruction	N=87 3 to 26 years	Primary: Number of stones formed before, during and after discontinuation of therapy Secondary: Urine composition before, during and after discontinuation of therapy	Primary: The number of new stones formed per year per patient before, during and after discontinuation of allopurinol and trichlormethiazide was 1.18, 0.24 and 0.13. In the allopurinol only group the number of new stones formed was 1.32, 0.20 and 0.09. Within each treatment group, the difference in stone formation before and during treatment (P<0.001) and during treatment and after treatment (P<0.05) were statistically significant. However, the differences between the two groups were not found to be statistically significant (P values not reported). Secondary: In the allopurinol and trichlormethiazide group there was a statistically significant decrease in calcium levels at 12 months (P<0.001), 36 months (P<0.01) and after treatment (P<0.05). There was also a significant decrease in sUA levels at 12 months (P<0.001), 36 months (P<0.001) and after treatment (P<0.05). There was a decrease in citrate levels at 12 months (P<0.01) and 36 months (P<0.05). There was a decrease in oxalate levels at 12 months (P<0.05) and 36 months (P<0.05). In the allopurinol and trichlormethiazide group there was a statistically significant decrease in calcium levels only at 12 months of treatment (P<0.05). There was also a significant decrease in uric acid levels at 12 months of treatment (P<0.001) and 36 months (P<0.001).
Pearle et al.[28] (1999) Thiazides (8 trials), allopurinol (4 trials), magnesium (2 trials), alkali citrate (3 trials), phosphate (3 trials)	MA (14 RCT) Patients with recurrent calcium oxalate nephrolithiasis	N=939 1 to 4 years	Primary: Reduction in stone recurrence rates expressed as stones/patient/ year, formal MA, analysis of individual treatment groups Secondary: Not reported	Primary: Out of the 14 studies, 13 reported sufficient data to express outcomes as stones/patient/year. The analysis of these studies indicated a statistically significant reduction in stone recurrence rates with drug therapy compared to no treatment or placebo (P=0.04). A formal MA could be performed on 11 of the trials. Overall, a risk difference of -22.6% (95% CI, -29 to -16.3; P<0.001) was reported when combining these 11 trials. Among the thiazide studies the risk reduction for active treatment groups compared to no treatment or placebo was 21.3% (95% CI, -29.2 to -13.4; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs no treatment or placebo				Analysis of the eight thiazide trials indicated a statistically significant reduction in mean recurrence rates with treatment compared to no treatment or placebo (P=0.02). The four allopurinol trials did not demonstrate a statistically significant advantage of allopurinol compared to no treatment or placebo (P=0.74). The phospate and magnesium trials failed to show a statistically significant difference between active treatment and no treatment or placebo (P values not reported). The alkali citrate trials could not be compared statistically. Secondary: Not reported
Hyperuricemia				
Stamp et al.[29] (2017) Allopurinol with monthly dose increases until serum urate <6 mg/dL vs allopurinol at original dose	OL, PG, RCT Patients with gout receiving at least CrCl-based dose of allopurinol for at least one month with serum urate ≥6 mg/dL at screening	N=183 12 months	Primary: Absolute reduction in serum urate at 12 months Secondary: Proportion of participants reaching and maintaining target serum urate levels, percentage reduction in serum urate at 12 months, proportion of individuals with any gout flare in the first and last months of randomized treatment and in three monthly intervals, functional status and pain changes from baseline to	Primary: The mean change in serum urate at 12 months was -0.34 mg/dL in the control group and -1.5 mg/dL in the dose escalation group (P<0.001) (mean difference, 1.2 mg/dL; 95% CI, 0.67 to 1.5; P<0.001). Secondary: Serum urate was <6 mg/dL at the final visit in 32% of the control group and 69% in the dose escalation group (OR, 4.3; 95% CI, 2.4 to 7.9; P<0.001). The mean percentage change in serum urate from baseline to 12 months was -3.3% in the control group compared with -17.8% in the dose escalation group (mean difference, 14.5%; 95% CI, 8.4 to 20.6%; P<0.001). During the study period, 59% of the control group and 54% of the dose escalation group experienced at least one self-reported gout flare (P=0.58). By the end of the study period there had been a reduction in use of prophylaxis in both groups. There was no significant difference in the mean change in index tophus size over the study period between randomized groups.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			month 12 visit, and index tophus size change from baseline	There was no significant difference in the mean change from baseline to 12 months between randomized groups in functional status or pain.
Stamp et al.[30] (2017) Allopurinol control to dose escalation vs allopurinol dose escalation to dose escalation	ES, OL, RCT Patients with gout who completed the first 12 months of clinical trial continued in the open label extension study. At study entry participants were required to have a serum urate >6 mg/dL at baseline despite CrCl-adjusted dose of allopurinol.	N=183 24 months total (12 months for extension study alone)	Primary: Mean change in serum urate from month 12 to 24, mean change in serum urate from baseline to months 24, and mean serum urate Secondary: Proportion of patients with serum urate <6 mg/dL, percentage reduction in serum urate from baseline to month 24 and from months 12 to 24, proportion of individuals with any gout flare in the first and last months of randomized treatment and in the month prior to each three month visit, functional status changes from baseline to month 24 and from month 12 to 24, index tophi size change from baseline to 24 months and months 12 to 24, and	Primary: The mean change in serum urate from month 12 to 24 was -1.1 mg/dL in the control to dose escalation group and 0.1 mg/dL in the dose escalation to dose escalation group (P<0.001) (mean difference, 1.3 mg/dL; 95% CI, 0.8 to 1.7; P<0.001). The mean change in serum urate from baseline to 24 months was -1.4 mg/dL in the control to dose escalation group and -1.7 (0.1) mg/dL in the dose escalation to dose escalation group (P=0.14) (mean difference, -0.3 mg/dL; 95% CI, -0.7 to 0.1; P=0.14). The mean serum urate was 7.13 mg/dL at baseline and 5.7 mg/dL at final visit in the control to dose escalation group, and 7.18 mg/dL and 5.4 mg/dL in the dose escalation to dose escalation group. Secondary: Serum urate was <6 mg/dL at the final visit in 69.1% of the control to dose escalation group and 79.7% in the dose escalation to dose escalation group (OR, 1.8; 95% CI, 0.8 to 3.8; P=0.16). The mean percentage change in serum urate from month 12 to 24 was -13.6% in the control to dose escalation group compared with 3.4% in dose escalation to dose escalation group (mean difference, 17.0%; 95% CI, 9.8% to 24.1%; P<0.001). The mean percentage change in serum urate from baseline to month 24 was -16.0% in the control to dose escalation group compared with -21.9% in the dose escalation to dose escalation group (mean difference, -5.9%; 95% CI, -12.9 to 1.2%; P=0.10). There was a significant reduction in the percentage of participants having a gout flare in the month prior to month 12 and month 24 in both groups compared with the month prior to baseline (P<0.001), but no difference between randomized groups (P=0.29).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			changes in use of prophylactic medication from baseline to month 24 and from month 12 to 24.	There was a significant reduction in the percentage of individuals having gout flares between baseline and month 24 in both groups (P<0.001). There was no difference in the flare reduction between groups (P=0.78). There was a significant reduction in the percentage of individuals using prophylaxis between months 12 and 24 in both groups (P<0.03), but no significant difference between randomized groups (P=0.84). There was a significant reduction in the use of prophylaxis over the 24-month period in both groups (P<0.001) but no significant difference between randomized groups (P=0.71). Of those with a tophus at baseline, 16.2% of the control to dose escalation group and 12.9% of the dose escalation to dose escalation group had complete resolution of all tophi between months 12 and 24 (P=0.75). Between baseline and month 24, of those with measurable tophi, 28.9% of the control to dose escalation group and 28.9% of the dose escalation to dose escalation group had complete resolution of all tophi (P=1.0). In the entire group, there was a significant decline in the mean tophus size over the 24 months (13.1±1.0 mm baseline vs 6.6±1.2mm month 24; P<0.001). There was no difference in the change in tophus size between randomized groups (P=0.27). There was no significant difference in the mean change from month 12 to month 24 or from baseline to month 24 between randomized groups for Health Assessment Questionnaire, pain visual analogue scale, swollen joint count or tender joint count.
White et al.[31] (2018) Allopurinol 300 mg QD increased by 100 mg monthly (if CrCl ≥60 mL/min) or 200 mg QD increased by 100	DB, MC, non-inferiority, RCT Patients with a diagnosis of gout and a history of major cardiovascular disease before randomization with	N= 6,190 Varied 32 months (median)	Primary: First occurrence of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or urgent revascularization for unstable angina Secondary:	Primary: A primary endpoint event occurred at similar rates in the allopurinol and febuxostat groups with 10.4% and 10.8% of patients having an event respectively. (HR, 1.03; upper bound of 98.5% CI, 1.23; P=0.002). Secondary: The HRs for nonfatal secondary end points were not statistically significant. However, the risk of death from any cause and the risk of cardiovascular death were higher in the febuxostat group than in the allopurinol group.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
mg monthly (CrCl between 60 to 30). vs febuxostat 40 mg QD (increased to 80 mg QD if ineffective)	a serum urate level of at least 7.0 mg per deciliter or at least 6.0 mg per deciliter with inadequately controlled gout, after a one to three-week washout period from previous gout therapies.		Composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke as well as the individual components of the primary endpoint	The rate of cardiovascular death was higher in the febuxostat group than in the allopurinol group (HR, 1.49; 95% CI, 1.01 to 2.22).
Scott et al.[32] (1966) Allopurinol 300 mg QD vs probenecid 1 g QD increased to 2 g QD after 2 weeks of treatment Allopurinol dose was increased when necessary. Patients were instructed to take colchicine 0.5 mg BID or TID during treatment with either drug to prophylax	PRO Male patients with primary and uncomplicated gout with or without some degree of renal function impairment who had not received any uricosuric therapy in the past 6 months	N=37 24 months	Primary: Frequency of acute gout attacks Secondary: Presence of tophi, sUA, laboratory values from blood sample, liver function testing, radiologic change, safety	Primary: Of the 20 patients receiving allopurinol, nine had no further acute gout attacks since starting treatment, six had only one further gout attack between one and nine months after starting treatment, four had two further attacks between two and 15 months after starting treatment and one continued to have attacks for the first six months after starting treatment. Of the 17 patients treated with probenecid, eight had no further gout attacks after starting treatment, six had one further attack occurring between two weeks and 15 months after starting treatment, two had two attacks between two weeks and 17 months after starting treatment, and one had three further attacks occurring between three and five months after starting treatment. In both groups approximately 50% of the patients had no further gout attacks after starting treatment and in the remaining patients' attacks became less frequent (P values not reported). Secondary: In two of the three patients who had tophi development, treatment with allopurinol led to tophi disappearance. The same result occurred in one of the two patients with tophi in the probenecid treatment group (P values not reported). Baseline sUA levels were 9.3 mg/dL in the allopurinol group and 8.5 mg/dL in the probenecid group. After two weeks of treatment these values had fallen to 5.8 mg/dL in the allopurinol group and 6.3 mg/dL in the probenecid group. At the last point of estimation sUA levels were 4.7

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
against acute gout flares. In those who became free of symptoms colchicine was withdrawn several months after the last attack of gout.				mg/dL in the allopurinol group and 5.2 mg/dL in the probenecid group (P values not reported). No significant change was observed in either treatment group with regard to blood urea, hemoglobin, packed cell volume, white cell count, reticulocyte count, or serum iron (P values not reported). Serum alkaline phosphatase was reported to be slightly increased in 15 of the allopurinol treated patients and slightly decreased in one of the allopurinol treated patients. In the probenecid group five patients showed a slight decrease. Serum albumin and globulin were normal in all patients in both groups. Serum glutamic oxaloacetic transaminase was normal in all patients except for one in each group. Serum glutamic pyruvic transaminase was raised in four patients in the allopurinol group and in one patient from the probenecid group (P values not reported). Patients had joint radiographs before and during treatment. However due to the short period of follow up radiological changes were only reported in two patients treated with allopurinol that showed healing of bony lesions (P values not reported). No serious adverse events were reported in either group. In the allopurinol group two patients developed skin rashes, one patient developed mild spontaneous bruising, one patient complained of persistent dyspepsia and one patient had mild leukoplakia-like lesions of the gums. In the probenecid group one patient reported difficulty swallowing, two patients reported flatulence and one patient reported pruritis (P values not reported).
Becker et al.[33] (2005) (FACT) Febuxostat 80 mg QD vs	AC, DB, MC, PG, RCT Adults with hyperuricemia (sUA level ≥8 mg/dL) and gout as defined by preliminary criteria	N=762 52 weeks (follow-up visits occurred at 2 weeks, 4 weeks, and monthly thereafter)	Primary: Proportion of patients with sUA levels <6 mg/dL at each of the last three-monthly visits Secondary:	Primary: A sUA level <6 mg/dL at each of the last three-monthly measurements was achieved by 53, 62 and 21% of the patients in the febuxostat 80 mg, 120 mg and allopurinol groups respectively. The difference between the febuxostat and allopurinol groups was statistically significant (P<0.001 for each febuxostat group). Secondary:

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febuxostat 120 mg QD vs allopurinol 300 mg QD Due to an increased risk of acute gouty attacks associated with the initiation of urate lowering therapy, all patients received naproxen 250 mg BID or colchicine 0.6 mg QD during the washout period (2 weeks) as well as the first 8-weeks after the initiation of the study drug.	of the American College of Rheumatology		The proportion of patients with sUA levels <6 mg/dL at each visit, the percent reduction in sUA levels from baseline at final visit, the proportion of patients requiring treatment for acute gout flares from weeks nine through 52, reduction in tophus area or the total number of tophi in patients with tophi at baseline, safety	The proportion of patients with sUA levels <6 mg/dL was significantly higher in the groups receiving febuxostat than in the allopurinol group at each visit (P<0.001). The mean percent reduction from baseline in sUA levels at the final visit was -44.73, -51.52 and -32.99% in the febuxostat 80 mg, 120 mg and allopurinol groups respectively. The difference between the febuxostat 80 and 120 mg groups was statistically significant (P<0.001) as was the difference between both febuxostat groups compared to the allopurinol group (P<0.001). During weeks nine through 52, the proportion of patients requiring treatment of an acute gouty flare was 64, 70 and 64%in the febuxostat 80 mg, 120 mg, and allopurinol groups respectively (P value not reported). During the eight-week prophylaxis period, a significantly greater proportion of patients in the febuxostat 120 mg group required treatment for gout flares than those patients in the febuxostat 80 mg or allopurinol group (P<0.001 for both comparisons). At study end, the median percent reduction in tophus area was 83, 66 and 50% in the febuxostat 80 mg, 120 mg and allopurinol groups respectively. The difference between groups was not statistically significant (P value not reported). There were no statistically significant differences among the groups in the reduction of the number of tophi from baseline (P values not reported). There was no significant difference in the incidence of treatment-related adverse events between groups. The most commonly reported adverse events were abnormal liver function test results, diarrhea, headaches, joint-related and musculoskeletal symptoms. Most adverse events were mild or moderate in severity. The discontinuation rate was significantly greater in the febuxostat 120 mg group compared to the febuxostat 80 mg and the allopurinol groups (P=0.003) but was similar between the febuxostat 80 mg and allopurinol groups (P value not reported).
Schumacher et al.[34]	AC, DB, MC, PC, PG, RCT	N=1,072	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
(2008) APEX Febuxostat 80 mg QD vs febuxostat 120 mg QD vs febuxostat 240 mg QD vs allopurinol 100 or 300 mg QD (dose depended on renal function) vs placebo Gout flare prophylaxis was provided with naproxen 250 mg BID or colchicine 0.6 mg QD, during the washout period (2 weeks) as well as the first 8 weeks	Adults 18 to 85 years of age with hyperuricemia (sUA level ≥8 mg/dL) and gout, as defined by preliminary criteria of the American College of Rheumatology; patients were required to have normal (SCr ≤1.5 mg/dL) or impaired (SCr >1.5 to ≤2.0 mg/dL) renal function	28 weeks (follow-up visits occurred every 4 weeks)	Proportion of patients with sUA levels <6 mg/dL at each of the last three clinic visits Secondary: Proportion of patients with sUA levels <6 mg/dL at week-28, percent reduction of sUA levels from baseline, proportion of patients requiring treatment for a gout flare after completing the eight-week prophylaxis period (weeks eight to 28), reduction in the total number of tophi in patients with palpable tophi at baseline, percent reduction in primary tophus size in patients with palpable tophi at baseline, safety	Significantly more patients receiving febuxostat 80, 120, or 240 mg achieved sUA levels <6 mg/dL at each of the last three clinic visits compared to the allopurinol and placebo groups, regardless of baseline renal function (48 vs 65 vs 69 vs 22 vs 0%, respectively; P<0.001). Of the patients with normal renal function at baseline, a significantly greater percentage achieved sUA levels <6 mg/dL at each of the last three clinic visits with febuxostat 80, 120, or 240 mg compared to allopurinol and placebo (48 vs 66 vs 69 vs 23 vs 0%, respectively; P<0.001). Of the patients with impaired renal function at baseline, a significantly greater percentage achieved sUA levels <6 mg/dL at each of the last three clinic visits with febuxostat 80, 120, or 240 mg compared to allopurinol 100 mg and placebo (44 vs 46 vs 60 vs 0 vs 0%, respectively; P<0.05). Among patients with a baseline sUA level ≥10 mg/dL, 36, 52, and 66% of patients achieved last three sUA levels <6 mg/dL while receiving febuxostat 80, 120, and 240 mg, respectively. In contrast, only 10% of patients with baseline sUA levels ≥10 mg/dL, achieved last three sUA levels <6 mg/dL, while receiving allopurinol (no P values reported). Secondary: Significantly more patients receiving febuxostat 80, 120, or 240 mg achieved sUA levels <6 mg/dL at week-28 of the study compared to the allopurinol group and the placebo group (76 vs 87 vs 94 vs 41 vs 1%, respectively; P≤0.05). None of the patients with renal impairment at baseline who were randomized to allopurinol therapy achieved sUA levels <6 mg/dL at week 28 of the study. At both week 28 and final visits, all groups receiving febuxostat therapy experienced a significant reduction in sUA levels from baseline compared to allopurinol and placebo groups (P≤0.05). Reductions in sUA levels were first observed at week-two and continued throughout the study. There was no significant difference between the study groups in the proportion of patients requiring for a gout flare during weeks eight to 28 (P value not reported).

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after the initiation of the study drug.				The reduction in the total number of tophi was not significantly different between the groups (P value not reported), with the exception of the febuxostat 120 mg treated patients who experienced a greater reduction in the number of tophi from baseline compared to placebo treated patients at week-28 ($P \leq 0.05$). The reduction in the median tophus size from baseline was not significantly different between the treatment groups (P value not reported). There were no significant differences between the groups in the incidence of adverse events; most were mild or moderate in severity. The most commonly reported adverse events were upper respiratory tract infections, signs and symptoms associated with musculoskeletal and connective tissues, diarrhea (occurring more frequently in patients treated with febuxostat 240 mg vs febuxostat 80 mg and 120 mg, allopurinol, and placebo; $P<0.05$), joint-related signs and symptoms, headaches and liver function test abnormality. The most common adverse event leading to discontinuation from the study was abnormal liver function tests.
Becker et al.[35] (2010) CONFIRMS Febuxostat 40 mg QD vs febuxostat 80 mg QD vs allopurinol 300 mg (for patients with normal renal function or mild renal impairment;	AC, DB, MC, PG, RCT Adults 18 to 85 years of age with hyperuricemia (sUA level ≥8 mg/dL) and gout, as defined by preliminary criteria of the American College of Rheumatology	N=2,269 6 months	Primary: Proportion of patients with sUA levels <6 mg/dL at the final visit Secondary: Proportion of patients with mild to moderate renal impairment achieving sUA levels <6 mg/dL at final visit, proportion of patients with sUA levels <6 mg/dL at each scheduled visit, proportion of patients with sUA levels <5	Primary: The proportion of patients with sUA levels <6 mg/dL at the final visit was 45.2, 67.1 and 42.1% in the febuxostat 40 mg, 80 mg and allopurinol groups respectively. Patients in the febuxostat 80 mg group had a significantly greater response than patients in both the febuxostat 80 mg group ($P<0.001$) and the allopurinol group ($P<0.001$). The difference in response rates between the febuxostat 40 mg group and the allopurinol group was not statistically significant (P value not reported). Secondary: A significantly greater percentage of patients with a CrCl 30 to 90 mL/minute achieved sUA levels <6 mg/dL by the final visit in the febuxostat 80 mg group with a 71.6% response rate compared to a 49.7 and 42.3% rate in the febuxostat 40 mg and allopurinol groups respectively ($P \leq 0.001$ for both comparisons). The response rate in the febuxostat 40 mg group was significantly higher than that in the allopurinol group ($P=0.021$).

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CrCl 60 to 89 mL/minute) or 200 mg QD (for patients with moderate renal impairment; CrCl 30 to 59 mL/minute) Gout flare prophylaxis was provided with naproxen 250 mg BID plus lansoprazole 15 mg QD or colchicine 0.6 mg QD for the entire 6 months of the study.			mg/dL at each scheduled visit, proportion of patients with sUA levels <4 mg/dL at each scheduled visit, rate of gout flares that required treatment, safety	A greater proportion of patients in the febuxostat 80 mg group reached sUA levels <6, <5 and <4 mg/dL, at any scheduled visit compared to febuxostat 40 mg and allopurinol (P≤0.001). Rates of gout flares that required treatment occurred in 10 to 15% of subjects in all groups during the first two months of treatment (P value not reported). There were no significant differences in the incidence of side effects between groups. Treatment-emergent adverse effects were mild to moderate in severity; the most common adverse event leading to discontinuation from the study were abnormal liver function tests. The rates of cardiovascular events were low. There was no statistically significant difference between groups in the incidence of cardiovascular events (P value not reported).
Becker et al.[36] (2009) EXCEL Febuxostat 80 mg QD vs febuxostat 120 mg QD vs allopurinol 100 QD for patients	AC, ES, MC, OL, PG Patients who completed either APEX or FACT were eligible to enroll; adults, 18 to 85 years of age with gout as defined by preliminary criteria of the American College of Rheumatology	N=1,086 Up to 40 months	Primary: Proportion of patients with sUA levels <6 mg/dL at each visit Secondary: Percent reduction in sUA levels from baseline, proportion of patients changing treatment who had achieved sUA levels <6 mg/dL, proportion of patients requiring treatment for a gout flare, percent	Primary: After one month of treatment, the goal sUA level <6 mg/dL was achieved by 81% of patients in the febuxostat 80 mg group, 87% of patients in the febuxostat 120 mg group, and 46% of patients in the allopurinol group (P value not reported). More than 80% of patients receiving febuxostat, regardless of dose, maintained sUA levels <6 mg/dL over the entire study period (P values not reported). Secondary: The percent reduction in sUA levels from baseline on the last visit was 47, 53 and 32% for the febuxostat 80 mg, 120 mg and allopurinol groups respectively (P values not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
with mild-moderate renal impairment (SCr >1.5 to 2 mg/dL) and 300 mg QD for patients with normal renal function (SCr ≤1.5 mg/dL) Gout flare prophylaxis was provided with naproxen 250 mg BID or colchicine 0.6 mg QD for the first 2 months of the study.			reduction in the number of tophi, reduction in size or disappearance of index tophus, safety	Of the 102 patients who did not achieve sUA level <6 mg/dL on febuxostat 80 mg, 61% achieved the goal after switching to febuxostat 120 mg. Of the 24 patients who did not respond to febuxostat 80 or 120 mg and were switched to allopurinol, 17% achieved the sUA goal. Of the 78 patients who did not achieve sUA levels <6 mg/dL with allopurinol 41% did achieve goal after switching to febuxostat 80 mg and an additional 23% did after switching to febuxostat 120 mg (P values not reported). Gout flares increased after the prophylaxis period (week eight), but decreased over time in all groups. After 18 months of treatment, the incidence of gout flares was <4% (P values not reported). Long-term maintenance of sUA levels <6 mg/dL was accompanied by reductions in tophus area, the number of tophi, and the proportion of resolved index tophi. Baseline tophus resolution was achieved in 46, 36 and 29% of patients in the febuxostat 80 mg, 120 mg and allopurinol groups respectively (P values not reported). Adverse events were similar across all treatment groups. No serious cardiac adverse effect was considered to be related to the study drug. Ten deaths occurred over the study period; however, no death was considered related to the study drug.
Dalbeth et al.[37] (2017) Febuxostat 40 mg (dose increased to 80 mg if the sUA level was ≥6.0 mg/dL on day 14) vs placebo	DB, MC, PC, RCT Patients were males ≥18 years of age, females ≥45 years of age and >2 years postmenopausal or females ≥55 years of age if receiving hormone replacement therapy, with a sUA of ≥7.0 mg/dl	N=314 24 months	Primary: Mean change from baseline to month 24 in the modified Sharp/van der Heijde erosion score for the single affected joint Secondary: Mean change from baseline to month 24 in the total modified Sharp/van der Heijde score for radiographs	Primary: The mean change from baseline to month 24 in modified Sharp/van der Heijde erosion scores of the single affected joint was not statistically significantly different between the placebo and febuxostat groups. Secondary: Radiographic assessments of the single affected joint and full hands and feet demonstrated that treatment with febuxostat or placebo for up to 24 months did not lead to any notable changes in joint erosion, At month 24, there were no statistically significant differences in the mean change from baseline in the modified Sharp/van der Heijde total or erosion scores of full hands and feet between the placebo and febuxostat groups.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	who met the American Rheumatology Association preliminary classification criteria for gout and had early gout (which was defined as one or two gout flares). Subjects with two gout flares could have experienced only one flare in the past 12 months.		of the single affected joint; the modified Sharp/van der Heijde total score for radiographs of full hands and feet; the modified Sharp/van der Heijde erosion score for radiographs of full hands and feet; and RAMRIS scores for erosion, edema, and synovitis based on MRI.	MRI assessments of the single affected joint demonstrated that there was no statistically significant improvement in bone marrow erosion or edema in patients treated with febuxostat for up to 24 months. A statistically significant reduction in the RAMRIS synovitis score was observed at months 12 (P=0.025) and 24 (P<0.001) in the febuxostat group compared with the placebo group.
Naoyuki et al.[38] (2011) Febuxostat 20 mg QD vs febuxostat 40 mg QD vs placebo To reduce the risk of induction of gouty arthritis due to a sudden reduction in sUA levels soon after	DB, MC, PC, PG, RCT Male and female patients with hyperuricemia including gout who were ≥20 years of age and whose preregistration sUA level >8 mg/dL	N=103 8 weeks	Primary: Percentage of patients achieving a sUA level ≤6 mg/dL at eight weeks Secondary: Percent change in sUA levels after eight weeks, percentage of patients achieving a sUA ≤6 mg/dL at eight weeks after initiation of treatment and the percent change of sUA levels in relation to the presence or absence of gout, safety	Primary: The percentage of patients who achieved a sUA level ≤6 mg/dL at eight weeks was 91.2, 45.7 and 0% in the febuxostat 40 mg, 20 mg and placebo groups respectively. The differences between the 40 mg and placebo groups were statistically significant (P<0.001) as were the differences between the 20 mg and placebo groups (P=0.007). Secondary: The percent change in sUA levels after eight weeks of treatment was -44.9, -28.9 and -0.6% in the febuxostat 40 mg, 20 mg and placebo groups respectively. The differences between the 40 mg and placebo groups were statistically significant (P<0.001) as were the differences between the 20 mg and placebo groups (P<0.001). The was no significant influences of the presence or absence of gout history on either the percentage of patients achieving a sUA level ≤6 mg/dL at eight weeks or the percent change of sUA levels. The overall incidence of adverse events was 67.6, 77.1 and 78.8% in the febuxostat 40 mg, 20 mg and placebo groups respectively (P values not reported). Major adverse events included nasopharyngitis which occurred

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
initiation of drug treatment all patients in the febuxostat groups received 10 mg QD for the first 2 weeks.				in 8.8, 20.0 and 12.1% in the febuxostat 40 mg, 20 mg and placebo groups respectively. Pharyngitis occurred in 2.9, 11.4 and 12.1% in the febuxostat 40 mg, 20 mg and placebo groups respectively. Upper-airway inflammation occurred in 5.9, 11.4 and 6.1% in the febuxostat 40 mg, 20 mg and placebo groups respectively. Gouty arthritis occurred in 17.6, 5.7 and 12.1% in the febuxostat 40 mg, 20 mg and placebo groups respectively. Increases in C-reactive protein occurred in 5.9, 31.4 and 27.3% in the febuxostat 40 mg, 20 mg and placebo groups respectively. Increases in blood creatinine phosphokinase occurred in 5.9, 14.3 and 15.2% in the febuxostat 40 mg, 20 mg and placebo groups respectively. Increases in ALT occurred in 5.9, 8.6 and 12.1% in the febuxostat 40 mg, 20 mg and placebo groups respectively (P values not reported).
Kamatani et al.[39] (2011) Febuxostat 40 mg QD vs allopurinol 100 mg BID To reduce the risk of induction of gouty arthritis due to a sudden reduction in sUA level after initiation of drug treatment a 12-day introduction period was included; during this period febuxostat 10 mg QD and	AC, DB, DD, MC, PG, RCT Male and female patients with hyperuricemia including gout who were ≥20 years of age and whose preregistration sUA level >8 mg/dL	N=244 8 weeks	Primary: Percent change in sUA after eight weeks Secondary: Percentage of patients achieving a sUA ≤6 mg/dL at eight weeks, safety	Primary: The sUA levels prior to treatment initiation were 8.83 and 8.89 mg/dL in the febuxostat and allopurinol groups respectively. This difference was not statistically significant (P value not reported). The percent change in the sUA levels at eight weeks was -40.75 and -34.41% in the febuxostat and allopurinol groups respectively. This difference was statistically significant (P<0.001). Secondary: In the febuxostat group 82% of patients achieved a sUA level ≤6 mg/dL at eight weeks after initiation of treatment compared to 70%of patients in the allopurinol group. This difference was statistically significant (P=0.034). Nasopharyngitis occurred in 11.5 and 14.9% in the febuxostat and allopurinol groups respectively. Upper respiratory infection occurred in 4.1 and 8.3% in the febuxostat and allopurinol groups respectively. Diarrhea occurred in 3.3 and 7.4% in the febuxostat and allopurinol groups respectively. Gouty arthritis occurred in 9.0 and 5.8% in the febuxostat and allopurinol groups respectively. Increases in AST occurred in 2.5 and 5.8% in the febuxostat and allopurinol groups respectively. Increases in β_2-microglobulin in urine occurred in 6.6 and 5.8% in the febuxostat and allopurinol groups respectively. Blood creatine phosphokinase increase occurred in 5.7 and 4.1% in the febuxostat and allopurinol groups respectively. Blood triglyceride increase occurred in 5.7 and 5.0% in the febuxostat and allopurinol groups respectively. C-

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
allopurinol 100 mg QD were administered.				reactive protein increase occurred in 14.8 and 9.1% in the febuxostat and allopurinol groups respectively. Urinary occult blood positive occurred in 1.6 and 5.0% in the febuxostat and allopurinol groups respectively. There were no significant differences on the incidence of adverse events with age or with the presence of comorbidities (hypertension, hyperlipidemia, diabetes, hepatic disease and renal disease); P values not reported.
Wells et al.[40] (2012) Febuxostat 40 mg QD vs febuxostat 80 mg QD vs allopurinol 300 mg (for patients with normal renal function or mild renal impairment; CrCl 60 to 89 mL/minute) or 200 mg QD (for patients with moderate renal impairment; CrCl 30 to 59 mL/minute) Gout flare prophylaxis was provided with naproxen 250 mg	Post hoc analysis of CONFIRMS Adults 18 to 85 years of age with hyperuricemia (sUA level ≥8 mg/dL) and gout, as defined by preliminary criteria of the American College of Rheumatology	N=2,269 (African American= 228; Caucasian= 1,863) 6 months	Primary: Proportion of African American patients compared to Caucasian patients with sUA levels <6 mg/dL at the final visit Secondary: Proportion of African American patients compared to Caucasian patients with mild to moderate renal impairment achieving sUA levels <6 mg/dL at final visit, proportion of African American patients compared to Caucasian patients who required treatment for acute gout flares during the six months of study, safety	Primary: The proportion of African American patients with sUA levels <6 mg/dL at the final visit was achieved in 34.9, 66.7 and 41.8% in the febuxostat 40 mg, 80 mg and allopurinol groups respectively. The febuxostat 80 mg group was significantly more efficacious than both the febuxostat 40 mg group (P<0.001) and the allopurinol group (P=0.004). In the Caucasian group the proportion of patients with sUA levels <6 mg/dL at the final visit was achieved in 46.8, 68.4 and 43.3% of patients in the febuxostat 40 mg, 80 mg and allopurinol groups respectively. The febuxostat 80 mg group was significantly more efficacious than both the febuxostat 40 mg group (P<0.001) and the allopurinol group (P<0.001). The only statistically significant difference between the African American and Caucasian patients was in the febuxostat 40 mg group (P=0.046) where less African American patients achieved the sUA level <6 mg/dL. Secondary: The proportion of African American patients with mild renal impairment with sUA levels <6 mg/dL at the final visit was 37.8, 75.0 and 44.4% in the febuxostat 40 mg, 80 mg and allopurinol groups respectively. The febuxostat 80 mg group was significantly more efficacious than both the febuxostat 40 mg group (P=0.002) and the allopurinol group (P=0.016). In the Caucasian group the proportion of patients with mild renal impairment who achieve a sUA level <6 mg/dL at the final visit was achieved in 54.9, 72.8 and 47.4% of patients in the febuxostat 40 mg, 80 mg and allopurinol groups respectively. The febuxostat 80 mg group was significantly more efficacious than both the febuxostat 40 mg group (P<0.001) and the allopurinol group (P<0.001). Efficacy rates between the African American and Caucasian patients were comparable (no P values reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
BID plus lansoprazole15 mg QD or colchicine 0.6 mg QD for the entire 6 months of the study.				In the African American group 30, 31 and 25% of patients required treatment for acute gout flares compared to 30, 31 and 25% of patients in the Caucasian group for the febuxostat 40 mg, 80 mg and allopurinol groups respectively (P values not reported). Adverse event rates were comparable across treatment groups for both African American and Caucasian patients. In the African American patients at least one adverse event was reported in 30, 31 and 30% compared to 30, 31 and 25% in the Caucasian group for the febuxostat 40 mg, 80 mg and allopurinol groups respectively (P values not reported).
Becker et al.[41] (2011) Febuxostat 40 mg QD vs febuxostat 80 mg QD vs allopurinol 300 mg (for patients with normal renal function or mild renal impairment; CrCl 60 to 89 mL/minute) or 200 mg QD (for patients with moderate renal impairment; CrCl 30 to 59 mL/minute)	Post hoc analysis of CONFIRMS Adults 18 to 85 years of age with hyperuricemia (sUA level ≥8 mg/dL) and gout, as defined by preliminary criteria of the American College of Rheumatology	N=2,269 (374 patients ≥65 years of age; 1,895 patients <65 years of age) 6 months	Primary: Proportion of patients ≥65 years of age compared to patients <65 years of age with sUA levels <6 mg/dL at the final visit Secondary: Proportion of patients ≥65 years of age compared to patients <65 years of age with mild to moderate renal impairment achieving sUA levels <6 mg/dL at final visit, safety	Primary: The proportion of patients ≥65 years of age with sUA levels <6 mg/dL at the final visit was achieved in 61.7, 82.0 and 47.3% in the febuxostat 40 mg, 80 mg and allopurinol groups respectively. The proportion of patients <65 years of age with sUA levels <6 mg/dL at the final visit was achieved in 42.2, 64.0 and 41.0% of patients in the febuxostat 40 mg, 80 mg and allopurinol groups respectively. Between the age groups there was a statistically significant greater efficacy with both the febuxostat 40 mg and 80 mg arms in the patients ≥65 years of age compared to the <65 years of age group (P<0.001 for both dosages). There was no significant difference in the efficacy of allopurinol between the two age groups (P=0.206). In both patient age groups, the urate lowering efficacy of febuxostat 80 mg was significantly great than febuxostat 40 mg (P<0.001in both groups) and allopurinol (P<0.001in both groups). Febuxostat 40 mg was only significantly more efficacious when compared to allopurinol in the ≥65 years of age group (P<0.029). Secondary: The proportion of patients ≥65 years of age with mild renal impairment who achieved sUA levels <6 mg/dL at the final visit was 73.3, 88.6 and 62.0% in the febuxostat 40 mg, 80 mg and allopurinol treatment groups respectively. The proportion of patients <65 years of age who achieved a sUA level <6 mg/dL at the final visit was 49.0, 69.3 and 43.8% of patients in the febuxostat 40 mg, 80 mg and allopurinol groups respectively. Between the age groups there was a statistically significant greater efficacy with febuxostat 40 mg, 80 mg and allopurinol in patients ≥65 years of age compared to patients <65 years of age (P=0.002 for

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Gout flare prophylaxis was provided with naproxen 250 mg BID plus lansoprazole 15 mg QD or colchicine 0.6 mg QD for the entire 6 months of the study.				febuxostat 40 mg, P=0.007 for febuxostat 80 mg and P=0.021 for allopurinol). In both patient age groups, the urate lowering efficacy of febuxostat 80 mg was significantly greater than that of allopurinol (P=0.004 in the ≥65 years of age group and P<0.001 in the <65 years of age group). Febuxostat 80 mg was only significantly greater than febuxostat 40 mg in the <65 years of age group (P=0.104 in the ≥65 years of age group and P<0.001 in the <65 years of age group). Febuxostat 40 mg was not significantly greater than allopurinol in either age group (P=0.278 in the ≥65 years of age group and P=0.198 in the <65 years of age group). The proportion of patients ≥65 years of age with moderate renal impairment who achieved a sUA level <6 mg/dL at the final visit was 53.7, 79.3 and 37.4% in the febuxostat 40 mg, 80 mg and allopurinol groups respectively. The proportion of patients <65 years of age who achieved a sUA level <6 mg/dL at the final visit was 31.7, 59.3 and 23.2% of patients in the febuxostat 40 mg, 80 mg and allopurinol groups respectively. Between the age groups there was a statistically significant greater efficacy with febuxostat 40 mg and 80 mg in the patients ≥65 years of age compared the patients <65 years of age group (P=0.014 for the febuxostat 40 mg, P=0.019 for the febuxostat 80 mg). In both patient age groups, the urate lowering efficacy of febuxostat 80 mg was significantly greater than that of allopurinol (P<0.001 in both age groups). Febuxostat 80 mg was significantly greater than febuxostat 40 mg in both age groups (P=0.001 in the ≥65 years of age group and P=0.005 in the <65 years of age group). Febuxostat 40 mg was not significantly greater than allopurinol in either age group (P=0.067 in the ≥65 years of age group and P=0.314 in the <65 years of age group). The percentage of patients reporting at least one adverse event was 60.4% in the ≥65 years of age group compared to 55.2% in the <65 years of age group. This difference was not statistically significant (P=0.068). Diarrhea occurred in 9.6% of patients ≥65 years of age compared to 6.0% of patients <65 years of age and this difference was statistically significant (P=0.012). Lower respiratory tract and lung infections occurred in 3.2% in the patients ≥65 years of age compared to 1.5% of patients <65 years of age and this difference was statistically significant (P=0.029). Elevated

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				ALT levels occurred in 3% of patients ≥65 years of age compared to 10% of patients <65 years of age and this difference was significant (P<0.001). Elevated AST levels occurred in 1% of patients ≥65 years of age compared to 6% of patients <65 years of age and this difference was significant (P<0.001). Five patients died during the study and two of the five patients were ≥65 years of age. None of the study deaths were related to the study medications.
Chohan et al.[42] (2012) Febuxostat 40 mg QD vs febuxostat 80 mg QD vs febuxostat 120 mg QD vs febuxostat 240 mg QD vs febuxostat 30 mg QD vs allopurinol 300 mg QD	Post hoc analysis of FACT, APEX and CONFIRMS Adults 18 to 85 years of age with hyperuricemia (sUA level ≥8 mg/dL) and gout, as defined by preliminary criteria of the American College of Rheumatology; APEX patients were included with normal (SCr ≤1.5 mg/dL) or impaired (SCr >1.5 to ≤2.0 mg/dL) renal function	N=4,101 (Women=226; men=3,875) FACT: N=760 52 weeks APEX: N=1,072 28 weeks CONFIRMS: N=2,269 24 weeks	Primary: Proportion of female patients with sUA levels <6 mg/dL at the final visit Secondary: Proportion of female patients with mild to moderate renal impairment achieving sUA levels <6 mg/dL at final visit, safety	Primary: The proportion of female patients with sUA levels <6 mg/dL at the final visit was 0% in the placebo group, 54.3% in the febuxostat 40 mg group, 85.1% in the febuxostat 80 mg group, 81.0% in the febuxostat 120 mg group, 100% in the febuxostat 240 mg group and 45.9% in the allopurinol group. Only the differences between the febuxostat 80 and 120 mg groups were statistically significant when compared to the allopurinol group (P<0.001 in the 80 mg group and P=0.006 in the 120 mg group). Secondary: For patients with normal renal function (CrCl ≥90 mL/minute), 0% in the placebo group achieved a sUA levels <6 mg/dL at final visit compared to 50% in the febuxostat 40 mg group, 100% in the febuxostat 80 mg group, 100% in the febuxostat 120 mg group and 50% in the allopurinol group. For mild renally impaired patients (CrCl ≥60 to <90 mL/minute), 0% in the placebo group achieved a sUA level <6 mg/dL at final visit compared to 80% in the febuxostat 40 mg group, 84% in the febuxostat 80 mg group, 80% in the febuxostat 120 mg group, 100% in the febuxostat 240 mg group, and 50% in the allopurinol. For moderate or severe renally impaired patients (CrCl <60 mL/minute), 0% in the placebo group achieved a sUA level <6 mg/dL at final visit compared to 43.5% in the febuxostat 40 mg group, 83.3% in the febuxostat 80 mg group, 80% in the febuxostat 120 mg group, 100% in the febuxostat 240 mg group and 44.4% in the allopurinol group. Statistical analysis could not be performed due to the small number of patients in each group (P values not reported). The most frequently reported adverse events among female patients were upper respiratory infections (15.5%), musculoskeletal/connective tissue disorders (11.1%) and diarrhea (10.6%). The majority of adverse events were transient and resolved during treatment (P values not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs allopurinol 100 or 300 mg QD (dose depended on renal function) vs allopurinol 300 mg (for patients with normal renal function or mild renal impairment; CrCl 60 to 89 mL/minute) or 200 mg QD (for patients with moderate renal impairment; CrCl 30 to 59 mL/minute) vs placebo Gout flare prophylaxis was provided with naproxen 250 mg BID or colchicine 0.6 mg QD for first 8 weeks in the FACT and APEX studies and				

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
for entire 6 months of the CONFIRMS study.				

Drug regimen abbreviations: BID=twice daily, IV=intravenous, QD=once daily, TID=three times daily
Study abbreviations: AC=active-controlled, CI=confidence interval, DB=double-blind, DD=double dummy, ES=extension study, HR=hazard ratio, ITT=intent to treat, MA=meta-analysis, MC=multicenter, OL=open-label, OR=odds ratio, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, XO=crossover
Miscellaneous abbreviations: ALL=acute lymphoblastic leukemia, ALT=alanine aminotransferase, AST=aspartate aminotransferase, AUC=area under the curve, CrCl=creatinine clearance, ECOG= Eastern Cooperative Oncology Group, FMF=Familial Mediterranean Fever, MRI= magnetic resonance imaging, NHL=non-Hodgkin lymphoma, PUA=plasma uric acid, RAMRIS=Rheumatoid Arthritis Magnetic Resonance Imaging Scoring, SCr=serum creatinine, sUA=serum uric acid, TLS=tumor lysis syndrome, VAS=visual analog scale, WBC=white blood cell

Additional Evidence

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

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

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

IX. Cost

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

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

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

Rx=prescription.

Table 9. Relative Cost of the Antigout Agents

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Single Entity Agents				
Allopurinol	injection, tablet	Aloprim®*	$$$$	$
Colchicine	capsule, oral solution, tablet	Colcrys®*, Gloperba®, Mitigare®*	$$$$$	$
Febuxostat	tablet	Uloric®*	$$$$$	$
Pegloticase	injection	Krystexxa®	$$$$$	N/A
Probenecid	tablet*	N/A	N/A	$
Combination Products				
Probenecid-colchicine	tablet*	N/A	N/A	$$

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

X. Conclusions

The antigout agents included in this review are approved either for the treatment of acute gout attacks, prophylaxis of gout attacks, or management of hyperuricemia in patients with gout. Agents such as allopurinol, colchicine, and probenecid have additional indications outside of the treatment of gout. All of these products, with the exception of Gloperba® and Krystexxa®, are available in a generic formulation.[5-11]

The consensus guidelines for the treatment of gout recommend the use of a xanthine oxidase inhibitor in patients requiring chronic pharmacotherapy.[2-4] Preference for allopurinol or febuxostat is given in the American College of Rheumatology, British Society for Rheumatology and European League Against Rheumatism guidelines which recommend the use of allopurinol first-line.[2-4] All guidelines recommend adjusting the dosing to reach a serum urate target of <6 mg/dL.[2-4] Uricosuric agents such as probenecid are recommended in patients with a contraindication, inadequate response, or adverse reaction to xanthine oxidase inhibitors.[2-4] The use of pegloticase is only discussed in the American College of Rheumatology and European League Against Rheumatism guidelines, both of which recommend it as last line for urate lowering in gout patients.[2,4] For the treatment of acute gout attacks, colchicine is the recommended antigout agent along with nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids. Colchicine is also discussed as appropriate therapy for gout attack prophylaxis.[2-4]

Though there have been multiple head to head studies comparing agents within this class, there is limited evidence to support significant benefit with one agent over another when used for the same indication.[22,31-35] There were a few trials that demonstrated a potential benefit with the use of febuxostat over allopurinol depending upon the dose; however, most of these trials utilized higher than FDA-approved doses of febuxostat. Additionally, the consensus guidelines do not reflect preference for febuxostat.[2-4,33-36] Benefits from treatment with the antigout agents have been demonstrated in comparison to placebo and therefore support the use of these medications for their FDA-approved indications.[14,16-21,24,27,28,37,38]

A clinical trial comparing the safety of allopurinol and febuxostat demonstrated an increased risk of death from any cause and death due to cardiovascular events in patients using febuxostat.[31] After reviewing the safety data available for febuxostat, the FDA concluded that there is an increased risk of death with this agent compared to other antigout agents.[43] The FDA deemed it appropriate to require a Boxed Warning and limit the use of febuxostat to those who have an inadequate response or are unable to tolerate allopurinol or in those for whom the use of allopurinol would not be advisable.[8,43]

There is insufficient evidence to support that one brand antigout agent is 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 antigout agents within the class reviewed, with the exception of pegloticase, are comparable to each other and to the generics in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use. Pegloticase possesses an extensive adverse effect profile compared to the other brands and generics in the class (if applicable) and should be managed through the medical justification portion of the prior authorization process.

XI. Recommendations

No brand antigout 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.

Pegloticase should not be placed in preferred status, regardless of cost.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Genitourinary Smooth Muscle Relaxants
AHFS Class 861204 – Antimuscarinics
November 8, 2023

I. Overview

Urinary incontinence is the involuntary leakage of urine, which may be classified as urgency, stress, overflow, or mixed incontinence.[1] Urgency incontinence is accompanied by a sense of urgency, while stress incontinence generally occurs with effort, exertion, sneezing, or coughing. Overflow incontinence is associated with dribbling and/or continuous leakage due to incomplete bladder emptying.[1] Overactive bladder is a functional disorder characterized by urinary urgency, daytime frequency (>8 voids during the daytime), nocturia (>1 void at night), with or without incontinence.[2] Urinary incontinence and overactive bladder may be due to lower urinary tract dysfunction or secondary to non-genitourinary disorders. The most common cause of overactive bladder is overactivity of the bladder's detrusor muscle. Symptoms may be assessed by patient history, the use of validated questionnaires, and/or bladder diaries. Clinical testing (e.g., bladder stress test, postvoid residual volume testing, urine flow rate, and urodynamic testing) may help identify the pathology, but are not always necessary for diagnosis or initiation of therapy.[1] Urinary incontinence and overactive bladder cause both physical and psychological morbidity, as well as adversely impact quality of life.[1] Initial treatment options include lifestyle modifications (weight loss and dietary changes) and behavioral therapy (bladder training, physical therapy, and toileting assistance).[3] Pharmacologic therapy is typically trialed if initial treatment is ineffective.[3] Neurogenic lower urinary tract disorder is caused by a lesion at any level of the nervous system.[4,5] The lesion interferes with the normal nerve pathways associated with urination. Early diagnosis and treatment of neurogenic lower urinary tract disorder is essential for both congenital and acquired disorders as irreversible changes may occur.[5]

Normal voiding is dependent on acetylcholine-induced stimulation of muscarinic receptors on bladder smooth muscle. There are five muscarinic receptor subtypes, of which M1, M2, and M3 mediate bladder contractility. Muscarinic receptors are also found in the gastrointestinal tract, salivary glands, and tear ducts. Antimuscarinic drugs increase bladder capacity, decrease urgency, and are useful for the treatment of urge incontinence.[3,6-16] Darifenacin, fesoterodine, solifenacin, tolterodine, and trospium are muscarinic receptor antagonists. Flavoxate is an antispasmodic which exerts its effects directly on muscle and counteracts the smooth muscle spasm of the urinary tract. Oxybutynin has a direct antispasmodic effect on smooth muscle and inhibits the muscarinic action of acetylcholine on smooth muscle. Some antimuscarinic agents claim to have greater affinity for specific receptor subtypes that mediate bladder contractility, but the clinical significance of this is unclear. The most common adverse effects associated with the use of antimuscarinic agents include dry mouth, blurred vision, abdominal discomfort, drowsiness, nausea, and dizziness. These agents may also cause confusion or cognitive impairment in the elderly.[3]

The genitourinary smooth muscle relaxants 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 November 2021.

Table 1. Genitourinary Smooth Muscle Relaxants Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Darifenacin	extended-release tablet	N/A	darifenacin
Fesoterodine	extended-release tablet	Toviaz®*	Toviaz®
Flavoxate	tablet	N/A	flavoxate
Oxybutynin	extended-release tablet, syrup, tablet, transdermal gel, transdermal patch	Ditropan XL®*, Gelnique®, Oxytrol®	oxybutynin, Oxytrol®
Solifenacin	oral suspension, tablet	VESIcare®*	solifenacin
Tolterodine	extended-release capsule, tablet	Detrol®*, Detrol LA®*	tolterodine
Trospium	extended-release capsule, tablet	N/A	trospium

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

II.Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the genitourinary smooth muscle relaxants are summarized in Table 2.

Table 2. Treatment Guidelines Using the Genitourinary Smooth Muscle Relaxants

Clinical Guideline	Recommendation(s)
National Institute for Health and Clinical Excellence: **Urinary Incontinence and Pelvic Organ Prolapse in Women: Management (2019)**[17] Last updated June 2019	<u>Behavioral therapy</u> • Bladder training should be offered for a minimum of six weeks as first-line treatment to women with urge or mixed urinary incontinence. • If women do not achieve satisfactory benefit from bladder training, the combination of an overactive bladder medicine with bladder training should be considered if frequency is a troublesome symptom. • Do not offer transcutaneous sacral nerve stimulation, transcutaneous posterior tibial nerve stimulation, or percutaneous posterior tibial nerve stimulation to women with urinary incontinence. <u>Pharmacologic therapy</u> • Before starting treatment with a medicine for overactive bladder, the following should be explained to the woman: the likelihood of the medicine being successful; the common adverse effects associated with the medicine; that some adverse effects of anticholinergic medicines, such as dry mouth and constipation, may indicate that the medicine is starting to have an effect; that she may not see substantial benefits until she has been taking the medicine for at least four weeks and that her symptoms may continue to improve over time; and that the long-term effects of anticholinergic medicines for overactive bladder on cognitive function are uncertain. • When offering anticholinergic medicines to treat overactive bladder, the following should be taken into consideration of the woman's: coexisting conditions (such as poor bladder emptying, cognitive impairment or dementia); current use of other medicines that affect total anticholinergic load; and risk of adverse effects, including cognitive impairment. • Flavoxate, propantheline and imipramine should not be offered for the treatment of urinary incontinence or overactive bladder in women. • Immediate-release oxybutynin should not be offered to older women who may be at higher risk of a sudden deterioration in their physical or mental health. • Anticholinergic medicine with the lowest acquisition cost should be offered to treat overactive bladder or mixed urinary incontinence in women. • If the first medicine for overactive bladder or mixed urinary incontinence is not effective or well-tolerated, another medicine with a low acquisition cost should be offered. • A transdermal overactive bladder treatment should be offered to women unable to tolerate oral medicines. • The use of desmopressin may be considered to reduce nocturia in women with urinary incontinence or overactive bladder who find it a troublesome symptom. • Duloxetine is not recommended as a first-line treatment for women with predominant stress urinary incontinence. Duloxetine should not routinely be used as a second-line treatment for women with stress urinary incontinence, although it may be offered as second-line therapy if women prefer pharmacological to surgical treatment or are not suitable for surgical treatment. • Systemic hormone replacement therapy is not recommended for the treatment of urinary incontinence. • Intravaginal estrogens are recommended for the treatment of overactive bladder symptoms in postmenopausal women with vaginal atrophy.

Clinical Guideline	Recommendation(s)
	• Mirabegron is recommended as an option for treating the symptoms of overactive bladder only for people in whom antimuscarinic drugs are contraindicated or clinically ineffective, or have unacceptable side effects. ○ People currently receiving mirabegron that is not recommended for them should be able to continue treatment until they and their clinician consider it appropriate to stop. Complementary therapy • Complementary therapies are not recommended for the treatment of urinary incontinence or overactive bladder.
European Association of Urology: **Non-neurogenic Female LUTS (2023)**[18]	Antimuscarinic drugs • Anticholinergic drugs are effective in improving overactive bladder (OAB) symptoms, decreasing urge urinary incontinence (UUI) episodes, decreasing daily urgency and frequency episodes and increasing mean voided volumes, compared with placebo. • Anticholinergic drugs caused higher adverse events than placebo including dry mouth, cognitive impairment, and constipation. • Once daily (extended release) formulations are associated with lower rates of adverse events compared to immediate release preparations. • Transdermal oxybutynin (patch) is associated with lower rates of dry mouth than oral anticholinergic drugs but has a higher rate of withdrawal due to skin reaction. • Higher doses of anticholinergic drugs are more effective to improve OAB symptoms but exhibit a higher risk of adverse effects. • No anticholinergic drug is clearly superior to another for cure or improvement of OAB/UUI. • The combination of antimuscarinics plus another treatment modality was more effective than antimuscarinics alone in improving OAB. • Adherence to anticholinergic treatment is low and decreases over time because of lack of efficacy, adverse events and/or cost. • Adherence to anticholinergic treatment is low and decreases over time because of lack of efficacy, adverse events and/or cost. • Most patients will stop anticholinergic agents within the first three months. • Recommendations: Offer anticholinergic drugs to woman with OAB who fail conservative treatment; Consider extended-release formulations of anticholinergic drugs whenever possible; If an anticholinergic treatment proves ineffective, consider dose escalation, offering an alternative anticholinergic formulation, or the use of mirabegron (alone or in combination with an anticholinergic); Encourage early review (of efficacy and adverse effects) of patients on anticholinergic medication for OAB. Beta-3 agonists • Mirabegron and vibegron are better than placebo for improvement of OAB/UUI symptoms. • Adverse event rates with mirabegron and vibegron are similar to placebo. • Beta-3 agonists are as effective as antimuscarinics in the management of OAB but with lower dry mouth rates. • Patients inadequately treated with solifenacin 5 mg may benefit more from the addition of mirabegron than dose escalation of solifenacin. • Recommendations: Offer beta-3 agonists as an alternative to anticholinergics to women with overactive bladder who fail conservative treatment; Offer mirabegron as an additional therapy in patients who are inadequately treated with solifenacin 5 mg. Anticholinergics and beta-3 agonists in the elderly • Anticholinergic drugs are effective in elderly patients suffering from OAB/UUI.

Clinical Guideline	Recommendation(s)
	• Mirabegron has been shown to be efficacious and safe in elderly women suffering from OAB. • In older women the cognitive impact of drugs which have anticholinergic effects is cumulative and increases with length of exposure. • Oxybutynin may worsen cognitive function in elderly women. • Darifenacin, fesoterodine, solifenacin and trospium have not been shown to cause cognitive dysfunction in elderly women in short-term studies. • Long-term anticholinergic treatment should be used with caution in elderly women, especially those who are at risk of, or have pre-existing cognitive dysfunction. • Assess anticholinergic burden and associated co-morbidities in patients being considered for anticholinergic therapy for overactive bladder syndrome. <u>Pharmacological management of mixed urinary incontinence</u> • Treat the most bothersome symptom first in patients with mixed urinary incontinence (MUI). • Offer anticholinergic drugs or beta-3 agonists to patients with urgency-predominant MUI. • Offer duloxetine (where licensed) to selected patients with stress-predominant MUI unresponsive to other conservative treatments and who want to avoid invasive treatment, counselling carefully about the risk of adverse events. <u>Pharmacological management of nocturia</u> • Offer desmopressin treatment for nocturia secondary to nocturnal polyuria to women, following appropriate counselling regarding the potential benefits and associated risks (including hyponatremia). • Carefully monitor serum sodium concentration in elderly patients treated with desmopressin. Avoid prescribing desmopressin to patients with a baseline serum sodium concentration below normal range. • Offer anticholinergic treatment for nocturia to women with urge urinary incontinence or other LUTS, following appropriate counselling regarding the potential benefits and associated risks. • Inform women with nocturia that combination of behavioral therapy and anticholinergic drugs is unlikely to provide increased efficacy compared with either modality alone. • Offer combination of anticholinergics and desmopressin to women with overactive bladder and nocturia secondary to nocturnal polyuria, following appropriate counselling regarding the potential benefits and associated risks. • Offer vaginal oestrogen treatment to women with nocturia, following appropriate counselling regarding the potential benefits and associated risks. • Offer timed diuretic treatment to women with nocturia secondary to polyuria, following appropriate counselling regarding the potential benefits and associated risks.
European Association of Urology: **Non-neurogenic Male LUTS (2023)**[19]	<u>Pharmacological treatment</u> • Offer α1-blockers to men with moderate-to-severe lower urinary tract symptoms (LUTS). • α1-blockers are effective in reducing urinary symptoms (International Prostate Symptom Score: IPSS) and increasing the peak urinary flow rate (Qmax) compared with placebo. • Alfuzosin, terazosin and doxazosin showed a statistically significant increased risk of developing vascular-related events compared with placebo. • Alfuzosin, doxazosin, tamsulosin or terazosin exposure has been associated with an increased risk of intra-operative floppy iris syndrome (IFIS).

Clinical Guideline	Recommendation(s)
	• Ejaculatory dysfunction is significantly more common with α1-blockers than with placebo, particularly with more selective α1-blockers such as tamsulosin and silodosin. • Use 5α-reductase inhibitors in men who have moderate-to-severe LUTS and an increased risk of disease progression (e.g., prostate volume > 40 mL). • Counsel patients about the slow onset of action of 5α-reductase inhibitors. • Use muscarinic receptor antagonists in men with moderate-to-severe LUTS who mainly have bladder storage symptoms. • Do not use antimuscarinic overactive bladder medications in men with a post-void residual volume > 150 mL. • Use beta-3 agonists in men with moderate-to-severe LUTS who mainly have bladder storage symptoms. • Use phosphodiesterase type 5 inhibitors in men with moderate-to-severe LUTS with or without erectile dysfunction. • Offer combination treatment with an α1-blocker and a 5α-reductase inhibitor to men with moderate-to-severe LUTS and an increased risk of disease progression (e.g., prostate volume > 40 mL). • Use combination treatment of a α1-blocker with a muscarinic receptor antagonist in patients with moderate-to-severe LUTS if relief of storage symptoms has been insufficient with monotherapy with either drug. Do not prescribe combination treatment in men with a post-void residual volume > 150 mL. • Use combination treatment of a α1-blocker with mirabegron in patients with persistent storage LUTS after treatment with α1-blocker monotherapy. • Offer antimuscarinic drugs or mirabegron to adults with urge urinary incontinence who failed conservative treatment. • Offer duloxetine to men with stress urinary incontinence. Inform patients about the possible adverse events of duloxetine and that its use is off label for this indication in Europe.
American Urological Association: **Diagnosis and Treatment of Overactive Bladder (Non-Neurogenic) in Adults: American Urological Association/ Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction Guideline (2012); Amended (2014, 2019)[20]**	<u>Diagnosis</u> • Overactive bladder is a symptom complex that is not generally life threatening. • The clinician should engage in a diagnostic process to document symptoms and signs that characterize overactive bladder and exclude other disorders that could be the cause of the patient's symptoms. • After assessment has been performed to exclude conditions requiring treatment and counseling, no treatment is an acceptable choice. <u>First line treatment</u> • Behavioral therapies (e.g., bladder training, bladder control strategies, pelvic floor muscle training, fluid management) should be offered as first line therapy. • Behavioral therapies can also be combined with pharmacologic management. <u>Second line treatment</u> • Clinicians should offer oral antimuscarinics or oral β3-adrenoceptor agonists as second line therapy. • If extended-release and immediate-release formulations are available, the extended-release should be preferred over the immediate-release given formulation due to lower rates of dry mouth. Transdermal oxybutynin is also an option. • If a patient experiences inadequate symptom control and/or unacceptable adverse drug events with one agent then a dose modification or a different antimuscarinic medication or β3-adrenoceptor agonist may be tried. • May consider combination therapy with an anti-muscarinic and β3-adrenoceptor agonist for patients refractory to monotherapy with either anti-muscarinics or β3-adrenoceptor agonists.

Clinical Guideline	Recommendation(s)
	• Anti-muscarinics should be avoided in patients with narrow-angle glaucoma unless approved by the treating ophthalmologist and should also be used with extreme caution in patients with impaired gastric emptying or a history of urinary retention. • Manage constipation and dry mouth before abandoning effective anti-muscarinic therapy. Management may include bowel management, fluid management, dose modification or alternative anti-muscarinics. • Use caution in prescribing anti-muscarinics in patients who are using other medications with anti-cholinergic properties. • Use caution in prescribing anti-muscarinics or β3-adrenoceptor agonists in the frail patient. • Patients who are refractory to behavioral and pharmacologic therapy should be evaluated by an appropriate specialist if they desire additional therapy. <u>Third line treatment</u> • Clinicians may offer intradetrusor onabotulinumtoxinA as a third-line option in the carefully selected patients who has been refractory to first and second line overactive bladder treatments. The patient must be able and willing to return for frequent post-void residual evaluation and able and willing to perform self-catheterization if necessary. • Clinicians can also offer peripheral tibial nerve stimulation as third-line treatment. • Clinicians may offer sacral neuromodulation as third line treatment in a carefully selected patient population characterized by server refractory overactive bladder symptoms or patients who are not candidates for second-line therapy and are willing to undergo a surgical procedure. • Patients should persist with new treatments for an adequate trial in order to determine whether the therapy is efficacious and tolerable. Combination therapeutic approaches should be assembled methodically, with the addition of new therapies occurring only when the relative efficacy of the preceding therapy is known. Therapies that do not demonstrate efficacy after an adequate trial should be ceased.
National Institute for Health and Clinical Excellence: **Urinary Incontinence in Neurological Disease (2012)**[21]	<u>Behavioral treatment</u> • For patients with neurogenic lower urinary tract dysfunction, behavioral management programs should be considered (e.g., timed voiding, bladder retraining or habit retraining). • When choosing a behavioral management program, take into account that prompted voiding and habit retraining are particularly suitable for people with cognitive impairment. <u>Antimuscarinics</u> • Antimuscarinic drugs should be offered to patients with spinal cord disease (e.g., spinal cord injury or multiple sclerosis) who have symptoms of overactive bladder such as increased frequency, urgency and incontinence. • In patients with conditions affecting the brain (e.g., cerebral palsy, head injury or stroke) with symptoms of an overactive bladder, antimuscarinic drugs should be considered. • Antimuscarinic drug treatment should be considered in patients with urodynamic investigations showing impaired bladder storage. • Residual urine volume should be monitored in patients not using intermittent or indwelling catheterization after beginning treatment. • Antimuscarinic treatment can reduce bladder emptying, which may increase the risk of urinary tract infections and may precipitate or exacerbate constipation. Antimuscarinics known to cross the blood-brain barrier (e.g. oxybutynin) have the potential to cause central nervous system related adverse effects (e.g., confusion).

Clinical Guideline	Recommendation(s)
	Botulinum toxin A • Bladder wall injection with botulinum toxin A should be offered to adult patients with spinal cord diseases (e.g., spinal cord injury or multiple sclerosis) and symptoms of overactive bladder and an inadequate response to or poorly tolerated antimuscarinic drugs. • Bladder wall injection with botulinum toxin A may be considered for children and young people with spinal cord disease and symptoms of overactive bladder for who antimuscarinic drugs were ineffective or poorly tolerated. • Bladder wall injection with botulinum toxin A may be considered in adults with spinal cord disease with urodynamic investigations showing impaired bladder storage for whom antimuscarinic drugs were ineffective or poorly tolerated. • Consider bladder wall injection with botulinum toxin A for children and young people with spinal cord disease with urodynamic investigations showing impaired bladder storage and for whom antimuscarinic drugs were ineffective or poorly tolerated. • A catheterization regimen is needed in most people with neurogenic lower urinary tract dysfunction after botulinum toxin A treatment. The patient must be able and willing to manage such a regimen should urinary retention develop after the treatment. • Monitor residual urine volume in patients who are not using a catheterization regimen during treatment with botulinum toxin A. • Monitor upper urinary tract in patients at risk of renal complications (e.g., those with high intravesical pressures on filling cystometry) during treatment. • People should be offered repeated botulinum toxin A injections and have prompt access to repeat injections when symptoms return.
International Scientific Committee: **Evaluation and Treatment of Urinary Incontinence, Pelvic Organ Prolapse, and Fecal Incontinence (2018)**[22]	Initial management of urinary incontinence in children • For children with mono-symptomatic nocturnal enuresis, initial treatment should include: o Parental and child counselling and motivation o Review of bladder diary with attention to night-time polyuria o Age appropriate education and demystification or explanation o Counselling, timed voiding, behavior modification and bowel management when necessary o Antimuscarinics may be used if the child has overactive bladder symptoms Initial management of urinary incontinence in men • For men with stress, urgency or mixed urgency/stress incontinence, initial treatment should include: o Lifestyle interventions. o Supervised pelvic floor muscle training for men with post-radical prostatectomy stress urinary incontinence. o Scheduled voiding regimes for overactive bladder. o Antimuscarinic/beta 3 agonist drugs for overactive bladder symptoms with or without urgency incontinence if the patient has no evidence of significant post-void residual urine. o Alpha adrenergic antagonists (α-blockers) can be added if it is thought that there may also be bladder outlet obstruction. Initial management of urinary incontinence in women • For women with stress, urgency or mixed urgency/stress incontinence, initial treatment should include: o Advice on caffeine reduction for overactive bladder and weight reduction.

Clinical Guideline	Recommendation(s)
	○ Supervised pelvic floor muscle training and vaginal cones training for women with stress incontinence. ○ Supervised bladder training for overactive bladder. ○ If estrogen deficiency and/or urinary tract infection is found, the patient should be treated at initial assessment and then reassessed after a suitable interval. ○ Antimuscarinics/beta-3 agonist for overactive bladder symptoms with or without urgency incontinence. ○ Duloxetine may be considered for stress urinary incontinence. <u>Initial management of neurogenic urinary incontinence</u> • Conservative treatment modalities (often in combination): ○ Intermittent catheterization. ○ Behavioral treatment. ○ Timed voiding. ○ Continence products. ○ Antimuscarinics. ○ Alpha-1-adrenergic blockers. ○ Oral cannabinoid agonists (MS) ○ Beta-3-agonist alone or as an add-on to antimuscarinics ○ Bladder expression. ○ Triggered voiding. ○ Indwelling catheter. <u>Management of urinary incontinence in frail older persons</u> • Initial treatment should be individualized and influenced by goals of care, treatment preferences, and estimated remaining life expectancy, as well as the most likely clinical diagnosis. • In some frail elders the only possible outcome may be contained urinary incontinence (managed with pads), especially for persons with minimal mobility (require assistance of >2 persons to transfer), advanced dementia (unable to state their name), and/or nocturnal urinary incontinence. • Conservative and behavioral therapy for urinary incontinence include lifestyle changes, bladder training for more fit alert patients, and prompted voiding for frailer, more impaired patients. • For select cognitively intact patients, pelvic muscle exercises may be considered. Antimuscarinics may be added to conservative therapy of urgency urinary incontinence. Alpha-blockers may be cautiously considered in frail men with suspected prostatic outlet obstruction. All drugs should be started at the lowest dose and titrated with regular review until either care goals are met or adverse effects are intolerable. • DDAVP (vasopressin) has a high risk of severe hyponatremia in frail persons and should not be used outside specialist centers or without very careful monitoring and long-term follow-up.
American College of Obstetricians and Gynecologists: **Practice Bulletin: Urinary Incontinence in Women (2015)**[23] Reaffirmed 2022	• Behavioral therapy (e.g., bladder training and prompted voiding) and pelvic floor muscle exercises improve symptoms of stress, urgency, and mixed urinary incontinence and may be recommended as an initial, noninvasive treatment in many women. • Moderate weight loss can improve urinary incontinence symptoms in overweight and obese women. • Pelvic floor muscle exercises appear to be an effective treatment for adult women with stress, urgency, or mixed incontinence and can be recommended as a noninvasive treatment for many women. • Current evidenced-based medical treatments typically are reserved for urgency urinary incontinence. Medical therapies for treatment of stress urinary

Clinical Guideline	Recommendation(s)
	incontinence are less effective and generally are not recommended. Available medical treatments for urgency urinary incontinence include antimuscarinic agents (also known as anticholinergic agents), β-agonists, onabotulinumtoxinA, and estrogen. • The antimuscarinic medications have been shown to have a small beneficial effect as therapy for urgency incontinence. Numerous antimuscarinic agents are available, including darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine, and trospium, that have similar efficacy and safety profiles; however, conclusions regarding comparative effectiveness and safety are limited by the lack of high-quality evidence from head-to-head trials between specific agents. • Antimuscarinic medications also were associated with significant discontinuation rates because of bothersome adverse effects, with dry mouth as the most frequently reported adverse event. • Compared with antimuscarinic treatment, intravesical onabotulinumtoxinA results in similar reduction of incontinence episodes, and more patients report complete resolution of incontinence. Thus, intradetrusor onabotulinumtoxinA may be a treatment option for overactive bladder in appropriate patients, and consideration of its use requires shared decision making between the patient and physician. • Systemic estrogen therapy, with or without progesterone, does not appear to be effective in the prevention or treatment of urinary incontinence; several large trials of hormone therapy have found an increased occurrence of stress incontinence in users of hormone therapy (estrogen alone or combined with progesterone). Locally administered (vaginal) estrogen, however, may be of some benefit in decreasing urinary incontinence.
European Association of Urology/European Society for Pediatric Urology: **Guidelines on Pediatric Urology: Management of Neurogenic Bladder in Children (2023)**[4]	Medical therapy • Antimuscarinic/anticholinergic medication reduces/prevents detrusor overactivity and lowers intravesical pressure. • Oxybutynin is the most frequently used in children with neurogenic bladder with a success rate of up to 93%. Dose-dependent side-effects (such as dry mouth, facial flushing, blurred vision heat intolerance etc.) limit its use. • Tolterodine, solifenacin, fesoterodine, trospium chloride and propiverine and their combinations can also be used in children. • Early prophylactic treatment with anticholinergics showed a lower rate of renal deterioration as well as a lower rate of progression to bladder augmentation. • Beta-3 agonists like mirabegron as an adjuvant treatment has been shown to be effective and safe in some recent studies of children (> five years) and adolescents. • Alpha-adrenergic antagonists may facilitate emptying in children with neurogenic bladder. Botulinum toxin injections • In neurogenic bladders that are refractory to anticholinergics, the off-label use of suburothelial or intramuscular injection of onabotulinum toxin A into the detrusor muscle is a treatment option. • Onabotulinum toxin A seems to be more effective in bladders with obvious detrusor muscle over-activity, whereas non-compliant bladders without obvious contractions are unlikely to respond. • Urethral sphincter onabotulinum toxin A injection has been shown to be effective in decreasing urethral resistance and improve voiding. The evidence is still too low to recommend its routine use in decreasing outlet resistance, but it could be considered as an alternative in refractory cases.
European Association of Urology: **Guidelines on Neuro-Urology**	• Use antimuscarinic therapy as the first-line medical treatment for neurogenic detrusor overactivity. Long-term efficacy and safety of antimuscarinic therapy for neurogenic detrusor overactivity (NDO) is well documented. • Prescribe α-blockers to decrease bladder outlet resistance.

Clinical Guideline	Recommendation(s)
(2022)[5]	• Do not prescribe parasympathomimetics for underactive detrusor. • Mirabegron does not improve urodynamic outcomes in NDO patients. • Maximize outcomes for NDO by considering combination therapy.

III.Indications

The Food and Drug Administration (FDA)-approved indications for the genitourinary smooth muscle relaxants 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 Genitourinary Smooth Muscle Relaxants: Antimuscarinics[6-16]

Indication	Darifenacin	Fesoterodine	Flavoxate	Oxybutynin	Solifenacin	Tolterodine	Trospium
Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency	✔	✔		✔ *†	✔	✔	✔
For symptomatic relief of dysuria, urgency, nocturia, suprapubic pain, frequency and incontinence as may occur in cystitis, prostatitis, urethritis, urethrocystitis and urethrotrigonitis			✔				
Relief of symptoms of bladder instability associated with voiding in patients with uninhibited neurogenic or reflex neurogenic bladder (i.e., urgency, frequency, urinary leakage, urge incontinence, dysuria)				✔ ‡			
Treatment of neurogenic detrusor overactivity in pediatric patients six years of age and older with a body weight greater than 25 kg		✔					
Treatment of neurogenic detrusor overactivity in pediatric patients aged two years and older					✔ ^		
Treatment of pediatric patients aged six years and older with symptoms of detrusor overactivity associated with a neurological condition (e.g., spina bifida)				✔ †			

*Transdermal formulations.
† Extended-release oral formulation.
‡Immediate-release oral formulation.
^Oral suspension formulation.

IV.Pharmacokinetics

The pharmacokinetic parameters of the genitourinary smooth muscle relaxants are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Genitourinary Smooth Muscle Relaxants: Antimuscarinics[7]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Darifenacin	15 to 25	98	Liver; Intestinal wall	Renal (60) Feces (40)	13 to 19
Fesoterodine	52	50	Liver	Renal (70) Feces (7)	4 to 7
Flavoxate	Not reported	Not reported	Not reported	Renal (57)	Not reported
Oxybutynin	IR: 6 ER: 156 to 187 (compared to IR)	>99	Liver; Intestinal wall	Renal (<0.1)	Gel: 30 ER: 13.2 IR: 2.0 to 3.0 Patch: 7 to 8
Solifenacin	90	98	Liver	Renal (3 to 6) Feces (22.5)	40 to 68
Tolterodine	IR: 77	Not reported	Liver	Renal (77) Feces (17)	1.9 to 3.7
Trospium	IR: 9.6	IR: 50 to 85 ER:48 to 78	Liver	Renal (5.8) Feces (85.2)	IR: 18.3 ER: 35

ER=extended-release formulation, IR=immediate-release formulation

V.Drug Interactions

Major drug interactions with the genitourinary smooth muscle relaxants are listed in Table 5.

Table 5. Major Drug Interactions with the Genitourinary Smooth Muscle Relaxants: Antimuscarinics[7]

Generic Name(s)	Interaction	Mechanism
Genitourinary smooth muscle relaxants (darifenacin, solifenacin)	Thioridazine	Coadministration may have additive effects on the prolongation of the QT interval.
Genitourinary smooth muscle relaxants (darifenacin, fesoterodine, flavoxate, oxybutynin, solifenacin, tolterodine, trospium)	Potassium preparations	Antimuscarinic agents may slow gastrointestinal motility and cause delay in tablet passage through the gastrointestinal tract.
Genitourinary smooth muscle relaxants (fesoterodine, solifenacin, tolterodine)	Imidazoles	Inhibition of cytochrome P450 3A4 by imidazoles may decrease the metabolic elimination of genitourinary smooth muscle relaxants. Plasma concentrations and pharmacologic effects of genitourinary smooth muscle relaxants may be increased.
Genitourinary smooth muscle relaxants (fesoterodine, solifenacin, tolterodine)	Macrolides	Inhibition of cytochrome P450 3A4 by macrolides may decrease the metabolic elimination of genitourinary smooth muscle relaxants. Plasma concentrations and pharmacologic effects of genitourinary smooth muscle relaxants may be increased.
Genitourinary smooth muscle relaxants (fesoterodine, solifenacin, tolterodine)	Protease inhibitors	Inhibition of cytochrome P450 3A4 by protease inhibitors may decrease the metabolic elimination of genitourinary smooth muscle relaxants. Plasma concentrations and pharmacologic effects of genitourinary smooth muscle relaxants may be increased.

Generic Name(s)	Interaction	Mechanism
Genitourinary smooth muscle relaxants (solifenacin, tolterodine)	Nefazodone	Inhibition of cytochrome P450 3A4 by nefazodone may decrease the metabolic elimination of genitourinary smooth muscle relaxants. Plasma concentrations and pharmacologic effects of genitourinary smooth muscle relaxants may be increased.
Genitourinary smooth muscle relaxants (darifenacin)	Desipramine, imipramine	Concurrent use may result in increased desipramine/imipramine exposure and potentially increased adverse effects. Probable mechanism is the competitive inhibition of CYP2D6-mediated desipramine/imipramine metabolism.
Genitourinary smooth muscle relaxants (darifenacin)	Flecainide	Concurrent use of darifenacin and flecainide may result in increased flecainide exposure with an increased risk of cardiac arrhythmias.

VI.Adverse Drug Events

The most common adverse drug events reported with the genitourinary smooth muscle relaxants are listed in Table 6.

Table 6. Adverse Drug Events (%) Reported with the Genitourinary Smooth Muscle Relaxants: Antimuscarinics[6-16]

Adverse Events	Darifenacin	Fesoterodine	Flavoxate	Oxybutynin (Oral)	Oxybutynin (Transdermal)	Solifenacin	Tolterodine	Trospium
Cardiovascular								
Arrhythmia	-	-	-	1 to 5		-	-	<1
Atrial fibrillation	✔	-	-	-	-	-	-	-
Chest pain	-	✔	-	1 to 5	✔ §	-	2	✔
Hypertension	≥1	-	-	1 to 5	-	≤1	-	✔
Hypotension	-	-	-	1 to 5	-	-	-	-
Myocarditis	-	-	-	-	✔ §	-	-	-
Palpitations	✔	✔	✔	1 to 5	-	-	✔	✔
Peripheral edema	≥1	1	-	1 to 5	-	-	✔	-
QT_c prolongation	-	✔	-	1 to 5	-	✔	-	-
Supraventricular tachycardia	-	-	-	-	-	-	-	✔
Syncope	-	-	-	-	-	-	-	✔
T-wave inversion	-	-	-	-	-	-	-	✔
Tachycardia	✔	✔	✔	1 to 5	✔ §	-	✔	1 to 2
Torsade de pointes	-	-	-	-	-	✔	-	-
Central Nervous System								
Agitation	-	-	-	1 to 5	-	-	-	-
Anxiety	-	-	-	-	-	-	1†	-
Confusion	✔	-	✔	-	-	✔	✔	-
Delirium	✔	-	-	-	-	-	-	✔
Depression	-	-	-	1 to 5	-	≤1	-	-
Disorientation	-	-	-	-	-	-	✔	-
Dizziness	1 to 2	-	-	4 to17	2 to 3‡	≤1	2†, 5γ	-
Drowsiness	-	-	✔	6 to 14	-	-	-	-
Dysphonia	✔	-	-	✔	-	-	-	-
Fatigue	-	-	✔	1 to 5	2‡	1 to 2	2†, 4γ	2
Hallucinations	✔	-	-	1 to 5	✔ §	✔	✔	✔
Headache	7	-	✔	6 to 10	2‡	3 to 6	7†, 6γ	4 to 7
Heat prostration	-	✔	-	-	-	-	-	-
Hyperpyrexia	-	-	✔	-	-	-	-	-
Insomnia	-	1	-	1 to 6	-	-	-	-

Adverse Events	Darifenacin	Fesoterodine	Flavoxate	Oxybutynin (Oral)	Oxybutynin (Transdermal)	Solifenacin	Tolterodine	Trospium
Memory impairment	-	-	-	1 to 5	-	-	✔	-
Nervousness	-	-	✔	1 to 7	-	-	-	-
Psychotic disorder	-	-	-	1 to 5	-	-	-	-
Seizure	-	-	-	1 to 5	-	-	-	-
Somnolence	✔	-	✔	2 to 14	-	-	3	✔
Vertigo	-	-	✔	-	-	-	5γ	-
Dermatological								
Application site reaction	-	-	-	-	5‡, 17§	-	-	-
Dermatitis	-	-	-	-	5‡	-	-	-
Dry skin	≥1	-	-	1 to 5	-	-	1γ	✔
Erythema	-	-	-	✔	5‡, 6 to 8§	✔	-	-
Flushing	-	-	-	1 to 5	-	-	-	-
Irritation	-	-	-	-	5‡	-	-	-
Papules	-	-	-	-	5‡	-	-	-
Pruritus	≥1	-	-	1 to 5	1 to 5‡, 14§	✔	-	-
Rash	≥1	≤1	✔	1 to 5	3§	✔	-	✔
Stevens-Johnson syndrome	-	-	-	-	-	-	✔	✔
Sweating decreased	-	-	-	1 to 5	✔ §	-	-	-
Urticaria	-	-	✔	-	-	✔	-	-
Vesicles	-	-	-	-	3§	-	-	-
Gastrointestinal								
Abdominal pain	2 to 4	1	-	1 to 5	-	1 to 2	4†, 5γ	1 to 3
Anorexia	-	-	-	✔	-	-	-	-
Aptyalism	-	-	-	1 to 5	-	-	-	-
Constipation	15 to 21	4 to 6	✔	7 to 15	1‡, 3§	5 to 13	6†, 7γ	9 to 10
Diarrhea	1 to 2	-	-	1 to 9	3§	-	✔	-
Diverticulitis	-	<1	-	-	-	-	-	-
Dysgeusia	-	-	-	1 to 5	-	-	-	-
Dyspepsia	3 to 8	2	-	5 to 7	-	1 to 4	3†, 4γ	1 to 2
Dysphagia	-	-	-	1 to 5	-	-	-	-
Eructation	-	-	-	1 to 5	-	-	-	-
Fecal impaction	-	-	-	-	-	✔	-	-
Feces hard	-	-	-	-	-	-	-	✔
Flatulence	-	-	-	1 to 5	-	-	-	1 to 2
Gastritis	-	-	-	-	-	-	-	✔
Gastroenteritis	-	<1	-	-	2‡	-	-	-

Adverse Events	Darifenacin	Fesoterodine	Flavoxate	Oxybutynin (Oral)	Oxybutynin (Transdermal)	Solifenacin	Tolterodine	Trospium
Gastrointestinal obstruction	-	-	-	-	-	✔	-	-
Gastroesophageal reflux disease	✔	-	-	1 to 5	-	-	-	-
Gastrointestinal motility decreased	-	-	-	1 to 5	-	-	-	-
Hoarseness	-	-	-	1 to 5	-	-	-	-
Irritable bowel syndrome	-	<1	-	-	-	-	-	-
Loose stools	-	-	-	1 to 5	-	-	-	-
Nausea	2 to 4	1 to 2	✔	2 to 12	-	2 to 3	-	≤1
Taste abnormality	-	-	-	1 to 5	-	-	-	✔
Thirst	-	-	-	1 to 5	-	-	-	-
Tongue coated	-	-	-	1 to 5	-	-	-	-
Vomiting	≥1	-	✔	1 to 5	-	≤1	-	✔
Weight gain	≥1	-	-	-	-	-	1	-
Xerostomia	19 to 35	19 to 35	✔	29 to 71	7 to 8‡, 4 to 10§	11 to 28	23†, 35γ	10 to 22
Genitourinary								
Cystitis	-	-	-	1 to 5	-	-	-	-
Dysuria	-	1 to 2	✔	1 to 5	2§	-	1†, 2γ	-
Impotence	-	-	-	1 to 5	✔ §	-	-	-
Pollakiuria	-	-	-	1 to 5	-	-	-	-
Urinary retention	✔	1 to 2	-	6	-	≤1	-	≤1
Urinary tract infection	4 to 5	2 to 4	-	5 to 7	7‡	3 to 5	-	1 to 7
Vaginitis	≥1	-	-	-	-	-	-	-
Hepatic								
Alanine transaminase increased	✔	≤1	-	-	-	-	-	-
Gamma-glutamyl transferase increased	-	≤1	-	-	-	-	-	-
Musculoskeletal								
Arthralgia	≥1	-	-	1 to 5	-	-	2	-
Back pain	≥1	1 to 2	-	1 to 5	-	-	-	✔
Rhabdomyolysis	-	-	-	-	-	-	-	✔
Weakness	<3	-	-	3 to 7	-	-	-	-
Respiratory								
Asthma	-	-	-	1 to 5	-	-	-	-
Bronchitis	≥1	-	-	1 to 5	-	-	-	-
Cough	-	1 to 2	-	1 to 5	-	≤1	-	-
Dry throat	-	1 to 2	✔	1 to 5	-	-	-	-
Nasal congestion	-	-	-	1 to 5	-	-	-	-

Adverse Events	Darifenacin	Fesoterodine	Flavoxate	Oxybutynin (Oral)	Oxybutynin (Transdermal)	Solifenacin	Tolterodine	Trospium
Nasal dryness	-	-	-	1 to 5	-	-	-	1
Nasopharyngitis	-	-	-	1 to 5	3‡	-	-	3
Pharyngitis	≥1	-	-	-	-	-	-	-
Rhinitis	≥1	-	-	2 to 6	-	-	-	-
Sinus congestion	-	-	-	1 to 5	-	-	-	-
Sinus headache	-	-	-	1 to 5	-	-	-	-
Sinusitis	≥1	-	-	1 to 5	-	-	2†	-
Upper respiratory tract infection	-	2 to 3	-	1 to 5	-	-	-	-
Special Senses								
Abnormal vision	≥1	-	-	-	-	-	1†, 2γ	-
Blurred vision	-	✔	✔	1 to 10	-	4 to 5	-	1
Cycloplegia	-	-	-	1 to 5	✔ §	-	-	-
Dry eyes	1.5 to 2.0	1 to 4	-	3 to 6	-	≤2	3	1 to 2
Eye irritation	-	-	-	1 to 5	-	-	-	-
Intraocular pressure increased	✔	-	✔	-	-	-	-	-
Keratoconjunctivitis sicca	-	-	-	1 to 5	-	-	-	-
Mydriasis	-	-	-	1 to 5	-	-	-	-
Vision changes	-	-	✔	-	3§	-	-	-
Other								
Anaphylactoid reactions	-	-	-	-	-	-	✔	-
Anaphylaxis	-	-	-	-	-	✔	-	✔
Angioedema	✔	-	-	✔	-	-	✔	-
Angioneurotic edema	-	-	-	✔	-	✔	-	✔
Edema	-	-	-	1 to 5	-	≤1	-	-
Extremity pain	-	-	-	1 to 5	-	-	-	-
Flank pain	-	-	-	1 to 5	-	-	-	-
Flu-like syndrome	1 to 3	-	-	-	-	-	3	-
Fungal infection	-	-	-	1 to 5	-	-	-	-
Hyperglycemia	-	-	-	1 to 5	-	-	-	-
Hyperkalemia	✔	-	-	-	-	-	-	-
Hypersensitivity	✔	-	-	-	-	✔	✔	-
Infection	-	-	-	-	-	-	1	-
Influenza	-	-	-	-	-	≤2	-	2
Lactation suppression	-	-	-	1 to 5	✔ §	-	-	-
Leukopenia	-	-	✔	-	-	-	-	-
Pain	≥1	-	-	1 to 7	-	-	-	-

Adverse Events	Darifenacin	Fesoterodine	Flavoxate	Oxybutynin (Oral)	Oxybutynin (Transdermal)	Solifenacin	Tolterodine	Trospium
Pharyngolaryngeal pain	-	-	-	1 to 5	-	-	-	-
Renal impairment	✔	-	-	-	-	-	-	-

✔ Percent not specified.
- Event not reported or incidence <1%.
†Extended-release formulation.
‡Transdermal gel formulation.
§Transdermal patch formulation.
γ Immediate-release formulation.

VII.Dosing and Administration

The usual dosing regimens for the genitourinary smooth muscle relaxants are listed in Table 7.

Table 7. Usual Dosing Regimens for the Genitourinary Smooth Muscle Relaxants: Antimuscarinics[6-16]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Darifenacin	Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and frequency: Tablet (ER): 7.5 to 15 mg once daily	Safety and efficacy in children have not been established.	Tablet (ER): 7.5 mg 15 mg
Fesoterodine	Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and frequency: Tablet (ER): 4 to 8 mg once daily	Treatment of neurogenic detrusor overactivity in pediatric patients ≥6 years of age and weighing >25 kg: Tablet (ER): for patients weighing 25 to 35 mg, 4 mg once daily with dosage increased to 8 mg if needed; for patients weighing >35 kg, 4 mg once daily with an increase to 8 mg once daily after one week	Tablet (ER): 4 mg 8 mg
Flavoxate	For symptomatic relief of dysuria, urgency, nocturia, suprapubic pain, frequency and incontinence as may occur in cystitis, prostatitis, urethritis, urethrocystitis and urethrotrigonitis: Tablet: 100 to 200 mg three or four times/day	For symptomatic relief of dysuria, urgency, nocturia, suprapubic pain, frequency and incontinence as may occur in cystitis, prostatitis, urethritis, urethrocystitis and urethrotrigonitis in patients ≥12 years of age: Tablet: 100 to 200 mg three or four times/day	Tablet: 100 mg
Oxybutynin	Relief of symptoms of bladder instability associated with voiding in patients with uninhibited neurogenic or reflex neurogenic bladder (i.e., urgency, frequency, urinary leakage, urge incontinence, dysuria): Tablet/syrup (IR): 5 mg two to three times/day; maximum, 5 mg four times/day Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and frequency: Tablet (ER): 5 to 10 mg once daily; maximum, 30 mg/day Transdermal gel in 10% packets: the contents of one sachet should be applied once daily	Relief of symptoms of bladder instability associated with voiding in patients with uninhibited neurogenic or reflex neurogenic bladder (i.e., urgency, frequency, urinary leakage, urge incontinence, dysuria) in patients ≥5 years of age: Tablet/syrup (IR): 5 mg twice daily; maximum, 5 mg three times daily Treatment of pediatric patients aged six years and older with symptoms of detrusor overactivity	Syrup: 5 mg/5 mL Tablet (ER): 5 mg 10 mg 15 mg Tablet (IR): 2.5 mg 5 mg Transdermal gel: 10% Transdermal patch: 3.9 mg/24 hours

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Transdermal patch: one 3.9 mg/day system applied twice weekly (every three to four days)	associated with a neurological condition (e.g., spina bifida): Tablet (ER): 5 mg once daily; maximum, 20 mg/day	
Solifenacin	Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and frequency: Oral suspension, tablet: 5 to 10 mg once daily	Treatment of neurogenic detrusor overactivity in pediatric patients ≥2 years of age: Oral suspension: 9 to 15 kg: Initial dose, 2 mg once daily; may titrate every 3 weeks to lowest effective dose. Maximum daily dose: 4 mg/day. >15 to 30 kg: Initial dose, 3 mg once daily; may titrate every 3 weeks to lowest effective dose. Maximum daily dose: 5 mg/day. >30 to 45 kg: Initial dose, 3 mg once daily; may titrate every 3 weeks to lowest effective dose. Maximum daily dose: 6 mg/day. >45 to 60 kg: Initial dose, 4 mg once daily; may titrate every 3 weeks to lowest effective dose. Maximum daily dose: 8 mg/day. >60 kg: Initial dose, 5 mg once daily; may titrate every 3 weeks to lowest effective dose. Maximum daily dose: 10 mg/day	Oral suspension: 1 mg/mL Tablet: 5 mg 10 mg
Tolterodine	Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and frequency: Capsule (ER): 4 mg once daily Tablet (IR): 2 mg twice daily	Safety and efficacy in children have not been established.	Capsule (ER): 2 mg 4 mg Tablet (IR): 1 mg 2 mg
Trospium	Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and frequency: Capsule (ER): 60 mg once daily Tablet (IR): 20 mg twice daily	Safety and efficacy in children have not been established.	Capsule (ER): 60 mg Tablet (IR): 20 mg

ER=extended-release, IR=immediate-release

VIII.Effectiveness

Clinical studies evaluating the safety and efficacy of the genitourinary smooth muscle relaxants are summarized in Table 8.

Table 8. Comparative Clinical Trials with the Genitourinary Smooth Muscle Relaxants: Antimuscarinics

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Buser et al.[24] (2008) Available antimuscarinic drugs at the time of the analysis, excluding drugs with less direct antimuscarinic effects (e.g., flavoxate)	MA Trials evaluating safety and efficacy in patients being treated for OAB	Efficacy comparison: N=38,662 (76 trials) Safety comparison: N=39,919 (90 trials)	Primary: Perception of cure or improvement, urgency episodes per 24 hours, leakage episodes per 24 hours, urgency incontinence episodes per 24 hours, micturitions per 24 hours, and nocturia episodes per 24 hours and safety outcomes Secondary: Not reported	Primary: 40 mg/day trospium chloride, 100 mg/g per day oxybutynin topical gel and 4 mg/day fesoterodine had the best efficacy, while higher dosages of orally administered oxybutynin and propiverine had the least favorable relationship of efficacy and adverse events. Secondary: Not reported
Chapple et al.[25] (2005) Darifenacin ER 7.5 to 15 mg once daily vs placebo	DB, PG, MC, RCT (Pooled analysis) Men and women ≥18 years of age with symptoms of OAB for ≥6 months, 5 to 50 episodes of incontinence/week, and a high voiding frequency (a mean of ≥8 voids/24 hours) and urgency	N=1,059 (3 trials) 12 weeks	Primary: Median change in the number of incontinence episodes/week Secondary: Number of significant leaks/week, voiding frequency, bladder capacity, frequency and severity of	Primary: The median change in weekly incontinence episodes from baseline was -8.8 (-68.4%) for darifenacin 7.5 mg and -10.6 (-76.8%) for darifenacin 15 mg compared to placebo (-53.8 and -58.3%; P=0.004 and P<0.001 vs placebo, respectively). Secondary: There was a decrease in the number of significant leaks (P<0.001), voiding frequency (P<0.001), number/severity of urgency episodes (P<0.001), and an increase in bladder capacity (P<0.001) with both doses of darifenacin compared to placebo.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	(a mean of ≥1 episode/24 hours)		urgency, number of nocturnal awakenings caused by OAB, responder rates, proportion of patients experiencing three or more dry days/week, or at least seven consecutive dry days, in the last two weeks of study treatment, adverse events	There was no difference in the number of nocturnal awakenings/week caused by OAB between the darifenacin and placebo groups (P=0.13 and P=0.06 for darifenacin 7.5 and 15 mg, respectively). The proportion of patients who achieved a ≥70% reduction from baseline in the number of incontinent episodes/week was 48% for 7.5 mg and 57% for 15 mg darifenacin, compared to 33 and 39% of patients in the placebo group (P<0.001). The proportion of patients who achieved a ≥90% reduction from baseline was 27 and 28% of patients in each of these groups, respectively, compared to 17% of patients in the placebo group (P<0.005). The OR for improvement compared to placebo were consistent for both doses across all responder rates analyzed (OR, 1.8 to 1.9 for 7.5 mg and 1.8 to 2.2 for 15 mg darifenacin; P<0.005). Responder rates for the reduction in urgency episodes also showed significant differences from placebo (P<0.05) for both doses of darifenacin at all levels of response (≥30%, ≥50%, ≥70%, ≥90%). The proportion of patients who attained a normal voiding frequency (<8 voids/day) after 12 weeks of treatment was significantly greater with both doses of darifenacin (7.5 mg, 34%; P=0.029 vs placebo; and 15 mg, 35%; P=0.007 vs placebo) than in the corresponding placebo groups (27 and 28%, respectively). Twenty-four percent of patients treated with darifenacin 15 mg were ‘dry’ for at least seven days, compared to 16% in the corresponding placebo group (P=0.011). More patients (55 and 61%) had ≥3 dry days/week in the darifenacin 7.5 and 15 mg groups, respectively, than in those taking placebo (43 and 48%, respectively; both P<0.001). The overall incidence of any cause was 54% with darifenacin 7.5 mg and 65.6% with 15 mg darifenacin compared to 48.7% with placebo. The most common all-cause adverse events were dry mouth and constipation, most of which were mild to moderate. The incidence of nervous system adverse events reported by patients taking 7.5 or 15 mg of darifenacin was comparable to placebo. The most common nervous system adverse events were central nervous system-related: dizziness (darifenacin 7.5 mg, 0.9%;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				15 mg, 2.1%; vs placebo 1.3%) and somnolence (0.3 and 0.9% vs 0.8%, respectively). The incidence of all-cause cardiovascular adverse events with darifenacin 7.5 mg (6.2%) or 15 mg (3.6%) was also comparable with that of placebo (2.3%).
Foote et al.[26] (2005) Darifenacin ER 7.5 to 15 mg once daily vs placebo	DB, MC, RCT (Pooled analysis) Men and women ≥65 years of age with symptoms of OAB for ≥6 months, 5 to 50 episodes of incontinence/week, and a high voiding frequency (a mean of ≥8 voids/24 hours) and urgency (a mean of ≥1 episode/24 hours)	N=317 (3 trials) 12 weeks	Primary: Median change in the number of incontinence episodes/week Secondary: Number of micturitions/24 hours, bladder capacity, number of urgency episodes per 24 hours, and adverse events	Primary: At week 12, the median reduction in the number of incontinence episodes/week was significantly greater for darifenacin 7.5 mg (-11.2; -66.7%) and darifenacin 15 mg (-10.8; 75.9%) compared to placebo (-4.8; -34.8 and -6.8; 44.8%, respectively; P<0.001). Secondary: There was a significant decrease in the frequency of micturition/24 hours (P<0.001) and urgency episodes (P<0.001), and increased bladder capacity (P<0.001) with both doses of darifenacin compared to placebo. Adverse events were reported by 53.6, 69.1 and 50.9% of patients treated with 7.5 mg darifenacin, 15 mg darifenacin or placebo. The most common treatment-related adverse events, dry mouth, constipation and dyspepsia. The incidence of nervous system and cardiovascular adverse events during darifenacin therapy was similar to that with placebo, and did not increase with increasing dose of darifenacin.
Haab et al.[27] (2006) Darifenacin ER 7.5 to 15 mg once daily	ES, MC, OL Men and women ≥65 years of age who had completed one of two RCTs (feeder studies) who had previously had symptoms of OAB for ≥6 months, 5 to 50 episodes of incontinence/week, and a high voiding frequency (a mean of ≥8 voids/24 hours) and urgency	N=716 2 years	Primary: Safety, tolerability and efficacy Secondary: Not reported	Primary: All-causality adverse events were reported by 80% of patients at some time during the two-year extension and resulted in discontinuation in 8.9% of patients. The most commonly reported adverse events were dry mouth and constipation (23.3 and 20.9%, respectively). There were no relevant changes in any bowel-habit variables from feeder-study end to ES end in the overall group. There were few treatment-related cardiovascular and nervous system adverse events; 0.4, 0.3 and 0.3% of patients reported hypertension, arrhythmias and tachycardia, respectively, while 0.4% of patients each reported hypertonia, somnolence and paresthesia.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	(a mean of ≥1 episode/24 hours)			Abnormal vision was reported in 0.6% of patients. No patient developed treatment-related glaucoma or reported worsening of a pre-existing glaucomatous condition. After 24 months of treatment with darifenacin, the median change from baseline of the feeder studies in incontinence episodes/week was -11.0 (84.4%), voids/24 hours was -1.4 (-13.9%), urgency episodes/24 hours was -3.9 (-56.4%), severity of urgency was -15.4 (-28.8%), nocturnal awakenings for OAB/week was -1.5 (-14.3%), and significant leaks/week was -4.7 (-100%). All variables were P<0.001 vs feeder study baseline. Overall, 62.3% of patients achieved a ≥70% reduction in incontinence episodes and 43.8% achieved a ≥90% reduction at two years. Secondary: Not reported
Hill et al.[28] (2007) Darifenacin ER 7.5 to 15 mg once daily	ES, MC, OL Men and women ≥18 years of age who had completed one of two RCTs (feeder studies) who had previously had symptoms of OAB for ≥6 months, 5 to 50 episodes of incontinence/week, and a high voiding frequency (a mean of ≥8 voids/24 hours) and urgency (a mean of ≥1 episode/24 hours)	N=214 2 years	Primary: Safety, tolerability and efficacy Secondary: Not reported	Primary: Dry mouth and constipation were the most common treatment-related (adverse events) adverse events in this older patient population (23.4 and 22.4%, respectively) and were associated with low discontinuation rates (2.3 and 4.2%, respectively). Treatment-related cardiovascular and peripheral/central nervous system adverse events were infrequently reported (1.4 and 3.3%, respectively). After 24 months of treatment with darifenacin, the median change from baseline of the feeder studies in incontinence episodes/week was -11.0 (83.7%), voids/24 hours was -1.2 (-12.4%), urgency episodes/24 hours was -3.7 (-52.0%), severity of urgency was -12.6 (-23.3%), nocturnal awakenings for OAB/week was -1.4 (-10.9%), and significant leaks/week was -4.9 (-100%). All variables were P<0.001 vs feeder study baseline. There were high proportions of responders by all definitions (≥50, ≥70 or ≥90% reductions in incontinence episodes/week), with 74.1%, 60.0% and 44.4%, patients age ≥65 years of age achieving these response levels at 24 months, respectively. Thirty-four percent of older patients experienced normalization of micturition (<8 micturitions/day) after three months of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				darifenacin treatment and this effect was maintained in approximately the same number of patients at the end of the two-year study (33.8%). Secondary: Not reported
But et al.[29] (2012) Darifenacin 7.5 mg once daily vs solifenacin 5 mg once daily	MC, OL, RCT Female patients with idiopathic OAB, defined as urgency intensity and urgency urinary incontinence of ≥3 on the UPS and frequency of ≥1 urgency episodes per day who have not received any anticholinergic drugs for at least 6 months	N=100 3 months	Primary: OAB symptoms Secondary: Changes in dose throughout the study, QOL scores, objective assessment of treatment improvement and safety evaluations.	Primary: Analyses of OAB symptoms at baseline were generally similar between the two treatment groups, although urgency (bothersome) scores were higher in the darifenacin group, and frequency scores were higher in the solifenacin group. Following one and three months of treatment, all measured OAB symptoms decreased, with no statistically significant treatment differences being seen between the groups. Nocturia decreased to a greater extent in the solifenacin group at one month and this group also used less incontinence pads than those in the darifenacin group at three months. Secondary: The majority of patients in the solifenacin group who completed the study maintained the same dose post-study (21/25 patients). However, in the darifenacin group only 11 patients who completed then maintained the same dose (11/24 patients). Patients treated with solifenacin indicated a greater improvement in QOL compared to patients treated with darifenacin. Overall patient subjective and objective assessment of treatment improvement was higher for solifenacin compared to darifenacin, with the difference again being statistically significant in favor of solifenacin (P=0.01). Adverse events of dry mouth, constipation, blurred vision, headache, dizziness, concentration problems, memory problems, and insomnia were solicited at the one month and three month assessments, as well as at baseline. Solifenacin showed statistically a decreased incidence of dry mouth after three months of treatment compared to the darifenacin group.
Zinner et al.[30] (2005)	DB, PC, RCT, XO	N=76	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Darifenacin ER 15 to 30 mg once daily vs oxybutynin IR 5 mg three times daily vs placebo	Patients 18 to 85 years of age with urge incontinence with ≥4 significant incontinent episodes/week (defined as leakage that would normally require a change of clothing or absorbent pad) and urinary frequency ≥8 voids/24 hours	2 weeks	Incontinence episodes/week, urgency episodes/day, severity of urgency episodes, and micturitions/day Secondary: Not reported	The mean number of incontinence episodes/week decreased from 20.4 to 10.93 with solifenacin 15 mg (P<0.05 vs placebo), 8.82 with solifenacin 30 mg (P<0.05 vs placebo), 9.45 with oxybutynin (P<0.05 vs placebo), and 14.64 with placebo. The mean number of urgency episodes/day decreased from 9.3 to 7.95 with solifenacin 15 mg (P<0.05 vs placebo), 7.59 with solifenacin 30 mg (P<0.05 vs placebo), 8.12 with oxybutynin (P<0.05 vs placebo), and 8.71 with placebo. The mean severity of urgency episodes decreased from 2.00 to 1.93 with solifenacin 15 mg (P<0.05 vs placebo), 1.84 with solifenacin 30 mg (P<0.05 vs placebo), 1.89 with oxybutynin (P<0.05 vs placebo), and 2.03 with placebo. The number of micturitions/day decreased from 10.4 to 9.93 with solifenacin 15 mg (P=NS vs placebo), 8.85 with solifenacin 30 mg (P<0.05 vs placebo), 9.24 with oxybutynin (P=NS vs placebo), and 9.62 with placebo. Dry mouth occurred in a similar percentage of patients receiving darifenacin 30 mg and oxybutynin, which was significantly higher than treatment with placebo or darifenacin 15 mg (P<0.05). There was no significant difference between darifenacin 15 mg and placebo. Constipation occurred more frequently with darifenacin and oxybutynin than placebo. There was no significant difference between darifenacin 15 mg and oxybutynin. Blurred vision and dizziness occurred in 3.3 and 1.6% of patients receiving oxybutynin, respectively. Secondary: Not reported
Chapple et al.[31] (2005) <u>Cohort 1</u> Darifenacin IR	DB, RCT, XO Patients 18 to 75 years of age with detrusor overactivity within	N=65 7 days	Primary: Urodynamic parameters, salivary flow, tolerability and safety	Primary: All urodynamic pressure parameters significantly decreased from baseline after seven days' therapy with each treatment. No significant differences between treatments were observed for any dose of darifenacin vs oxybutynin.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
2.5 mg three times daily for 7 days vs oxybutynin 2.5 mg three times daily for 7 days <u>Cohort 2</u> Darifenacin ER 15 mg once daily for 7 days vs oxybutynin 5 mg three times daily for 7 days <u>Cohort 3</u> Darifenacin ER 30 mg once daily for 7 days vs oxybutynin 5 mg three times daily for 7 days	the previous 6 months (either idiopathic or neurogenic with ≥2 associated symptoms (average of ≥7 micturitions per day, ≥7 episodes of urgency/week, ≥1 urge incontinence episode/week necessitating change of clothing or pads)		Secondary: Not reported	There were no differences between treatments in responder rates for any of the ambulatory urodynamic parameters. Reduction in salivary flow was significantly less with darifenacin ER (15 and 30 mg) than with oxybutynin (5 mg three times daily). Salivary flow was comparable for darifenacin IR (2.5 mg three times daily) and oxybutynin (2.5 mg three times daily). The mean maximum decrease in salivary flow from baseline to day seven was significantly greater with oxybutynin 5 mg three times daily than with darifenacin ER 15 mg (P<0.01). There were no differences in mean heart rate for darifenacin and oxybutynin on day seven. There were no significant differences with darifenacin and oxybutynin for visual nearpoint. The most common adverse events were dry mouth and constipation, which were generally mild or moderate in severity. Dry mouth was reported more frequently in oxybutynin-treated patients than in darifenacin-treated patients. Secondary: Not reported
Wyndaele et al.[32] (2009) Fesoterodine ER 4 to 8 mg once daily	MC, OL Men and women ≥18 years of age with self-reported OAB symptoms for ≥3 months, mean	N=516 12 weeks	Primary: Number of micturitions, number of UUI episodes, number of micturition-related urgency	Primary: The change from baseline to week 12 in the number of micturitions was -3.0 (-22%; P<0.0001), -1.7 for the number of UUI episodes (-100%; P<0.0001), and -5.0 for urgency episodes (-57%; P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	micturition frequency of ≥8 micturitions/24 hours, mean number of urgency episodes ≥3/24 hours, and treated with tolterodine or tolterodine ER for OAB within 2 years who reported being 'somewhat dissatisfied' or 'very dissatisfied' with tolterodine treatment on the TSQ		episodes/24 hours, and the percentage of patients reporting treatment satisfaction at week 12 ('very satisfied' or 'somewhat satisfied' on the TSQ) Secondary: Change from baseline to week 12 in nocturnal micturitions, severe micturition-related urgency episodes, frequency-urgency sum/24 hours, change from baseline in PPBC, UPS and OAB-q scores at week 12	At 12 weeks, 80% of patients who responded to the TSQ reported being satisfied with fesoterodine treatment, with 38.4% of patients being 'very satisfied' and 41.4% of patients being 'somewhat satisfied'. Secondary: The change from baseline to week 12 in the number of nocturnal micturitions was -0.8 (-31%; P<0.0001), -3.5 for severe urgency episodes (-94%; P<0.0001), and -15.2 for frequency-urgency sum/24 hours (P<0.0001). Mean PPBC scores improved from 4.9 at baseline to 3.1 at week 12 (P<0.0001). Mean UPS scores improved from 1.8 at baseline to 2.4 at week 12 (P<0.0001). The mean change in OAB-q Symptom Bother score (29-point improvement) from baseline to week 12 was statistically significant (P<0.0001). Mean changes in total HRQOL (26-point improvement) and all four HRQOL domain (Concern, 29-point improvement; Coping, 31-point improvement; Sleep, 25-point improvement; Social Interaction, 17-point improvement) scores were also significant at 12 weeks, compared to baseline (P<0.0001). The improvements for all scales and domains were above the minimally important difference of 10 points, indicating that these changes were clinically meaningful. Dry mouth (23%) and constipation (5%) were the most frequently reported adverse events.
Nitti et al.[33] (2007) Fesoterodine ER 4 to 8 mg once daily vs	DB, MC, PC, RCT Men and women ≥18 years of age with OAB syndrome for ≥6 months, urinary	N=836 12 weeks	Primary: Number of micturitions/24 hours, number of UUI episodes/24 hours and treatment response	Primary: The mean change from baseline in the number of micturitions/24 hours was significantly improved with fesoterodine 4 mg (-1.61, -14.9%; P<0.001) and fesoterodine 8 mg (-2.09, -16%; P<0.001) compared to placebo (-1.08, -6.9%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo	frequency (≥8 micturitions/24 hours) and urinary urgency (≥6 episodes during the 3-day diary period) or UUI		Secondary: Mean volume voided/micturition, daytime micturitions, nocturnal micturitions, urgency episodes/24 hours and continent days/week	The mean change from baseline in the number of UUI episodes/24 hours was significantly improved with fesoterodine 4 mg (-1.65, -67.4%; P<0.001) and fesoterodine 8 mg (-2.28, -81.8%; P<0.001) compared to placebo (-0.96, -40%). Subject-reported treatment response rates with fesoterodine 4 mg (64%) and fesoterodine 8 mg (74%) were significantly higher than those with placebo (45%) at study end point (P<0.001). Secondary: Fesoterodine 4 mg showed significant improvements in the mean change from baseline compared to placebo for the number of nocturnal micturitions (P<0.05), urgency episodes (P<0.001) and continent days/week (P<0.001). Fesoterodine 8 mg was significantly better than placebo for MVV/micturition, number of urgency episodes, number of daytime micturitions and continent days/week (each P<0.001). Treatment-emergent adverse events occurred in 55, 61 and 69% of patients receiving placebo, and 4 and 8 mg fesoterodine, respectively. Dry mouth was the most commonly reported adverse event. It was usually mild to moderate in severity and it occurred in 7, 16 and 36% of patients receiving placebo, and 4 and 8 mg fesoterodine, respectively.
Chapple et al.[34] (2014) EIGHT Fesoterodine 4 mg once daily vs fesoterodine 8 mg once daily vs	DB, MC, PC, RCT Patients ≥18 years of age with OAB symptoms including UUI	N=1955 12 weeks	Primary: Change from baseline to week 12 in UUI episodes per 24 hours Secondary: Changes in micturitions and urgency episodes per 24 hours, patient reported outcomes	Primary: Fesoterodine 8 mg treatment resulted in significantly greater improvements in the change from baseline in UUI episodes/24 hours at week 12 compared with placebo (P<0.001) and compared with fesoterodine 4 mg (P=0.011). Secondary: Patients receiving fesoterodine 8 mg also had significantly greater improvements in micturition frequency and urgency episodes/24 h than patients receiving placebo (both P<0.001) or fesoterodine 4 mg (both P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo				Improvements in scores on the PPBC, UPS, and all OAB-q scales and domains at week 12 were significantly greater with fesoterodine 8 mg compared with placebo (all P<0.001) and fesoterodine 4 mg (all P<0.01).
Kitta et al.[35] (2023) Fesoterodine 4 or 8 mg ER tablets vs oxybutynin XL tablets titrated to >10 mg/day	MC, OL, PG, RCT Patients six to <18 years old weighing >25 kg with stable neurologic disease and clinically or urodynamically proven neurogenic detrusor overactivity	N=124 12-week active comparator-controlled phase	Primary: Mean change from baseline in maximum cystometric bladder capacity (MCC) at Week 12 Secondary: Detrusor pressure at maximum bladder capacity; presence of involuntary detrusor contractions; bladder compliance; micturitions; incontinence episodes	Primary: At Week 12, fesoterodine 4 mg and 8 mg and oxybutynin treatment resulted in significant improvements (increases) in MCC from baseline (4 mg, P=0.001; 8 mg, P<0.001; oxybutynin, P<0.001). MCC improvement was numerically higher for fesoterodine 8 versus 4 mg; similar magnitudes of MCC improvement were observed for fesoterodine 8 mg and oxybutynin. Secondary: Significant improvements from baseline following fesoterodine 4- and 8-mg treatment were observed for bladder volume at first involuntary detrusor contraction and mean number of incontinence episodes per 24 hours. Significant improvements from baseline following oxybutynin treatment were seen for bladder volume at first involuntary detrusor contraction, bladder compliance, and mean number of incontinence episodes per 24 hours.
Chapple et al.[36] (2007) Fesoterodine ER 4 to 8 mg once daily vs tolterodine ER 4 mg once daily vs	AC, DB, PC, RCT Men and women ≥18 years of age with a medical history of OAB symptoms with urinary urgency for ≥6 months, ≥8 micturitions/24 hours, and either ≥6 urgency episodes or ≥3 UUI/24 hours,	N=1,135 12 weeks	Primary: Micturitions/24 hours and treatment response Secondary: Mean volume voided/micturition, daytime micturitions/24 hours, nocturnal micturitions/24 hours, urgency	Primary: The mean number of micturitions/24 hours was significantly reduced from baseline in patients receiving tolterodine (-1.73, -13.8%; P=0.001 vs placebo), fesoterodine 4 mg (-1.76, -16.7%; P<0.001 vs placebo), and fesoterodine 8 mg (-1.88, -18.6%; P<0.001 vs placebo). Treatment with tolterodine resulted in significantly greater proportion of patients who responded to treatment compared to placebo (P<0.001). The proportion of patients reporting a positive treatment response was significantly greater among patients receiving tolterodine (72%; P<0.001) fesoterodine 4 mg (75%; P<0.001) and fesoterodine 8 mg (79%; P<0.001) compared to placebo (53%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo	and self-reported perception of moderate problems using a Likert scale		episodes/24 hours, continent days/week, adverse events	The mean reduction from baseline in UUI episodes/24 hours was significantly greater for patients receiving tolterodine (-1.74, -70%; P=0.008 vs placebo), fesoterodine 4 mg (-1.95, -80%; P=0.001 vs placebo), and fesoterodine 8 mg (-2.22, -87.5%; P<0.001 vs placebo). Secondary: Active treatment significantly increased MVV from baseline (P≤0.002) compared to placebo. The increases in MVV were 2.5, 3.0, and 3.6 times greater than placebo in the patients receiving tolterodine, fesoterodine 4 mg, or fesoterodine 8 mg, respectively. The mean number of daytime micturitions/24 hours was significantly reduced from baseline in patients receiving tolterodine (-1.35, -13.6%; P=0.003), fesoterodine 4 mg (-1.37, -14.3%; P=0.001), and fesoterodine 8 mg (-1.48, -16.9%; P<0.001) compared to placebo (-0.60, -9.5%). The mean number of nocturnal micturitions/24 hours did not differ significantly from placebo in patients receiving tolterodine (-0.40, -25%; P=0.815), fesoterodine 4 mg (-0.39, -28.6%; P=0.982), and fesoterodine 8 mg (-0.39, -23.1%; P<0.896). The mean number of urgency episodes/24 hours was significantly reduced from baseline in patients receiving tolterodine (-2.03, -16%; P=0.004), fesoterodine 4 mg (-1.88, -17.6%; P=0.002), and fesoterodine 8 mg (-2.36, -19.1%; P<0.001) compared to placebo (-1.07, -11.1%). Significant improvements in change from baseline compared to placebo in number of continent days/week were observed in patients receiving fesoterodine 4 or 8 mg. The most frequent adverse event was dry mouth, which was mild to moderate in most patients; however, 3% of patients receiving fesoterodine 8 mg reported severe dry mouth.
Chapple et al.[37] (2008) Fesoterodine ER	AC, DB, PC, RCT (Post-hoc analysis)	N=1,135 12 weeks	Primary: Number of micturitions/24	Primary: There was no significant difference in the number of micturitions/24 hours or rate of treatment response reported with tolterodine 4 or fesoterodine 8 mg.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
4 to 8 mg once daily vs tolterodine ER 4 mg once daily vs placebo Only the results of fesoterodine ER 8 mg vs tolterodine ER 4 mg are reported.	Men and women ≥18 years of age with a medical history of OAB symptoms with urinary urgency for ≥6 months, ≥8 micturitions/24 hours, and either ≥6 urgency episodes or ≥3 UUI/24 hours, and self-reported perception of moderate problems using a Likert scale		hours and treatment response Secondary: Mean volume voided/micturition, urgency episodes/24 hours, continent days/week, HRQOL (KHQ and ICIQ-SF), adverse events	Fesoterodine 8 mg led to a significant improvement in UUI episodes/24 hours compared to tolterodine 4 mg in 'incontinent patients' (P<0.001). Secondary: Fesoterodine 8 mg led to a significant improvement in MVV/void in 'all patients' and 'incontinent patients' compared to tolterodine (P<0.05). Fesoterodine 8 mg led to a significant improvement in continent days/week (P<0.05) and severe urgency episodes/24 hours (P<0.05) in 'incontinent patients' compared to tolterodine 4 mg. There was no significant difference in the median percent change in number of urgency episodes/24 hours reported in 'all patients' and 'incontinent patients' with fesoterodine 8 mg or tolterodine 4 mg. Scores from the KHQ and ICIQ-SF showed a significant improvement in HRQOL for the groups treated with fesoterodine 8 mg and tolterodine 4 vs placebo. The fesoterodine 8 mg dose produced significant improvements on eight of the nine domains assessed compared to placebo. Tolterodine-treated patients reported significant improvements in six of nine KHQ domains compared to placebo. Both fesoterodine 8 mg and tolterodine 4 mg treatment resulted in a ≥5-point improvement from baseline (which constitutes a meaningful change for the patient) for all domains except General Health. A major improvement in the severity of bladder-related problems from baseline to the end of treatment was reported by 39% of fesoterodine 8 mg and 34% of tolterodine 4 patients (P=0.01 for both groups vs placebo), compared to 25% on placebo. Adverse events reported in ≥2% of patients in the active-treatment groups and occurring more frequently than placebo included dry mouth, constipation, dry eye, dry throat, and elevated levels of alanine aminotransferase. More patients treated with fesoterodine 8 mg had dry mouth than those receiving tolterodine 4 mg or placebo. Most cases of dry mouth were mild or moderate; 3% of patients on fesoterodine 8 mg reported severe dry mouth. More patients on fesoterodine 8 mg reported constipation than those receiving tolterodine 4 or placebo; most cases were

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				mild to moderate. Overall, 3.2% of patients discontinued the study prematurely because of an adverse event: placebo, 2%; tolterodine 4 mg, 3%; fesoterodine 8 mg, 5%.
Ginsberg et al.[38] (2013) Fesoterodine ER 4 mg once daily for 1 week, then 8 mg once daily vs tolterodine ER 4 mg once daily vs placebo	DB, DD, RCT Men and women ≥18 years of age with a medical history of OAB symptoms with self-reported symptoms ≥3 months in 3-day baseline diaries and had ≥8 micturitions and ≥1 UUI episode per 24 hours	N=4,129 Two 12-week studies	Primary: Change from baseline to week 12 in UUI episodes Secondary: Changes from baseline in three-day bladder diary variables, scores from the PPBC, UPS, and OAB-q, diary-dry rate, proportion of subjects with >0 UUI episodes according to baseline diary and no UUI episodes according to post-baseline diary and safety evaluations	Primary: At week 12, women showed significantly greater improvement with fesoterodine than with ER tolterodine (-1.9 vs -1.7; P≤0.007) and placebo (-1.9 vs -1.6; P≤0.001) in UUI episodes. In men, there were no significant differences in improvement in UUI episodes between any treatment groups at week 12 (-1.4 for all groups; P>0.05 for both comparisons). Secondary: At week 12, women showed significantly greater improvement with fesoterodine 8 mg than with ER tolterodine 4 mg and placebo in micturition frequency, urgency episodes, and all other diary endpoints (except nocturnal micturitions vs ER tolterodine), and also in scores on the PPBC, UPS, and all OAB-q scales and domains (all P<0.005). Improvements in men were significantly greater with fesoterodine than with ER tolterodine for severe urgency and the OAB-q Symptom Bother domain and were also significantly greater with fesoterodine than with placebo for micturition frequency, urgency episodes, severe urgency episodes, PPBC responses and scores on all OAB-q scales and domains at week 12 (all P<0.04). The most frequently reported treatment-emergent adverse events in both genders were dry mouth (women: fesoterodine, 29%; ER tolterodine, 15%; placebo, 6%; men: fesoterodine, 21%; ER tolterodine, 13%; placebo, 5%) and constipation (women: fesoterodine, 5%; ER tolterodine, 4%; placebo, 2%; men: fesoterodine, 5%; ER tolterodine, 3%; placebo, 1%).
Van Kerrebroeck et al.[39] (2010) Fesoterodine ER 4 to 8 mg once daily	ES, OL Men and women ≥18 years of age with a medical history of OAB	N=417 24 to 32 months	Primary: Safety and tolerability Secondary:	Primary: A total of 161 patients (39%) discontinued treatment before or at the 24-month study visit. Primary reasons for discontinuation were adverse events (n=47), withdrawal of consent (n=46), and insufficient clinical response (n=36).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	symptoms with urinary urgency for ≥6 months, ≥8 micturitions/24 hours, and either ≥6 urgency episodes or ≥3 UUI/24 hours, and self-reported perception of moderate problems using a Likert scale		Bladder diary variables and PROs	A total of 264 patients (63%) received fesoterodine for ≥24 months during the DB and the OL extension phases. Patients received the higher fesoterodine 8 mg dose for an average of 80% of their respective treatment days during OL extension. A total of 315 patients (76%) experienced at least one treatment emergent adverse event, of which 219 cases were related to fesoterodine. The most common treatment emergent adverse events were dry mouth (34%), constipation (7%), and UTI (15%). Overall, ≥88% of patients rated treatment tolerance with fesoterodine "good" or "excellent" at months four, 12, and 24. Secondary: Compared to OL baseline, there were significant mean improvements in all diary variables throughout the 24-month extension (all P<0.001). Diary variables included UUI episodes per 24 hours, micturitions per 24 hours, urgency episodes per 24 hours, and MVV per micturition. There were significant improvements in all KHQ domains (P≤0.002), except for general health perception at months 12 and 24. Changes in mean scores typically exceeded the minimally important difference of 5. There were significant mean improvements in ICIQ-SF scores at months four, 12, and 24 (P<0.0001 for all). In the overall population, patient-reported treatment satisfaction was 97% at month 24.
Scarpero et al.[40] (2011) Fesoterodine ER 4 to 8 mg once daily	ES, OL (Pooled analysis) Men and women ≥18 years of age with OAB syndrome for ≥6 months, urinary frequency (≥8	N=890 (2 trials) 24 to 36 months	Primary: Safety and tolerability Secondary: Bladder diary entries (number of UUI episodes,	Primary: Overall, 55% of men (n=102) and 50% of women (n=349) discontinued treatment within the first 24 months of the OL extension. The most common reasons for discontinuation in men and women were insufficient clinical response (16 and 13%), adverse events (16 and 12%), and withdrawal of consent (14 and 13%). Both men and women were treated with the higher 8 mg dose for the majority of days on OL fesoterodine (89 and 83%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	micturitions/24 hours) and urinary urgency (≥6 episodes during the 3-day diary period) or UUI		micturitions, and urgency episodes	A total of 539 women (77%) and 140 men (76%) experienced ≥1 treatment emergent adverse event. A total of 351 women (50%) and 86 men (47%) experienced ≥1 treatment emergent adverse event that were determined to be related to fesoterodine. The most commonly reported treatment emergent adverse events in men were dry mouth (24%) and constipation (6%), compared to dry mouth (32%) and UTI (18%) in women. The majority of men and women (≥92 and ≥91%, respectively) reported "good" or "excellent" treatment tolerance at months four, 12, and 24. Secondary: Among women, improvements in all diary variables (mean UUI episodes per 24 hours, micturitions per 24 hours, urgency episodes per 24 hours, and MVV per micturition) were significant at each time point during OL treatment compared to both DB baseline (P<0.0001) and OL baseline (P<0.0001). Among men, improvements in all diary variables were significant at each time point during OL treatment compared to DB baseline (P<0.05). Improvements in micturitions and urgency episodes per 24 hours were significant at months one, four, eight, and 12 compared to OL baseline (P<0.05). At month 24, there were no statistically significant differences from OL baseline for any diary variable.
Kelleher et al.[41] (2008) Fesoterodine ER 4 to 8 mg once daily vs tolterodine ER 4 mg once daily vs	DB, MC, PC, RCT (Pooled analysis) Men and women ≥18 years of age with OAB syndrome for ≥6 months	N=1,971 (2 trials) 12 weeks	Primary: Treatment-related effects on HRQOL using the KHQ (disease-specific questionnaire to assess LUTS), ICIQ-SF (questionnaire to evaluate patients with UI including	Primary: The fesoterodine 8 mg group had statistically significant improvements over placebo in eight of nine KHQ domains. Fesoterodine 4 mg and tolterodine showed statistically significant improvements over placebo in seven of nine domains of the KHQ. Fesoterodine 8 mg led to better results than 4 mg in two domains (Emotions and Severity/Coping; P<0.05). There were no significant differences between fesoterodine 8 mg and tolterodine 4 mg. In all treatment groups, all but one KHQ domain (General Health) showed improvements meaningful to the patient (i.e., changes of ≥5 points from baseline).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo			urinary frequency, urine leakage and perceived impact of these symptoms on patients' daily lives) and a six-point Likert Scale used by patients to rate the severity of problems related to their bladder condition, and treatment response Secondary: Not reported	All active-treatment groups reported a significant improvement in the ICIQ-SF score vs placebo (P<0.001). There were no significant differences between active treatment groups. Baseline scores for the six-point Likert scale were 3.6, which indicates moderate to severe problems. At the end of the study, the scores were 2.3 to 2.8, which indicate minor problems. The percentage of patients reporting scores of 1 to 3 was <1% at baseline and increased after 12 weeks. There was also a similar change in scores with placebo. A major improvement in bladder condition (i.e., ≥2-point change) was reported by 33% of patients on fesoterodine 4 mg, 38% on fesoterodine 8 mg, and 34% on tolterodine compared to 21% on placebo (P<0.001). The percentage of patients reporting a positive treatment response was significantly higher in those receiving fesoterodine than those receiving placebo. There were significant differences between the doses in favor of fesoterodine 8 mg at two weeks and 12 weeks. Secondary: Not reported
Herschorn et al.[42] (2010) Fesoterodine ER 4 to 8 mg once daily vs tolterodine ER 4 mg once daily vs placebo	DB, MC, PC, RCT Men and women ≥18 years of age with symptoms of OAB for ≥3 months	N=1,697 12 weeks	Primary: Changes from baseline to week 12 in UUI episodes Secondary: Total and nocturnal voids, urgency episodes, severe urgency episodes, frequency-urgency sum per 24 hours, and MVV per void, UPS, OAB-q, and PPBC	Primary: The mean reduction in the number of UUI episodes/24 hours was significantly greater in the fesoterodine group than in the tolterodine group (P=0.017) and placebo group (P<0.001). The median percentage reduction in UUI episodes was 100% for fesoterodine. Tolterodine ER also produced a significantly greater improvement in UUI episodes than placebo (P=0.011). The diary-dry rate at week 12 was significantly greater for patients receiving fesoterodine than for those receiving tolterodine ER (64 vs 57.2%; P=0.015) or placebo (45%; P<0.001). The difference between tolterodine ER and placebo in diary-dry rate was also significant (P<0.001). Secondary: Fesoterodine produced a significantly greater increase in MVV per void than tolterodine ER (P=0.005) or placebo (P<0.001). Compared to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				placebo, fesoterodine also significantly reduced voids, urgency episodes, severe urgency episodes, and frequency-urgency sum per 24 hour (all P<0.001 vs placebo). Fesoterodine did not significantly improve nocturnal voids (P=0.327). Compared to tolterodine ER, total voiding, urgency episodes, severe urgency episodes, and frequency-urgency sum per 24 hours were not statistically different. Compared to placebo, tolterodine ER significantly improved total voids, urgency episodes, severe urgency episodes, and frequency-sum per 24 hours (all P<0.001). The categorical change in PPBC score was significantly more favorable in the fesoterodine group than in patients on placebo (P<0.001) and tolterodine ER (P<0.001). The change between tolterodine ER and placebo was also significant (P<0.001). The categorical change in UPS was significantly more favorable for fesoterodine than placebo (P<0.001) and tolterodine (P=0.014). The difference between tolterodine ER and placebo was NS. Improvements in the OAB-q scores were significantly greater in the fesoterodine than the placebo group on the Symptom Brother scale, total HRQOL scale, and all four HRQOL domains (all P<0.001). In a post-hoc analysis, improvements with fesoterodine were also significantly greater than tolterodine ER on the Symptom Bother (P<0.001) and total HRQOL (P=0.006) scales and the Concern (P=0.008), Coping (P=0.002), and Social Interaction (P=0.019) domains. Six patients (2%) receiving placebo, 28 (4%) receiving tolterodine ER, and 42 (6%) receiving fesoterodine discontinued treatment due to treatment-emergent adverse effects. The most frequent treatment emergent adverse event in the fesoterodine and tolterodine groups were dry mouth (28 vs 16%), headache (6 vs 3%), and constipation (5 vs 4%). Sixteen (2%) of patients in the fesoterodine group had a non-fatal serious adverse events during treatment, two of which were considered related to fesoterodine. One patient with BPH developed urinary retention requiring catheterization.
Kaplan et al.[43] (2011) Fesoterodine ER 4 to 8 mg once daily	DB, PC, PG, RCT Men and women ≥18 years of age who have self-	N=2,417 12 weeks	Primary: Change in UUI episodes from baseline to week 12	Primary: The median percentage reduction in UUI episodes at week 12 was 100% in all groups; however, the treatment differences between the fesoterodine group and the tolterodine ER group (P=0.0093) and placebo (P=0.0001)

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs tolterodine ER 4 mg once daily vs placebo	reported OAB symptoms for ≥3 months and had a mean of at least one UUI episode and ≥8 micturitions per 24 hours in 3-day bladder diary		Secondary: Change from baseline in micturitions, nocturnal micturitions, urgency episodes, severe urgency episodes, frequency-urgency sum per 24 hours, three-day diary-dry rate, and MVV per micturition	were significant. Additionally, the difference between groups was shown as early as week four. Secondary: At week 12, fesoterodine 8 mg had significantly greater mean improvements than patients receiving tolterodine ER for micturitions (P=0.0016), urgency episodes (P<0.0001), severe urgency episodes (P<0.0001), and frequency-urgency sum (P<0.0001). Compared to tolterodine, fesoterodine did not improve nocturnal micturition or MVV. Fesoterodine also significantly improved all diary endpoints compared to placebo at week 12 (all P<0.02). Tolterodine ER significantly improved UUI episodes (P=0.0228), MVV (P=0.0021), and micturitions (P=0.0407) compared to placebo at week 12. The three-day diary-dry rate at week 12 was significantly better in the fesoterodine group vs tolterodine ER and placebo (P=0.0169 and P=0.0003). PPBC, UPS, and OAB-q scores were better at week 12 with fesoterodine compared to both tolterodine ER and placebo. These changes were also better for tolterodine ER compared to placebo. The most frequent treatment emergent adverse events in all groups were dry mouth, constipation, and headache.
Herschorn et al.[44] (2017) SYNERGY Solifenacin 5 mg plus mirabegron 25 mg (combined S5 + M25 group) vs	DB, MC, RCT Patients aged ≥18 years with wet OAB (urgency, urinary frequency and urinary incontinence) for ≥3 months who recorded on average ≥8 micturitions/24 h, ≥1 urgency	N=3,398 18 weeks (4-week placebo run-in, 12-week DB treatment period, 2-week placebo run-out period)	Primary: Change from baseline to end of treatment in the mean number of urinary incontinence episodes/24 h and micturitions/24 h, assessed using a 7-day electronic micturition diary	Primary: Although the combined S5 + M50 group significantly reduced urinary incontinence episodes compared to solifenacin 5 mg, with a mean (SE) adjusted difference of −0.20 (0.12) urinary incontinence episodes/24 hours (95% CI, −0.44 to 0.04, P=0.033), statistical “superiority” versus mirabegron 50 mg was not demonstrated (mean adjusted difference, −0.23 UI episodes/24 hours; 95% CI, −0.47 to 0.01; P=0.052). Therefore, the primary objective for the combined S5 + M50 therapy was not met. Because the null hypothesis for this test was not rejected, the subsequent hypotheses for mean number of micturitions/24 h and the MVV/micturition could not be tested. Also, no hypothesis testing could be performed for the combined S5 + M25 group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
solifenacin 5 mg plus mirabegron 50 mg (combined S5 + M50 group) vs solifenacin 5 mg vs mirabegron 25 mg vs mirabegron 50 mg vs placebo	episode/24 h, and ≥3 urinary incontinence episodes over the 7-day micturition diary		Secondary: Change from baseline in the mean volume voided/micturition, change from baseline in mean number of urinary incontinence episodes/24 h, micturitions/24 h, urgency episodes/24 h, UUI episodes/24 h and nocturia episodes/24 h; the percentage of patients (responders) achieving zero urinary incontinence episodes/24 h in the last 7 days prior to each visit, micturition frequency normalization (<8 episodes/24 h), and the number of UUI episodes and nocturia episodes in the 7-day diary; safety	Urinary incontinence episodes decreased vs baseline for all treatment arms. The mean adjusted change from baseline to end of treatment was greater in the combined therapy groups vs monotherapies and placebo. Secondary: For micturitions/24 hours, adjusted change from baseline was greater in the combined therapy groups vs monotherapies (combined S5 + M50 group, nominal P values 0.006 and <0.001 versus solifenacin 5 mg and mirabegron 50 mg, respectively; combined S5 + M25 group, nominal P values 0.040 and 0.001 versus solifenacin 5 mg and mirabegron 25 mg, respectively). All active treatment groups had greater improvements in the mean numbers of micturitions/24 hours versus placebo, with effect sizes for the combined therapy groups (combined S5 + M25 group: -0.85 micturitions/24 h; combined S5 + M50 group: -0.95 micturitions/24 h) higher than with mirabegron monotherapy (25 mg: -0.36; 50 mg: -0.39 micturitions/24 h) and solifenacin 5 mg (-0.56 micturitions/24 h). The combined S5 + M50 group was statistically significantly improved compared to both monotherapies at end of treatment for UUI episodes, urgency episodes, and nocturia, with effect sizes that appeared to be additive. The combined S5 + M25 group demonstrated statistically significant improvement compared to mirabegron 25 mg for the same variables, except for nocturia. In responder analyses at the end of treatment, odds ratios in favor of both combined therapies vs monotherapies were shown for the proportion of patients with zero urinary incontinence episodes and those achieving micturition frequency normalization. There was a slightly increased frequency of treatment-emergent adverse events in the combined therapy groups vs monotherapies and placebo. Most of the treatment-emergent adverse events were mild or moderate in severity. There were slightly higher frequencies of dry mouth, constipation, and dyspepsia in the combined therapy groups versus monotherapies.
Drake et al.[45] (2016)	DB, MC, RCT	N=2,174	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
BESIDE Solifenacin 5 mg and mirabegron 50 mg (combination) vs solifenacin 5 mg vs solifenacin 10 mg	Adult OAB patients remaining incontinent despite daily solifenacin 5mg during 4-wk single-blind run-in	12 weeks	Change from baseline to end of treatment in the mean number of incontinence episodes/24 hours Secondary: Change from baseline to end of treatment in the mean number of micturitions/24 hours, number of incontinence episodes; safety	The adjusted change from baseline to end of treatment in the mean number of incontinence episodes per 24 hours was greater with combination (−1.80) versus solifenacin 5 mg (−1.53; P=0.001) and versus solifenacin 10 mg (−1.67; P=0.008). Secondary: At end of treatment, reductions in mean daily micturitions and in three-day incontinence episodes were significantly greater with combination versus solifenacin 5 mg (P<0.001). Combination was noninferior to solifenacin 10 mg for both key secondary end points and superior to solifenacin 10 mg for the reduction in micturition frequency. Significant differences in favor of the combination were evident as early as week four versus solifenacin 5 mg and week eight versus solifenacin 10 mg. The incidence of treatment-emergent adverse events was lowest with solifenacin 5 mg (33.1%), highest with solifenacin 10 mg (39.4%), and 35.9% with combination; dry mouth and constipation were the most common treatment-emergent adverse events. Incidence of dry mouth was lower with combination (5.9%) versus solifenacin 10 mg (9.5%) and similar to solifenacin 5 mg (5.6%).
Gratzke et al.[46] (2019) SYNERGY II Solifenacin succinate 5 mg plus mirabegron 50 mg combination therapy vs solifenacin 5 mg monotherapy vs	DB, MC, PG, RCT Patients completed either BESIDE or SYNERGY study or male or female and ≥18 years of age with symptoms of wet OAB (urinary frequency and urgency with incontinence) for ≥3 months	N=1,829 12 months	Primary: Safety, measured as treatment emergent adverse events Secondary: Change from baseline to the end of treatment in the mean number of incontinence episodes per 24 hours and micturitions per 24 hours	Primary: Overall, 856 patients (47%) experienced ≥1 treatment emergent adverse events. Treatment emergent adverse events frequency was slightly higher in the combination group (combination, 49%; mirabegron, 41%; solifenacin, 44%). Across all groups, the majority of the treatment emergent adverse events were mild or moderate in severity (mild, 24%; moderate, 19%; severe, 4.0%). There were no clinically relevant differences across groups in the frequency of treatment emergent adverse events leading to permanent treatment discontinuation (difference vs combination −0.2% for mirabegron and 0.4% for solifenacin). Serious treatment emergent adverse events were reported by 67 patients (3.7%); one was considered possibly treatment-related (mirabegron group, atrial fibrillation). Dry mouth was the most common treatment emergent adverse events (combination, 6.1%; solifenacin, 5.9%; mirabegron, 3.9%). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mirabegron 50 mg monotherapy				Combination therapy was statistically superior to both monotherapies in terms of change from baseline to end of treatment in the mean number of incontinence episodes per 24 hours (adjusted mean difference: mirabegron, -0.5; 95% CI, -0.7 to -0.2; P<0.001; solifenacin, -0.1; 95% CI, -0.4 to 0.1; P=0.002) and the mean number of micturitions per 24 hours (adjusted mean difference: mirabegron, -0.5; 95% CI, -0.8 to -0.2; P<0.001; solifenacin, -0.4; 95% CI, -0.7 to -0.1; P=0.004).
Inoue M et al.[47] (2019) Solifenacin 5 mg once daily for four weeks followed by mirabegron 50 mg once daily for four weeks (group S) vs mirabegron 50 mg once daily for 4 weeks followed by solifenacin 5 mg once daily for 4 weeks (group M)	PRO, RCT, XO Female patients ≥20 years, an OABSS of 3 or higher and urgency once or more per week	N=47 8 weeks	Primary: Efficacy outcomes including change in OABSS, IPSS and VAS Secondary: Not reported	Primary: The IPSS was significantly improved after the patients received solifenacin (P value not reported). After they received mirabegron, the IPSS was also improved, but not significantly. The OABSS was significantly improved in both groups after treatment. There were no significant differences between the two groups. In group M, the OABSS after eight weeks was significantly improved compared to that after four weeks. On the other hand, in group S, it was not significantly improved. In group M, the VAS values for urgency and incontinence were significantly improved after treatment. In addition, the VAS values for urgency and incontinence after eight weeks were significantly improved compared to those after four weeks. In group S, on the other hand, they were not significantly improved.
Chapple et al.[48] (2013) Mirabegron 100 mg once daily vs mirabegron 50 mg once daily vs	DB, MC, RCT Patients ≥18 years of age with OAB symptoms for ≥3 months and with an average baseline micturition frequency of ≥8 micturitions/24 hours and ≥3 urgency episodes	N=2,444 12 months	Primary: Incidence and severity of treatment-emergent adverse events, vital signs and laboratory tests Secondary: Change from baseline in micturition	Primary: The incidence of treatment-emergent adverse events was similar among patients treated with mirabegron 50 mg (59.7%), 100 mg (61.3%) or tolterodine ER (62.6%). Most events were categorized as mild or moderate in severity. The most frequent treatment-related adverse events included hypertension, dry mouth, constipation, and headache, occurring at a similar incidence across all treatment groups, except for dry mouth, which was highest in the tolterodine group. Discontinuations resulting from adverse events were similar between treatment groups, with 6.4, 5.9 and 6.0% of patients treated with

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
tolterodine ER 4 mg once daily	with or without incontinence during the 3-day micturition diary period		frequency and urgency frequency at one, three, six, nine and 12 months; OAB-q, PPBC and VAS scores, proportion of treatment responders (≥50% decrease from baseline in the incontinence episodes/24 hours or those with zero incontinence episodes at final visit)	mirabegron 50 mg, 100 mg and tolterodine ER 4 mg, discontinuing treatment, respectively. Urinary retention occurred in one patient each in the mirabegron 50 mg and 100 mg group compared to three patients treated with tolterodine ER. Urinary retention requiring catheterization was reported in one patient receiving mirabegron 100 mg and tolterodine ER. There was a higher incidence of cardiac arrhythmias with tolterodine ER 4 mg (6.0%) compared to mirabegron 50 mg (3.9%) and 100 mg (4.1%). Mean changes from baseline in systolic blood pressure with mirabegron 50 mg, 100 mg and tolterodine were 0.2, 0.4 and -0.5 mm Hg for morning measurements and -0.3, 0.1 and 0.0 mm Hg for evening measurements, respectively. The mean changes in diastolic blood pressure were -0.3, 0.4, and 0.1 mm Hg, respectively for morning measurements and 0.0, 0.1 and 0.6 mm Hg, respectively for evening measurements. There was a higher incidence of neoplasm (benign, malignant and unspecified including cysts and polyps) in the mirabegron 100 mg group (1.3%) compared to the 50 mg group (0.1%) and tolterodine ER 4 mg (0.5%). Secondary: There were similar improvements between treatments with regard to the mean number of micturitions/24 hours (-1.27 for mirabegron 50 mg, -1.41 for mirabegron 100 mg and -1.39 for tolterodine ER 4 mg; P values not reported). Improvements in the mean number of incontinence episodes/24 hours (-1.01 for mirabegron 50 mg, -1.24 for mirabegron 100 mg and -1.26 for tolterodine ER 4 mg) and MVV (17.5 mL for mirabegron 50 mg, 21.5 mL for mirabegron 100 mg and 18.1 mL for tolterodine ER 4 mg) were similar among treatment groups (P values not reported). At the final visit, the proportion of treatment responders (≥50% reduction from baseline in the mean number of incontinence episodes/24 hours was 63.7, 66.3 and 66.8% for patients treated with mirabegron 50 mg, 100 mg and tolterodine ER, respectively; P values not reported). The proportion of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				patients who reported zero incontinence episodes at the final visit was 43.4, 45.8 and 45.1%, respectively; P values not reported). Both doses of mirabegron showed numerical improvements on the other secondary efficacy variables including OAB-q symptom bother and QOL, treatment satisfaction, number of nocturia episodes and PPBC.
Khullar et al.[49] (2013) SCORPIO Mirabegron 100 mg once daily vs mirabegron 50 mg once daily vs tolterodine SR 4 mg once daily vs placebo	AC, DB, MC, PC, PG, RCT Patients ≥18 years of age, with OAB symptoms for ≥3 months and an average baseline micturition frequency of ≥8 micturitions/24 hours and ≥3 urgency episodes with or without incontinence during the 3-day micturition diary period	N=1,978 12 weeks	Primary: Change from baseline to end of treatment in the mean number of incontinence episodes per 24 hours, change from baseline to end of treatment in the mean number of micturitions per 24 hours Secondary: Change from baseline to end of treatment in the mean VVPM, change from baseline to week four in the mean number of incontinence episodes per 24 hours, change from baseline to week 4 in the mean number of micturitions per 24 hours, change from	Primary: Change from baseline to end of treatment in the mean number of incontinence episodes per 24 hours was -1.46 in the mirabegron 100 mg group, -1.57 in the mirabegron 50 mg group, -1.27 in the tolterodine SR group and -1.17 in the placebo group. When compared to placebo the change from baseline was statistically significant in the mirabegron 100 mg (P<0.05) and 50 group (P<0.05) but not in the tolterodine SR group (P value not reported). Change from baseline to end of treatment in the mean number of micturitions per 24 hours was -1.77 in the mirabegron 100 mg group, -1.93 in the mirabegron 50 mg group, -1.59 in the tolterodine SR group and -1.34 in the placebo group. When compared to placebo the change from baseline was statistically significant in the mirabegron 100 mg (P<0.05) and 50 group (P<0.05) but not in the tolterodine SR group (P value not reported). Secondary: Change from baseline to end of treatment in the mean VVPM was 25.6 mL in the mirabegron 100 mg group, 24.2 mL in the mirabegron 50 mg group, 25.0 mL in the tolterodine SR group and 12.3 mL in the placebo group. When compared to placebo the change from baseline was statistically significant in the mirabegron 100 mg (P<0.05) and 50 group (P<0.05) and tolterodine SR group (P<0.05). Change from baseline to week four in the mean number of incontinence episodes per 24 hours was -1.03 in the mirabegron 100 mg group, -1.04 in the mirabegron 50 mg group, -1.00 in the tolterodine SR group and -0.65 in the placebo group. When compared to placebo the change from baseline was statistically significant in the mirabegron 100 mg (P<0.05) and 50 group (P<0.05) and tolterodine SR group (P<0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			baseline to final visit in mean level of urgency, change from baseline to final visit in mean number of urgency incontinence episodes per 24 hours, change from baseline to final visit in grade 3 or 4 urgency episodes per 24 hours, change from baseline to final visit in mean number of nocturia episodes, safety	Change from baseline to week four in the mean number of micturitions per 24 hours was -1.29 in the mirabegron 100 mg group, -1.16 in the mirabegron 50 mg group, -1.10 in the tolterodine SR group and -0.77 in the placebo group. When compared to placebo the change from baseline was statistically significant in the mirabegron 100 mg (P<0.05) and 50 group (P<0.05) and tolterodine SR group (P<0.05). Change from baseline to final visit in mean level of urgency was -0.30 in the mirabegron 100 mg group, -0.31 in the mirabegron 50 mg group, -0.29 in the tolterodine SR group and -0.22 in the placebo group (P values not reported). Change from baseline to final visit in mean number of urgency incontinence episodes per 24 hours was -1.33 in the mirabegron 100 mg group, -1.46 in the mirabegron 50 mg group, -1.18 in the tolterodine SR group and -1.11 in the placebo group (P values not reported). Change from baseline to final visit in grade 3 or 4 urgency episodes per 24 hours was -1.96 in the mirabegron 100 mg group, -2.25 in the mirabegron 50 mg group, -2.07 in the tolterodine SR group and -1.65 in the placebo group (P values not reported). Change from baseline to final visit in mean number of nocturia episodes was -0.56 in the mirabegron 100 mg group, -0.41 in the mirabegron 50 mg group, -0.50 in the tolterodine SR group and -0.45 in the placebo group (P values not reported). Mirabegron and tolterodine SR were well tolerated and the incidence of adverse events was similar across all groups. Adverse events reported in ≥2% of the placebo, mirabegron 50 mg group, mirabegron 100 mg and tolterodine SR group respectively included hypertension (7.7 vs 5.9 vs 5.4 vs 8.1%), nasopharyngitis (1.6 vs 2.8 vs 2.8 vs 2.8%), dry mouth (2.6 vs 2.8 vs 2.8 vs 10.1%), headache (2.8 vs 3.7 vs 1.8 vs 3.6%), influenza (1.6 vs 2.2 vs 2.0 vs 1.4%), UTI (1.4 vs 1.4 vs 1.8 vs 2.0%), constipation (1.4 vs 1.6 vs 1.6 vs 2.0%).
Yamaguchi et al.[50]	AC, DB, PC, RCT	N=1139	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2014) mirabegron 50 mg once daily vs placebo once daily vs tolterodine 4 mg once daily (as an active comparator)	Patients ≥20 years of age experiencing OAB symptoms for ≥24 weeks	12 weeks	Change in the mean number of micturitions/24 h from baseline Secondary: Micturition variables related to urgency and/or incontinence and quality-of-life domain scores on KHQ, adverse events	Mirabegron 50 mg was associated with a significantly greater change from baseline in the mean number of micturitions/24 h compared with placebo (P<0.001). Secondary: The mean [SD] change from baseline to final assessment for the secondary efficacy variables showed significant improvements for mirabegron vs placebo for number of urgency episodes/24 h (–1.85 [2.555] vs –1.37 [3.191]; P=0.025); number of incontinence episodes/24 h (–1.12 [1.475] vs –0.66 [1.861]; P=0.003); number of urgency incontinence episodes/24 h (–1.01 [1.338] vs –0.60 [1.745]; P=0.008); and volume voided/micturition (24.300 [35.4767] vs 9.715 [29.0864] mL; P<0.001); but not for number of nocturia episodes (–0.44 [0.933] vs –0.36 [1.062]; P=0.277). The percentage of subjects with zero incontinence episodes at the final assessment in the placebo, mirabegron, and tolterodine groups was 39.4, 50.8, and 48.8%, respectively. Treatment with mirabegron for 12 weeks was associated with significant improvements compared with placebo in seven of the nine quality-of-life domain scores in the KHQ. The overall incidence of treatment-related AEs was similar in the mirabegron (24.5%) and placebo (24.0%) groups, but higher in the tolterodine group (34.9%).
Staskin et al.[51] (2009) Oxybutynin 10% topical gel 1 g applied once daily vs placebo	DB, MC, PC, PG, RCT Patients ≥18 years of age with OAB, urge or mixed urinary incontinence with predominance of UUI episodes as well as ≥8 daily urinary voids and ≥4 daily UUI episodes	N=789 12 weeks	Primary: Change in mean number of daily incontinence episodes Secondary: Mean change in urinary frequency, urinary volume per void, number of nocturia episodes, proportion of patients achieving complete urinary continence and safety	Primary: Patients receiving oxybutynin topical gel reported a significantly greater decrease in the mean number of daily incontinence episodes compared to patients receiving placebo (-3.0 vs -2.5; P<0.0001). Secondary: Oxybutynin topical gel was associated with a significant improvement in the mean number of episodes of urinary frequency (-2.7 vs -2.0; P=0.0017) and voided urinary volume compared to placebo (21.0 vs 3.8 mL; P=0.0018). The difference between groups in the number of nocturia episodes did not reach statistical significance (-0.75 daily for oxybutynin topical gel compared to -0.65 daily for placebo; P=0.1372). Complete urinary continence was demonstrated in 27.8% patients receiving oxybutynin topical gel patients compared to 17.3% of patients randomized to placebo (P value not reported).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Compared to placebo, oxybutynin topical gel was associated with a higher incidence of dry mouth (6.9 vs 2.8%; P=0.0060) and application site dermatitis (1.8 vs 0.3%; P=0.0358).
Goldfischer et al.[52] (2013) Oxybutynin 3% topical gel 84 g applied once daily vs Oxybutynin 3% topical gel 56 g applied once daily vs placebo	DB, MC, PC, RCT Patients ≥18 years of age with symptoms of urgency and/or mixed UI and a predominance of urgency incontinence for ≥3 months and who had a history of at least 1 to 2 urinary urgency episodes and ≥8 voids per day; were treatment-naive or had a previous beneficial response to anticholinergic treatment; and, if on anticholinergic medication or any pharmacologic treatment for OAB at screening, were willing to undergo a 2-week washout period.	N=626 12 weeks	Primary: Change from baseline to week 12 in mean number of weekly UI episodes Secondary: Change from baseline to week 12 in daily urinary frequency, average urinary void volume per void, daily UI episodes and change from baseline to week one in these analyses and safety endpoints	Primary: At 12 weeks, the 84 and 56 mg/day arms achieved significantly greater improvement vs placebo in weekly UI episodes (mean change from baseline: -20.4 and -16.4 vs -18.1; P<0.05 and P=0.04, respectively). Secondary: At 12 weeks, the 84 mg/day arm achieved significantly greater improvement vs placebo in daily urinary frequency (-2.6 vs -1.9; P=0.001) and urinary void volume (32.7 vs 9.8; P<0.0001). For oxybutynin gel 56 mg/day, the changes from baseline in these secondary endpoints were not significantly different from placebo. The 84-mg/day arm also reduced the number of daily UI episodes from baseline by a mean of 2.9 episodes, and significant changes from baseline in weekly and daily UI episodes, daily urinary frequency, and urinary void volume were achieved within one week after the start of treatment. The most common treatment-emergent adverse events (>2% of patients) that occurred significantly more often in patients receiving oxybutynin gel than in those receiving placebo, were dry mouth and application site erythema.
Anderson et al.[53] (1999) Oxybutynin ER 5 to 30 mg daily	AC, DB, MC, RCT Community dwelling men and women with urge	N=97 Not specified	Primary: Urge incontinence episodes/week Secondary:	Primary: The mean number of weekly urge incontinence episodes decreased from 27.4 to 4.8 in the ER group and from 23.4 to 3.1 in the IR group (P=0.6). The percentage reduction in weekly urge incontinence episodes was 84% in the ER group and 88% in the IR group (P=0.71).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs oxybutynin IR 5 mg 1 to 4 times/day	incontinence or mixed incontinence with a primary urge component who had at least 6 urge incontinence episodes a week when not taking medication (who had previously responded to oxybutynin)		Proportion of participants achieving elimination of urge incontinence episodes, number of incontinence episodes, proportion of those achieving continence, adverse events	Secondary: Of the participants, 52% in the ER group and 51% in the IR group had no urge incontinence episodes at the end of treatment (P=0.7). Total incontinence (urge, stress and other) episodes decreased from 29.3 to 6.0 in the ER group and from 26.3 to 3.8 in the IR group from baseline to the end of the study (P=0.6). The percentage reduction in any incontinence episodes was 82% in the ER group and 88% in the IR group (P=0.5). The proportions of patients who were totally continent was 41% in the ER group and 40% in the IR group (P=0.9). Normal void frequency increased 54% in the ER group and 17% in the IR group (P<0.001). At least one anticholinergic event occurred in 87% of patients in the ER group and 94% of patients in the IR group. The most common anticholinergic event in both groups was dry mouth (68% of the ER group and 87% of the IR group; P=0.04). Fewer participants reported moderate or severe dry mouth with ER oxybutynin (25 vs 46%; P=0.03). There was no significant difference among the treatment groups for other anticholinergic adverse events. There were few reports of moderate to severe dry mouth at the 5 mg dose, and there was a trend in both groups toward increasing frequency of dry mouth as doses increased.
Barkin et al.[54] (2004) Oxybutynin ER 15 mg daily vs oxybutynin IR 5 mg three times daily	DB, MC, PG, RCT Men and women >18 years of age with UUI who demonstrated >7 UI episodes/week and >8 voids/day	N=123 9 weeks	Primary: Void frequency, UI episodes, treatment-related changes in QOL as assessed by the IIQ and UDI, and adverse events Secondary: Not reported	Primary: The mean number of incontinence episodes/week decreased from 24.3 to 10.4 in the ER group (P<0.001 vs baseline) and from 23.0 to 6.1 in the IR group (P<0.001 vs baseline). There was no significant difference among the treatment groups (P=0.404). The mean voluntary micturition episodes/day decreased from 11.4 to 9.6 in the ER group (P<0.001 vs baseline) and from 11.0 to 8.6 in the IR group (P<0.001 vs baseline). There was no significant difference among the treatment groups (P=0.286).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				There was no significant difference among the treatment groups in mean urine voided/micturition (P=0.533), incidence of urgency (P=0.116), or severity of urgency (P=0.255). There was a significant reduction from baseline in the mean number of pads/day in the ER group (2.3. to 1.7; P<0.001); however, there was no change from baseline in the IR group (2.4 to 1.9; P=NS). Patients in both treatment groups demonstrated significant improvements from baseline in mean IIQ scores (ER; P<0.001, IR; P<0.001) and mean UDI scores (ER; P<0.001, IR; P<0.001). There were no significant differences among the treatment groups. The most frequently reported adverse events in the ER and IR oxybutynin groups were dry mouth (68 and 72%, respectively) and dry throat (31 and 37%, respectively). There was no significant difference in the incidence of moderate and severe dry mouth among the treatment groups (ER, 26% and IR, 42%). More patients in the ER group rated their medication tolerable compared to the IR group (P=0.020). More patients discontinued treatment in the IR oxybutynin group than in the ER oxybutynin group (P=0.047), primarily due to adverse events. Secondary: Not reported
Birns et al.[55] (2000) Oxybutynin ER 10 mg once daily vs oxybutynin IR 5 mg twice daily	DB, MC, PC, RCT Patients 18 to 76 years of age with detrusor instability or detrusor hyperreflexia whose symptoms were stabilized on conventional oral oxybutynin tablets	N=130 6 weeks	Primary: Proportion of patients with daytime continence at completion of the study Secondary: Percentage of patients with nighttime continence, median	Primary: At the completion of the study, 53% of patients receiving oxybutynin ER were continent during the day compared to 58% of patients receiving oxybutynin IR (P=0.62). Secondary: There was no significant difference between the treatment groups in the percentage of patients with nighttime continence at the completion of the study or the median change in the number of voluntary daytime voids, voluntary nighttime voids, daytime episodes of incontinence and nighttime episodes of incontinence from the week preceding treatment to the completion of the study.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	(5 mg twice daily) for 2 weeks		change in the number of voluntary daytime voids, voluntary nighttime voids, daytime episodes of incontinence and nighttime episodes of incontinence from the week preceding treatment to the completion of the study, adverse events	Dry mouth and vision abnormalities were more common in patients receiving oxybutynin ER than in those receiving oxybutynin IR; however, this was NS (P=NS).
Versi et al.[56] (2000) Oxybutynin ER 5 to 20 mg/day vs oxybutynin IR 5 to 20 mg/day	DB, MC, PG, RCT Patients with 7 to 45 urge incontinence episodes/week and ≥4 days of incontinence/week who had previously responded to treatment with antimuscarinic drugs	N=226 Duration not specified	Primary: Number of incontinence episodes and total incontinence episodes Secondary: Not reported	Primary: Urge incontinence episodes decreased from 18.6 to 2.9/week with oxybutynin ER (83% reduction; P<0.001) and from 19.8 to 4.4/week with oxybutynin IR from baseline (76% reduction; P<0.001). There was no significant difference between the treatment groups (P=0.36). Total incontinence episodes decreased from 20.2 to 3.5/week with oxybutynin ER (81% reduction; P<0.001) and from 22.4 to 5.4/week with oxybutynin IR from baseline (75% reduction; P<0.001). There was no significant difference between the treatment groups (P=0.41). There was no significant difference in anticholinergic adverse events among the treatment groups. Dry mouth occurred in 47.7% and 59.1% of patients receiving oxybutynin ER and IR, respectively. Secondary: Not reported
Nilsson et al.[57] (1997) Oxybutynin ER	XO Female patients 37 to 65 years of age with symptoms of	N=17 120 days	Primary: Frequency of voluntary voiding, the maximal volume of	Primary: The frequency of voids/24 hour was reduced by 23% with oxybutynin ER and by 24% with oxybutynin IR (P=0.51).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
10 mg daily for 60 days vs oxybutynin IR 5 mg twice daily for 60 days	urge incontinence and detrusor instability		urine/single void, and the total volume of voluntarily voided urine/24 hour Secondary: Not reported	Treatment with oxybutynin ER resulted in a 28% reduction in the total weight of pads compared to a 21% reduction with oxybutynin IR (P=0.80). The total volume of voluntary voided urine/day increased by 15% with both treatments (P=0.75), and the maximal volume of urine/void increased by 26% and 34% with oxybutynin ER and oxybutynin IR, respectively (P=0.95). There were no significant differences in adverse events among the treatment groups, including dry mouth (P=0.41), headache (P=1.00), dyspepsia (P=0.26), or vision abnormality (P=0.32). Secondary: Not reported
Appell et al.[58] (2001) Oxybutynin ER 10 mg daily vs tolterodine IR 2 mg twice daily	DB, PG, MC, RCT Participants with OAB who had between 7 and 50 episodes of urge incontinence/week and 10 or more voids/24 hours	N=378 12 weeks	Primary: Number of urge incontinence episodes/week, number of total incontinence episodes/week and micturition frequency episodes/week Secondary: Not reported	Primary: The number of urge incontinence episodes/week decreased from 25.6 to 6.1 in the oxybutynin group and from 24.1 to 7.8 in the tolterodine group (P=0.03). The number of total incontinence episodes/week decreased from 28.6 to 7.1 in the oxybutynin group and from 27.0 to 9.3 in the tolterodine group (P=0.02). Micturition frequency episodes/week decreased from 91.8 to 67.1 in the oxybutynin group and from 91.6 to 71.5 in the tolterodine group (P=0.02). Both drugs improved symptoms of OAB significantly from baseline to the end of the study as assessed by the three main outcome measures (P<0.001). Overall, 92.6 and 95.3% of the patients in the oxybutynin and tolterodine groups, respectively, had fewer incontinence episodes at the end of the study period compared to baseline. The incidence of dry mouth was similar among the treatment groups (28.1% for oxybutynin and 33.2% for tolterodine; P=0.32). Moderate to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				severe dry mouth was also similar among the treatment groups (10.2% for oxybutynin and 10.9% for tolterodine; P=0.87). Other adverse events were similar among the treatment groups. Overall, the discontinuation rates for adverse events were 7.6% in the oxybutynin group and 7.8% in the tolterodine group (P=0.99). Secondary: Not reported
Sand et al.[59] (2004) Oxybutynin ER 10 mg once daily vs tolterodine IR 2 mg twice daily	DB, RCT Women with urge or mixed incontinence (≥7 and ≤50 urge incontinence episodes/week and ≥10 voids/24 hours)	N=315 12 weeks	Primary: Number of urge incontinence episodes, total incontinence, micturition frequency, tolerability Secondary: Not reported	Primary: The number of urge incontinence episodes decreased from 28.1 to 6.2/week in the oxybutynin ER group compared to a reduction from 28.9 to 8.5/week in the tolterodine IR group (P=0.038). Total incontinence episodes decreased from 25.2 to 7.3/week in the oxybutynin ER group compared to a reduction from 25.1 to 10.1/week in the tolterodine IR group (P=0.030). Micturition frequency decreased from 91.7 to 68.0/week in the oxybutynin ER group compared to a reduction from 91.6 to 71.2/week in the tolterodine IR group (P=0.272). There was no significant difference in dry mouth, central nervous system events or other adverse events among the treatment groups. Secondary: Not reported
Diokno et al.[60] (2003) Oxybutynin ER 10 mg daily vs tolterodine ER 4 mg daily	AC, DB, MC, RCT Women ≥18 years of age with OAB who documented 21-60 UUI episodes/week and ≥10 voids/day	N=790 12 weeks	Primary: Mean weekly UUI episodes, weekly total incontinence episodes and weekly micturition frequency, adverse events Secondary: Not reported	Primary: The mean weekly episodes of UUI decreased from 37.1 to 10.8 in the oxybutynin group and from 36.7 to 11.2 in the tolterodine group (P=0.28). The mean number of total incontinence episodes decreased from 43.4 to 12.3 in the oxybutynin group and from 42.4 to 13.8 in the tolterodine group (P=0.08). Patients receiving oxybutynin had a greater decrease in the mean weekly micturition frequency compared to tolterodine participants (P=0.003).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The proportion of participants who reported total dryness (no incontinence episodes) in their last seven-day 24-hour voiding diary was 23.0% in the oxybutynin group compared to 16.8% in the tolterodine group (P=0.03). The proportion of participants who reported no UUI episodes at the last assessment was 26.7% in the oxybutynin group compared to 20.9% in the tolterodine group (P=0.06). Dry mouth was more common in the oxybutynin group than in the tolterodine group (29.7 vs 22.3%, respectively; P=0.02). Most reports of dry mouth events were mild. Other anticholinergic adverse events (constipation, impaired urination-retention, and blurred vision) and central nervous system adverse effects (dizziness, somnolence, depression, and confusion) occurred at similar frequencies in each group. Adverse events led to discontinuation of study medication by 20 patients receiving oxybutynin and 19 receiving tolterodine. Secondary: Not reported
Reinberg et al.[61] (2003) Oxybutynin ER 5 mg/day vs tolterodine ER 2 mg/day vs tolterodine IR 2 mg/day	OL Pediatric patients with a history of non-neurogenic diurnal urinary incontinence and symptoms of OAB	N=132 Duration not specified	Primary: Urinary frequency, incontinence and safety Secondary: Not reported	Primary: Oxybutynin ER led to a greater reduction in urinary frequency compared to tolterodine IR (P<0.01). Both oxybutynin ER and tolterodine ER were significantly better than tolterodine IR in improving symptoms of diurnal incontinence and urinary frequency (P<0.01 and P<0.05, respectively). Oxybutynin ER was significantly more effective than tolterodine ER in completely resolving diurnal incontinence (P<0.05). There were no significant differences in the peripheral or central nervous system anticholinergic side effects among the treatment groups. Secondary: Not reported
Nelken et al.[62] (2011)	PRO, RCT	N=59	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Oxybutynin IR 5 mg twice daily vs estradiol vaginal ring 7.5 µg/day	Women who had ≥10 voids in a 24 hour period, as recorded in a 72 hour voiding diary, and were postmenopausal	12 weeks	Change from baseline in number of daily voiding episodes Secondary: Change in vaginal pH levels, vaginal maturation index, and QOL scores, as assessed by the UDI-6 and the IIQ-7	After 12 weeks, both groups had a significant decrease in the number of daily voids (14.7 to 11.7 for oxybutynin [P=0.003] and 14.9 to 10.4 for estradiol ring [P<0.001]). The difference between groups was not statistically significant. Secondary: There was a significant decrease in UDI-6 (12.1 to 9.4 for oxybutynin [P=0.003] and 11.4 to 7.8 for estradiol [P<0.001]) and IIQ-7 (14.7 to 11.3 for oxybutynin [P=0.02] and 13.2 to 8.1 for estradiol [P<0.001]) scores in both treatment groups. Mean vaginal pH levels in the oxybutynin group remained unchanged after 12 weeks of treatment, but those who received the estradiol ring had a significant decrease in mean pH (6 to 4.9; P=0.002). Mean maturation index did not significantly change in the oxybutynin group, whereas mean maturation index increased significantly after 12 weeks of therapy with an estradiol ring (24.3 to 70.1; P<0.001). Dry mouth, constipation, and blurry vision occurred significantly more in patients who received oxybutynin, whereas more women in the estradiol group reported vaginal discharge.
Davila et al.[63] (2001) Oxybutynin transdermal 2 to 4 patches applied twice weekly vs oxybutynin IR 5 to 7.5 mg orally two or three times daily	DB, MC, PC, RCT Patients ≥18 years of age with a history of urge or mixed urinary incontinence with a predominance of urge symptoms who had symptomatic improvement during a minimum of 6 weeks of oral oxybutynin	N=76 6 weeks	Primary: Average number of daily incontinence episodes, patient-completed VAS for efficacy, dry mouth on an anticholinergic symptoms questionnaire, cystometric comparisons Secondary:	Primary: The average daily incontinence episodes were reduced by approximately five episodes in both groups (P<0.0001), with no significant difference between transdermal and oral therapy. The change in the mean VAS score for each group was 5.8 vs 6.0 cm for the transdermal and oral groups, respectively (P<0.0001). The difference in mean VAS score between transdermal and oral therapy was 0.1 cm (P=0.9). Dry mouth occurred in 38% of patients in the transdermal group compared to 94% of patients in the oral group (P<0.001). Blurred vision, dizziness, drowsiness, palpitations, nausea and impotence were comparable between the groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Not reported	Average bladder volume at first detrusor contraction increased by 66 mL in the transdermal (P<0.0055) and 45 mL in the oral groups (P=0.1428). There was no significant difference among the transdermal and oral groups (P=0.57). Average maximum cystometric capacity increased 53 and 51 mL in the transdermal (P<0.0011) and the oral (P<0.0538) groups, respectively. Post-void residual volume increased by an average of 13 and 16 mL in the oral and transdermal groups, respectively (P=NS). The most frequent treatment related adverse events were dry mouth, constipation, somnolence, dizziness, blurred vision and impaired urination, which occurred more frequently in the oral group. Secondary: Not reported
Dmochowski et al.[64] (2003) Oxybutynin transdermal delivery system (OXY-TDS) 3.9 mg/day applied twice weekly vs tolterodine ER (TOL-LA) 4 mg daily vs placebo	DB, RCT Patients ≥18 years of age who were receiving pharmacologic treatment for OAB and who had a beneficial response to the pre-study treatment	N=361 12 weeks	Primary: Change from baseline in the number of incontinence episodes/day, average daily urinary frequency, average urinary volume/void, and changes in the QOL instruments Secondary: Not reported	Primary: There was a significant reduction in the number of urinary incontinence episodes/day in patients treated with OXY-TDS compared to placebo (median change -3 vs -2, respectively; P=0.0137). There was a significant reduction in the number of urinary incontinence episodes/day in patients treated with TOL-LA compared to placebo (median change -3 vs -2, respectively; P=0.0011). There was no significant difference between OXY-TDS and TOL-LA in the reduction of incontinent episodes (P=0.2167). The reduction in incontinence episodes corresponded to a 75% improvement in the OXY-TDS group, 75% in the TOL-LA group, and 50% in the placebo group. Complete continence was achieved by 39% of patients in the OXY-TDS group, 38% of patients in the TOL-LA group, and 22% of patients in the placebo group (both, P=0.014 vs placebo). The mean decrease in average daily urinary frequency was -1.9 micturitions/day with OXY-TDS (P=0.1010 vs placebo) -2.2

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				micturitions/day with TOL-LA (P=0.0025 vs placebo), and -1.4 micturitions/day with placebo. There was no significant difference between OXY-TDS and TOL-LA (P=0.2761). The median increases in average urinary volume/void was 24 mL with OXY-TDS (P=0.0010 vs placebo), 29 mL with TOL-LA (P=0.0017 vs placebo) and 5.5 mL in the placebo group. There was no significant difference between OXY-TDS and TOL-LA (P=0.7690). The patients' Global Assessment of Disease State scores were significantly improved with OXY-TDS (P=0.0106) and TOL-LA (P=0.0001) compared to placebo. There was no significant difference between OXY-TDS and TOL-LA (P=0.1861). The total IIQ scores improved significantly with OXY-TDS (P=0.0018) and TOL-LA (P=0.0045) compared to placebo. Significant improvements in irritative symptoms of the UDI questionnaire were also observed with OXY-TDS (P=0.0156) and TOL-LA (P=0.0010) compared to placebo. The most common treatment-related adverse events in the OXY-TDS group were application site reactions, including erythema (8.3%) and pruritus (14.0%). Dry mouth (4.1 vs 1.7% with placebo; P=0.2678) and constipation (3.3%) were also reported. Adverse events led to treatment discontinuation in 10.7% of patients receiving OXY-TDS. Anticholinergic adverse events were the most common treatment-related events in the TOL-LA group (13.0%). Dry mouth occurred at a greater rate with TOL-LA (7.3%) than placebo (1.7%; P=0.0379). Constipation occurred in 5.7% of TOL-LA patients. Adverse events led to treatment discontinuation in 1.6% of patients receiving TOL-LA. Secondary: Not reported
Metello et al.[65] (2007) Solifenacin 5 mg once daily	OL Women ≥18 years of age with OAB symptoms (≥8	N=40 30 days	Primary: Patient self-assessment of improvement after 30 days using the	Primary: After 30 days of therapy, treatment with solifenacin led to a significant improvement in USS scores when assessed in all patients (P<0.001). There was no significant difference in USS scores among patients who were drug naïve compared to those who had previously failed trospium.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	voids/24 hours and ≥1 incontinence episode/24 hours) for ≥3 months who had either not received any previous medication or who had been previously unsuccessfully treated with trospium		USS in both treatment groups Secondary: Reduction of the daily number of voids and urgency or involuntary leakage episodes	Overall 16% of patients experienced no improvement, 13.5% had mild improvement and 69.5% had great improvement. Secondary: Treatment with solifenacin resulted in a significant reduction in urgency episodes, involuntary leakage episodes, and number of voids/24 hours when assessed in all patients (P<0.001). There was no significant difference in these endpoints among patients who were drug naïve compared to those who had previously failed trospium. Overall, 16% of patients had no improvement in the number of involuntary leakage episodes, 11% of patients had mild improvement and 73% of patients had great improvement. For daily urgency episodes, 13.5% of patients had no improvement, 27.0% had a mild reduction, and 59.0% had a great reduction.
Chancellor et al.[66] (2008) Solifenacin 5 to 10 mg once daily	MC, OL Patients ≥18 years of age with symptoms of OAB for ≥3 months who had been treated with tolterodine ER 4 mg for ≥4 weeks, and wished to switch therapy because of a lack of sufficient subjective improvement in urgency (≥3 urgency episodes/24 hours)	N=441 12 weeks	Primary: Change in urgency episodes compared to pre-washout (when patients were receiving tolterodine ER 4 mg) Secondary: Change in micturitions, incontinence episodes, nocturia episodes, and nocturnal voids compared to pre-washout and post-washout; PRO using the PPBC	Primary: The mean change in the number of urgency episodes/24 hours was −3.4 from pre-washout to study end (P<0.001). The median percent change was -75%. Secondary: The mean change in micturitions, incontinence episodes, nocturia episodes, and nocturnal voids from pre-washout to study end was –1.6, –1.9, –0.7, and –0.8, respectively (all, P<0.001). The median percent change from pre-washout was –15.0% for the number of micturitions, –96.4% for incontinence episodes, –40.8% for nocturia episodes, and –40.0% for nocturnal voids. The median change in micturitions, incontinence episodes, nocturia episodes, and nocturnal voids from post-washout to study end was –2.0 (-19.5%), –2.0 (-100%), –0.7 (-43.7%), and –0.7 (-40.0%), respectively (all, P<0.001). The mean PPBC score decreased from pre-washout by 1.2 points (95% CI, –1.3 to –1.1; P<0.001) and from post-washout by 1.2 points (95% CI, –1.3 to –1.0; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			and the OAB-q was also assessed	Patients had significant improvements on the OAB-q at study end compared to both pre-washout and post-washout (all, P<0.001). The mean changes in OAB-q scores at study end relative to pre-washout and post-washout were –27.4 and –29.5, respectively, for symptom bother; 23.1 and 27.9 for coping; 25.2 and 29.7 for concern; 21.9 and 24.5 for sleep; 11.1 and 15.0 for social interaction; and 21.1 and 25.2 for total HRQOL. The most common adverse events were dry mouth (17.5%), constipation (11.6%), and blurred vision (2.3%).
Zinner et al.[67] (2008) Solifenacin 5 to 10 mg once daily	MC, OL Patients ≥18 years of age with OAB symptoms for ≥3 months who were previously treated with tolterodine ER 4 mg/day for ≥4 weeks, and who wished to switch to solifenacin due to lack of sufficient improvement in urgency episodes while receiving tolterodine (≥3 urgency episodes/24 hours)	N=441 12 weeks	Primary: WPAI-SHP, HUI, and a resource utilization questionnaire administered at pre-washout and week 12 Secondary: Not reported	Primary: Patients reported significantly fewer physician office visits (0.2 vs 1.2; P<0.0001), UTIs (0.1 vs 0.2; P<0.0001), and pads/diapers (7.9 vs 10.7/week; P=0.0009) with solifenacin compared to the pre-washout period. There were no significant differences in the numbers of skin rashes or falls reported at end of the study compared to pre-washout. Patients reported using fluid management as a behavioral management strategy on fewer days with solifenacin compared to when they were taking tolterodine ER 4 mg/day (14.2 vs 18.0 days; P=0.0381). There were no significant differences in other behavioral management strategies. Based on the WPAI-SHP, patients who were working reported a reduction in percent of work time missed (0.2 vs 2.1%; P=0.0017), a reduction in percent of impairment while working (11.3 vs 22.9%; P<0.0001), a reduction in percent of overall work impairment (11.9 vs 24.0%; P<0.0001), and a reduction in percent of activity impairment (18.4 vs 31.6%; P<0.0001) after 12 weeks of therapy with solifenacin. There was no significant difference in the health utility score between pre-washout and end of study based on the HUI 2/3. Secondary: Not reported
Wong et al.[68]	OL	N=9	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2009) Solifenacin 5 to 10 mg once daily	Women with OAB who had previously taken oxybutynin IR without benefit or developed intolerable adverse effects	12 weeks	Daytime frequency, nocturia, number of incontinence episodes, average urinary voided volume, and quality-of-life (OAB-q short form symptom bother) Secondary: Not reported	The mean number of daytime micturitions was reduced from 11.4 to 7.3 with solifenacin (P=0.0002). The mean number of nocturia episodes was reduced from 2.8 to 0.9 with solifenacin (P=0.0004). The total number of incontinence episodes/day was reduced from 4.9 to 1.9 with solifenacin (P=0.02). The mean micturition volumes were increased from 160 to 280 ml with solifenacin (P=0.002). The symptom severity domain of the OAB-q showed a value of 60.8% at baseline and 32.0% at 12 weeks with solifenacin (P=0.001). The HRQOL domain of the OAB-q showed a value of 45.5% at baseline and 73.3% at 12 weeks with solifenacin (P=0.0006). Secondary: Not reported
Garely et al.[69] (2006) Solifenacin 5 to 10 mg once daily	MC, OL Patients ≥18 years of age with OAB (urgency, urge urinary incontinence, frequency, and/or nocturia for ≥3 months)	N=2,225 12 weeks	Primary: PPBC scale, OAB-q, and a VAS for the degree of bother caused by individual OAB symptoms Secondary: Not reported	Primary: The mean PPBC scale score decreased significantly to 2.9 (mean change, -1.4; 95% CI, -1.49 to -1.38; P<0.001), which corresponded to a perception of "some minor problems" associated with their bladder condition. There were significant improvements in all of the OAB-q scoring domains (symptom severity, coping, concern, sleep, social interaction, and overall HRQoL) with solifenacin (all subscales, P<0.001). Significant improvements in urinary urgency, urge urinary incontinence, frequency, or nocturia were observed with solifenacin on the VAS. For urinary urgency, 88.2% of patients indicated less bothersome symptoms; for urge urinary incontinence, 89.4% of patients indicated less bothersome symptoms; for frequency, 88.3% of patients indicated frequency was less bothersome; for nocturia, 87.5% of patients indicated that nocturia was less bothersome.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Anticholinergic adverse events occurred as follows: dry mouth (21.4%), constipation (13.3%), headache (3.4%), blurred vision (2.6%), nausea (1.8%), dyspepsia (1.5%), and dry eyes (1.3%). A total of 9.7% of patients discontinued treatment due to an adverse event. The most frequently reported treatment-emergent adverse events that resulted in discontinuation were dry mouth (1.9%) and constipation (1.9%). Secondary: Not reported
Haab et al.[70] (2005) Solifenacin 5 to 10 mg once daily	ES, OL Patients ≥18 years of age with symptoms of OAB (≥8 micturitions/24 hours and either ≥1 urgency episode/24 hours or ≥1 incontinence episode/24 hours) for >3 months	N=1,633 40 weeks	Primary: Safety and tolerability Secondary: Efficacy	Primary: Dry mouth occurred in 10% of patients receiving solifenacin 5 mg and 17% of patients receiving solifenacin 10 mg. The discontinuation rate due to dry mouth was 0.4%. After 40 weeks, 85% of patients indicated satisfaction with solifenacin tolerability, and 99% of patients rated solifenacin tolerability as either ‘‘satisfactory’’ or ‘‘acceptable.’’ Secondary: The mean number of urgency episodes/24 hours decreased by 63%. For patients with ≥1 episode of urgency/24 hours at baseline, 40% had no symptomatic urgency at end point. The mean number of incontinence episodes/24 hours decreased by 66%. For patients with ≥1 episode of incontinence at baseline, 58% were continent at end point. The mean number of micturitions/24 hours decreased by 2.97 (23%) with solifenacin. A total of 39% of patients had <8 micturitions/24 hours by study end. The mean number of nocturia episodes/24 hours decreased by 32% and the mean volume voided/micturition increased by 31%.
Bolduc et al.[71] (2010)	OL, PRO Children with OAB (neurogenic and	N=72 ≥3 months	Primary: Efficacy for continence, safety and tolerability	Primary: Subjective continence improved in all cases. Patients/parents rated improvement as 100% (complete dryness in 24 patients, >90% improvement in 42 patients, and a 50 to 89% decrease in six patients).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Solifenacin 0.15 to 0.25 mg/kg once daily	non-neurogenic) who failed intensive medical and behavioral therapy		Secondary: Not reported	MVV and cystometric bladder capacity improved without deterioration in compliance (P<0.001). Maximum detrusor contraction pressure decreased overall as well (P<0.0001). There were no significant differences in response in neurogenic vs non-neurogenic cases. The mean PPBC score at baseline was 4.9 (mod-severe problems), which significantly improved to 1.8 (minor problems) at study end (P<0.0001). No adverse events were reported in 50 patients (70%). The most common adverse event was dry mouth (n=14). Secondary: Not reported
Chapple et al.[72] (2006) Solifenacin 5 to 10 mg once daily vs placebo	DB, MC, PC, RCT (Pooled analysis) Patients ≥18 years of age with OAB (≥8 micturitions/24 hours, and either a mean of ≥1 incontinence episode/24 hours or a mean of ≥1 urgency episode/24 hours)	N=2,848 (4 trials) 12 weeks	Primary: Urgency episodes (mean absolute values and median percentage values), incontinence episodes, micturition frequency, nocturia episodes/24 hours, and volume voided/micturition Secondary: Not reported	Primary: Treatment with solifenacin 5 and 10 mg resulted in a -2.9 (-66.1%) and -3.4 (-70.0%) reduction in urgency episodes, respectively, compared to a -2.0 (-40.0%) reduction with placebo (P<0.001). Treatment with solifenacin 5 and 10 mg resulted in a -1.5 (-100%) and -1.8 (-100%) reduction in incontinence episodes, respectively compared to a -1.1 (-63.6%) reduction with placebo (P<0.001). The frequency of micturition was significantly reduced with solifenacin 5 mg (-2.3; -19.4%) and 10 mg (-2.7; -22.5%) compared to placebo (-1.4; -12.0%; P<0.001). The number of nocturia episodes were significantly reduced with solifenacin 5 mg (-0.6; -35.5%) and 10 mg (-0.6; -36.4%) compared to placebo (-0.4; -25.0%; P<0.05 and P<0.001 for solifenacin 5 and 10 mg, respectively). The volume voided/micturition increased significantly with solifenacin 5 mg (32.3 mL; 19.0%) and 10 mg (42.5 mL; 25.7%) compared to placebo (8.5 mL; 3.1%; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The most common adverse events were dry mouth, constipation, and blurred vision. The incidence of dry mouth was higher in the 10 mg solifenacin group compared to the 5 mg group. The numbers of patients discontinuing treatment due to adverse events were as follows: 4.4, 2.8, and 6.8% with placebo, solifenacin 5 mg and solifenacin 10 mg. Secondary: Not reported
Abrams et al.[73] (2005) Solifenacin 5 to 10 mg once daily vs placebo	DB, MC, PC, RCT (Pooled analysis) Subgroup of patients >18 years of age with symptoms of OAB (≥8 micturitions/24 hours or ≥1 urgency episode/24 hours) who did not experience incontinence episodes at baseline	N=975 (4 trials) 12 weeks	Primary: Urgency episodes, micturition frequency, and nocturia episodes/24 hours, and volume voided/micturition Secondary: Not reported	Primary: The mean change from baseline in urgency episodes/24 hours (-3.2, -3.2, -2.1), micturition frequency/24 hours (-2.6, -2.8, -1.6), and volume voided/micturition (24.9 mL, 33.9 mL, 7.0 mL) were significantly greater with solifenacin 5 and 10 mg than placebo, respectively (all P<0.001). The mean change from baseline in nocturia episodes/24 hours was significantly greater for solifenacin 10 mg than placebo (P<0.01). The percentage of patients with resolution of urgency (36.6, 32.9, 24.6%) and normalization of micturitions (29, 34.7, 18.5%) was significantly greater with solifenacin 5 mg and solifenacin 10 mg compared to placebo, respectively (P<0.05 to P<0.001). The percentage of patients with resolution of nocturia (14.1, 20.9, 12.8%) was significantly greater with solifenacin 10 mg compared to placebo (P<0.01). Dry mouth was reported in 3.6, 10.8, and 24.4% of patients receiving placebo, 5 mg solifenacin, and 10 mg solifenacin, respectively. The incidence of constipation was 1.3, 4.0, and 12.2% with placebo, 5 mg, and 10 mg, respectively. Discontinuations due to adverse events for the solifenacin 5 mg group (2.8%) and solifenacin 10 mg group (7.8%) were comparable with or less than that of the placebo group (6.2%). Secondary: Not reported
Millard et al.[74] (2006) Solifenacin 5 to 10 mg once daily	DB, MC, PC, RCT (Pooled analysis) Subgroup of patients ≥18 years	N=2,848 (4 trials) 12 weeks	Primary: Responder rates, urgency episodes, incontinence episodes,	Primary: For those with >3 incontinence episodes/24 hours, the percentage of patients who were continent at study end point was significantly higher with solifenacin 5 mg (28.4%; P<0.01) and 10 mg (30.5%; P<0.001) compared to placebo (15.3%). The mean change in the number of episodes

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo	of age with severe OAB (>3 incontinence episodes/24 hour, >8 urgency episodes/24 hours, or >13 micturition episodes/24 hours)		micturition, frequency, nocturia episodes/24 hours, and volume voided/micturition Secondary: Not reported	of incontinence and urgency, the frequency of micturitions and volume voided/micturition was significantly greater with solifenacin 5 mg (P<0.01) and 10 mg (P<0.001) than with placebo. For those with >8 urgency episodes/24 hours, the percentage of patients with resolution of urgency at study end point was significantly higher with solifenacin 5 mg (12.4%; P<0.01) and 10 mg (13.9%; P<0.001) compared to placebo (4.6%). The mean change in the number of episodes of incontinence and urgency, the frequency of micturitions and volume voided/micturition was significantly greater with solifenacin 10 mg compared to placebo (P<0.001). For solifenacin 5 mg, the mean change for all efficacy parameters was significantly greater than placebo (P<0.05; except micturition frequency/24 hours). For those with >13 micturitions/24 hours, the percentage of patients who achieved normalization of micturition frequency (<8 micturitions/24 hours) at study end point was significantly higher with solifenacin 10 mg (13.3%; P<0.001) compared to placebo (4.0%). There was no significant difference between solifenacin 5 mg and placebo. The mean change in the number of episodes of incontinence and urgency, the frequency of micturitions and volume voided/micturition was significantly greater with solifenacin 5 mg (P<0.05) and 10 mg (P<0.001) compared to placebo. The incidence of adverse events was comparable among the treatment groups. Dry mouth, constipation, UTI, blurred vision, and nausea occurred at a higher incidence with solifenacin 5 or 10 mg than with placebo. Discontinuations due to adverse events occurred in 4.1, 7.5, and 4.8% of patients in the solifenacin 5 and 10 mg and placebo groups, respectively. Secondary: Not reported
Wagg et al.[75] (2006) Solifenacin 5 to 10 mg once daily	DB, MC, PC, RCT (Pooled analysis) Subgroup of patients ≥65years of age with OAB (≥8	N=1,554 (5 trials) 12 to 40 weeks	Primary: Urgency episodes (mean absolute values and median percentage values), incontinence	Primary: In the 12-weeks studies, elderly patients had significantly greater decreases in the mean number of incontinence episodes/24 hours with solifenacin 5 and 10 mg compared to placebo (P=0.013 and P<0.001, respectively). The median change in the number of incontinence episodes/24 hours was -1.0 (-92.4%) and -1.5 (-91.9%) with solifenacin 5

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo	micturitions/24 hours, and either a mean of ≥1 incontinence episode/24 hours or a mean of ≥1 urgency episode/24 hours)		episodes, micturition frequency, nocturia episodes/24 hours, and volume voided/micturition Secondary: Not reported	and 10 mg, respectively, and -0.7 (-50%) with placebo (P<0.001 for 10 mg dose). There was no significant difference between solifenacin 5 mg and placebo. A greater percentage of elderly patients who were incontinent at baseline were continent with solifenacin 5 and 10 mg (49.1 and 47.3%, respectively) compared to placebo (28.9%; P<0.001). In 12-week studies, elderly patients had significantly greater decreases in the mean number of urgency episodes/24 hours with solifenacin 5 and 10 mg compared to placebo (P<0.001). The median change in the number of urgency episodes was -2.3 (-76.1%) and -2.7 (-66.7%) with solifenacin 5 and 10 mg, respectively, and -1.5 (-33.3%) with placebo (P<0.001 for 10 mg dose). A greater percentage of elderly patients with urgency at baseline had resolution of urgency with solifenacin 5 and 10 mg (34.6 and 24.9%, respectively) compared to placebo (16.9%; P<0.001 for 5 mg and P<0.01 for 10 mg). In 12-week studies, elderly patients had significantly greater decreases in the mean number of micturitions/24 hours with solifenacin 5 and 10 mg compared to placebo (P<0.001). The median change in the number of micturitions was -2.0 (-18.3%) and -2.3 (-22%) with solifenacin 5 and 10 mg, respectively, and -1.0 (-10.3%) with placebo (P=0.008 for the 5 mg dose and P<0.001 for the 10 mg dose. In 12-week studies, elderly patients had a significantly greater increase in the mean volume voided/micturition with solifenacin 5 and 10 mg compared to placebo (P<0.001).The median change in volume voided/micturition was 27.2 (17.8%) and 40.1 (28.5%) with solifenacin 5 and 10 mg, respectively, and 6.2 (3.7%) with placebo (P<0.001). During the 40-week extension trial, elderly patients maintained improvements in the number of incontinence episodes/24 hours, urgency episodes/24 hours, and number of micturitions/24 hours, and experienced an increase in the volume voided/micturition compared to baseline. A total of 59.5% of elderly patients were continent and 37.8% reported resolution of urgency at the end of the study period.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				During the 12-week trials, the most commonly reported adverse events were dry mouth, constipation, and UTI. Rates of discontinuation were 5.5% in the placebo group, 4.7% in the solifenacin 5 mg group, and 9.3% in the solifenacin 10 mg group. During the 40-week extension, the most common adverse events were dry mouth, constipation, and UTI. A total of 9.2% of patients discontinued therapy due to any type of adverse event. Secondary: Not reported
Kelleher et al.[76] (2005) Solifenacin 5 to 10 mg once daily vs placebo	DB, MC, PC, RCT (Pooled analysis) Patients ≥18 years of age with symptoms of OAB (≥8 micturitions/24 hours and either ≥1 urgency episode/24 hours or ≥1 incontinence episode/24 hours) for >3 months	N=3,237 (3 trials) 12 to 40 weeks	Primary: QOL data using the KHQ Secondary: Not reported	Primary: In the 12-weeks studies, there was a significant improvement in all QOL domains (except personal relationships) with solifenacin compared to placebo (P<0.05 to P<0.001). In the 40-week ES, there was a significant improvement in all QOL domains with solifenacin (17% for the general health perception and 35 to 48% for all the other domains). Secondary: Not reported
Herschorn et al.[77] (2010) Solifenacin 5 mg once daily vs oxybutynin IR 5 mg three times daily	DB, MC, RCT Patients ≥18 years of age with OAB symptoms (>1 urgency episode per 24 hours and ≥8 micturitions per 24 hours for ≥3 months)	N=132 8 weeks	Primary: Incidence and severity of dry mouth reported after direct questioning Secondary: Three-day diary changes in urgency, frequency, incontinence,	Primary: Significantly fewer patients on solifenacin reported dry mouth after direct questioning compared to oxybutynin IR (35 vs 83%; 95% CI, 33 to 62; P<0.0001). Additionally, in those reporting dry mouth, solifenacin was associated with significantly lower severity than that of oxybutynin IR (P=0.001). Secondary: Patients in both groups showed improvement in bladder diary documented urgency, incontinence, frequency, nocturia, and VVPM from baseline to end of treatment. PPBC and OAB-q scores also significantly improved with both groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			nocturia, voided volume, PPBC, and the OAB-q	Overall adverse events were significantly fewer with solifenacin than with oxybutynin IR (72 vs 92%; P=0.003). Besides dry mouth, the incidence of other adverse events was 59% for solifenacin and 70% for oxybutynin (P=0.17). Fewer patients that received solifenacin withdrew from the study due to dry mouth compared to oxybutynin IR (3 vs 19%; P=0.003).
Herschorn et al.[78] (2011) Solifenacin 5 mg once daily vs oxybutynin IR 5 mg three times daily	DB, MC, RCT (Subgroup analysis) Patients ≥18 years of age with OAB symptoms (>1 urgency episode per 24 hours and ≥8 micturitions per 24 hours for ≥3 months)	N=132 8 weeks	Primary: Adverse events in patients ≤ 65 years of age and in those >65 years of age Secondary: Not reported	Primary: In both age groups, solifenacin 5 mg/day was associated with numerically fewer episodes of dry mouth compared to oxybutynin IR. Patients receiving oxybutynin IR were >8 times more likely to have dry mouth than those receiving solifenacin, regardless of age (OR, 8.88; 95% CI, 3.91 to 20.17). Additionally, oxybutynin IR caused more severe dry mouth compared to solifenacin. The incidence and severity of other adverse events with solifenacin were similar between age groups. Discontinuation of oxybutynin IR treatment occurred more often than solifenacin, irrespective of age. Although the numbers were low, there was a higher incidence of constipation and fatigue in patients >65 years who received solifenacin compared to oxybutynin IR. Secondary: Not reported
Amarenco et al.[79] (2017) SONIC Solifenacin 5 mg, 10 mg vs placebo vs	DB, MC, PRO, RCT Patients 18 to 65 years of age with neurogenic detrusor overactivity due to multiple sclerosis or spinal cord injury	N=189 4 weeks	Primary: Change in maximum cystometric capacity from baseline Secondary: Change from baseline in urodynamic variables as measured by	Primary: Mean increase from baseline to end of treatment in maximum cystometric capacity was 134.2 mL with solifenacin 10 mg versus 5.4 mL with placebo (P<0.001). Maximum cystometric capacity was also significantly improved with solifenacin 5 mg and oxybutynin versus placebo, with increases of 77.8 and 165.4 mL, respectively (P=0.007 and P<0.001 vs placebo). Secondary: Improvements in secondary urodynamic variables were greater with solifenacin and oxybutynin compared with placebo. Compared with placebo, all active treatment groups showed reductions in patient perception of bladder condition from baseline to end of treatment, but

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
oxybutynin hydrochloride 15 mg			cystometry, and patient-reported outcomes	these were statistically significant only for solifenacin 10 mg versus placebo (–0.6 vs –0.1; P=0.041). Of the I-QoL subscales, changes in "avoidance and limiting behavior" reached statistical significance for both solifenacin doses versus placebo (5 mg, P=0.014; 10 mg, P=0.030), whereas oxybutynin had no significant effect on any I-QoL subscore compared with placebo.
Hsiao et al.[80] (2011) Solifenacin 5 mg once daily vs tolterodine ER 4 mg once daily	OL, RCT Women ≥18 years who had ≥3 month history of OAB symptoms (including urgency, urinary frequency, nocturia or urge incontinence) and a mean of ≥8 micturitions per 24 hours	N=48 12 weeks	Primary: Changes in total voided volume, VVPM, and the episodes of micturition, urgency, incontinence and nocturia in 24 hours Secondary: Not reported	Primary: In the solifenacin group, there was a decrease in the PPBC and the micturition, urgency and incontinence episodes per 24 hours and the VVPM increased at most follow-up visits. In the tolterodine group, there was a decrease in the PPBC and the nocturia episodes per 24 hours, but the heart rate increased at most follow-up visits. There were no between- or within-group differences in the changes of the number of episodes of micturition, urgency, incontinence, nocturia or total voided volume per 24 hours or VVPM at weeks four, eight or 12. Compared to baseline, the volume voided was significantly increased after solifenacin treatment (P=0.04). The strong desire to void and pad test result improved after tolterodine treatment (P=0.02 and P=0.03, respectively). At 12 weeks, there were no between-group differences in changes of urodynamic data and pad test results. Changes in the heart rate differed significantly between these two groups at visit two (solifenacin vs tolterodine ER, -4.3; 95% CI, -7.2 to -1.3 vs 3.8; 95% CI, 0.3 to 7.3; P=0.02 and visit three (-3.2; 95% CI, -7.4 to 1.0 vs 4.8; 95% CI, 1.2 to 8.3; P=0.03). There was no difference in the number of patients who experienced adverse events between groups (P=0.23). Ten patients in the solifenacin group experienced adverse events, including dry mouth (n=7), constipation (n=3), palpitations (n=1), dizziness (n=1) and fatigue (n=1). Five patients in the tolterodine group experienced adverse events, including dry mouth (n=3), constipation (n=1), and palpitations (n=1). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Armstrong et al.[81] (2007) Oxybutynin XL 10 mg once daily vs tolterodine LA 4 mg once daily vs tolterodine IR 2 mg twice daily	MA of 2 studies Present study is a MA of the OPERA and OBJECT studies (Appell et al and Diokno et al)	N=1,168 12 weeks	Primary: Adverse events Secondary: Not reported	Primary: Gastrointestinal adverse events occurred in 41.8, 36.3 and 45.1% of patients receiving oxybutynin XL, tolterodine LA and tolterodine IR therapy, respectively (P value not reported). The most common adverse event was dry mouth, occurring in 29.3, 22.3 and 33.2% of patients receiving oxybutynin XL, tolterodine LA and tolterodine IR therapy, respectively (P value not reported). The incidence of nervous system adverse events in the oxybutynin XL, tolterodine LA, and tolterodine IR groups was comparable (10.2 vs 8.3 vs 10.9%, respectively; P value not reported). Most adverse events were mild or moderate in intensity. Severe drug-related adverse events occurred in 4.3, 1.5 and 2.6% of patients in the oxybutynin XL, tolterodine LA and tolterodine IR groups, respectively. The most common adverse event resulting in early discontinuation from the study was dry mouth, with 1.2, 1.0 and 1.6% of patients discontinuing treatment with oxybutynin XL, tolterodine LA and tolterodine IR, respectively (P value not reported). Secondary: Not reported
Madhuvrata et al.[82] (2012) Fesoterodine 4 to 8 mg once daily vs oxybutynin IR 2.5 to 5 mg twice daily to four times daily	MA of 86 studies Patients with a symptomatic diagnosis of OAB syndrome with or without a urodynamic diagnosis of detrusor overactivity	N=31,249 Up to 52 weeks	Primary: Condition-specific QOL and psychosocial measures Secondary: Patient observations, quantification of symptoms, clinician's	Primary: There was no significant difference between tolterodine and oxybutynin with regard to QOL (SMD, -0.00; 95% CI, -0.18 to 0.18). The results from three studies reported a statistically significant improvement in QOL for patients treated with solifenacin compared to tolterodine (SMD, -0.12; 95% CI, -0.23 to -0.01). Treatment with fesoterodine was associated with a significant improvement in QOL compared to tolterodine LA (SMD, -0.20; 95% CI, -0.27 to -0.14).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs oxybutynin XL 5 to 20 mg once daily vs tolterodine IR 1 to 2 mg twice daily vs tolterodine LA 2 to 4 mg once daily vs trospium IR 20 mg twice daily vs solifenacin 5 to 10 mg once daily vs placebo			measures, socioeconomics	Secondary: There was no statistically significant difference between tolterodine and oxybutynin with regard to the proportion of patients reporting a symptomatic cure or improvement (RR, 1.01; 95% CI, 0.93 to 1.11), fewer leakage episodes or voids over 24 hours (WMD, 0.33; 95% CI, -0.08 to 0.73). There was no difference in patient reported cure or improvement between patients receiving oxybutynin or trospium (RR, 1.00; 95% CI, 0.90 to 1.11). Moreover, there was no significant difference between the treatments with regard to cystometric capacity or residual bladder volume. Trospium was associated with fewer treatment withdrawals (RR, 0.66; 95% CI, 0.48 to 0.91) and a lower risk of dry mouth compared to oxybutynin (RR, 0.64; 95% CI, 0. 52 to 0.77). Compared to oxybutynin, tolterodine was associated with significantly lower rates of withdrawal due to adverse events (RR, 0.52; 95% CI, 0.40 to 0.66) and a lower incidence of dry mouth (RR, 0.65; 95% CI, 0.60 to 0.71). Treatment with solifenacin was associated with a higher patient report of cure or improvement compared to tolterodine (RR, 1.25; 95% CI, 1.13 to 1.39). There was a statistically significant reduction in the number of leakage episodes/24 hours (WMD, -0.30; 95% CI, -0.53 to -0.08 and urgency episodes/24 hours with solifenacin compared to tolterodine (WMD, -0.43; 95% CI, -0.74 to -0.13). Withdrawal rates due to adverse events and the incidence of dry mouth were similar between solifenacin and tolterodine; however, following the exclusion of one study with tolterodine LA, dry mouth rates were significantly lower with solifenacin compared to tolterodine LA (RR, 0.69; 95% CI, 0.51 to 0.94).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Fesoterodine treatment was associated with a higher rate of patient reported cure or improvement compared to tolterodine LA (RR, 1.11; 95% CI, 1.06 to 1.16). Compared to tolterodine LA, patients taking fesoterodine reported significant reductions in leakage episodes (WMD, -0.19; 95% CI, -0.30 to -0.09), frequency (WMD, -0.27; 95% CI, -0.47 to -0.06) and urgency episodes/24 hours (WMD, -0.44; 95%CI, -0.72 to -0.16). Patients receiving treatment with fesoterodine had a higher risk of withdrawal due to adverse event compared to tolterodine LA treatment (RR, 1.45; 95% CI, 1.07 to 1.98) and higher risk of dry mouth (RR, 1.80; 95% CI, 1.58 to 2.05). Similar improvements in leakage episodes and micturitions/24 hours were reported for 1, 2 and 4 mg doses of tolterodine IR administered twice daily. There was a higher incidence of dry mouth with both the 2 and 4 mg doses relative to the lower doses of tolterodine IR. Fesoterodine 8 mg was associated with a greater clinical efficacy (patient reported cure, leakage episodes, micturition/24 hours) compared to the 4 mg fesoterodine. There was no difference in efficacy between the 4 mg and 12 mg doses, although higher dose was associated with a greater incidence of dry mouth. The 8 mg strength was also associated with a higher risk of dry mouth compared to fesoterodine 4 mg. Both tolterodine LA and oxybutynin XL were associated with a lower risk of dry mouth compared to their respective IR formulations; however, no significant differences in cure, improvement, leakage episodes, micturitions/24 hours, or withdrawal events were reported between. There was a lower risk of dry mouth with tolterodine LA compared to oxybutynin XL (RR, 0.75; 95% CI, 0.59 to 0.95). There was no difference in the incidence of dry mouth between transdermal oxybutynin and tolterodine LA, although there was a higher withdrawal rate with transdermal oxybutynin due to a skin reaction at the transdermal patch site at 12 weeks.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Ho et al.[83] (2010) Solifenacin 5 mg once daily vs tolterodine ER 4 mg once daily	OL, PRO, RCT Male or female patients ≥18 years of age with OAB symptoms (urinary frequency, urgency, or urge incontinence) ≥3 months, who experienced frequency (defined as ≥8 micturitions per 24 hours)	N=75 12 weeks	Primary: Change from baseline to endpoint for the mean number of micturitions per 24 hours Secondary: Change from baseline to endpoint for MVV per micturition, mean urgency episode per 24 hours, mean incontinence per 24 hours, PPBC, patient and physician assessment of treatment benefit	Primary: Compared to baseline, both treatment groups showed significant improvements in reducing mean micturition numbers per 24 hours from week four. At week 12, the mean changes were not significantly different between solifenacin and tolterodine (-2.56 vs -2.44; P=0.58). Secondary: Both groups significantly improved urgency and incontinence episodes per 24 hours. At week 12, the mean changes from baseline were not significant for urgency episodes between solifenacin and tolterodine (-1.7 vs -1.15; P=0.37), nor were the mean changes for incontinence episodes (-2.79 vs -4.67; P=0.28). A significant increase in MVV per micturition was only observed in the solifenacin group (27.61±51.74 mL). PPBC was significantly improved with both groups compared to baseline. At week 12, the mean changes from baseline were -1.4 and -1.4 in the solifenacin and tolterodine groups, respectively. The difference between solifenacin and tolterodine was not statistically significant. Patient and physician assessment of treatment benefit showed that improvements were made in both groups compared to baseline, but not between each other. The most common adverse events for solifenacin and tolterodine were dry mouth (18.0 vs 8.3%; P=0.31) and constipation (12.8 vs 2.8%; P=0.2).
Chapple et al.[84] (2005) Solifenacin 5 to 10 mg once daily vs tolterodine ER 4 mg once daily	DB, MC, RCT Patients ≥18 years of age with OAB symptoms (≥8 micturitions/24 hours, ≥1 incontinence episode/24 hours, or ≥1 urgency	N=1,200 12 weeks	Primary: Micturition frequency Secondary: Urgency episodes, urge incontinence, total incontinence, nocturia, proportion of	Primary: The mean number of micturitions was reduced with solifenacin (-2.45) compared to treatment with tolterodine (-2.24; P=0.004 for non-inferiority). Secondary: Treatment with solifenacin led to a reduction in the number of urgency episodes/24 hours (-2.85) compared to treatment with tolterodine (-2.42; P<0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	episode/24 hours) for ≥3 months		patients who experienced a 50% reduction in incontinence episodes, pad usage, and QOL using a six-point categorical scale to assess perception of bladder condition	Treatment with solifenacin led to a reduction in the number of urge incontinence episodes/24 hours (-1.42) compared to treatment with tolterodine (-0.83; P<0.01). Treatment with solifenacin led to a reduction in the number of total incontinence episodes/24 hours (-1.60) compared to treatment with tolterodine (-1.11; P<0.01). There was no significant difference in nocturia among the treatment groups (P=0.730). Approximately 74% of patients receiving solifenacin who were incontinent at baseline experienced ≥50% reduction in incontinence episodes compared to 67% of patients receiving tolterodine (P=0.021). The percentage of patients who were incontinent at baseline who became continent at study end point was 59% (solifenacin) and 49% (tolterodine; P=0.006). The mean volume voided/micturition increased with solifenacin (38 mL) compared to tolterodine (31 mL; P=0.010). Solifenacin decreased the number of incontinence pads used compared to tolterodine (P=0.0023). Patient-reported perception of bladder condition was significantly improved with solifenacin compared to tolterodine (P=0.006). Approximately 5.9% of patients receiving solifenacin and 7.3% of patients receiving tolterodine discontinued treatment (for any reason); 1.2% and 2.0% discontinued therapy due to insufficient therapeutic response with solifenacin and tolterodine, respectively. The most common adverse events were dry mouth, constipation and blurred vision. The percentage of patients discontinuing treatment due to adverse events was similar between the treatment groups (3.5% of patients receiving solifenacin and 3.0% of patients receiving tolterodine). A total of 1.2 and 2.0% of patients discontinued therapy due to an insufficient therapeutic response with solifenacin and tolterodine, respectively.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Chapple et al.[85] (2004) Solifenacin 2.5 to 20 mg once daily vs tolterodine IR 2 mg twice daily vs placebo	DB, PC, RCT Patients 18 to 80 years of age with OAB and urodynamic evidence of detrusor overactivity (>8 voids/24 hours and >3 episodes of incontinence or urgency)	N=225 6 weeks	Primary: Number of voids/24 hours Secondary: Volume voided/ void; incontinence episodes/24 hours; urgency episodes/24 hours; and total sum score of Contilife items 1 to 27, sum scores of the five Contilife domains (i.e., daily activities, effort, self-image, emotional consequences, and sexuality), and overall Contilife QOL score	Primary: The mean change in number of voids/24 hours was significantly lower with solifenacin 5 mg (-2.21), 10 mg (-2.47) and 20 mg (-2.75) compared to placebo (-1.03; all P<0.05). There was no significant difference with tolterodine (-1.79) compared to placebo (P=NS). Secondary: The mean volume voided/void was significantly greater for solifenacin 5 mg, 10 and 20 mg than for placebo (all P<0.01). There was no significant difference with tolterodine compared to placebo. There was no significant difference in the mean number of incontinence episodes/24 hours with solifenacin or tolterodine compared to placebo. There was no significant difference in the number of urgency episodes/24 hours with solifenacin or tolterodine compared to placebo. Treatment with solifenacin led to significant improvements over baseline based on the results of the Contilife sum score QOL analysis compared to placebo. There was no significant difference with tolterodine compared to placebo. Treatment with solifenacin led to significant improvements in the daily life activities (all groups; P<0.01), self-image (10 and 20 mg; P<0.05), emotional consequences (5, 10 and 20 mg; P<0.05) and sexuality (10 and 20 mg; P<0.05) compared to placebo. Tolterodine resulted in significant improvements in the daily life activities domain only compared to placebo (P<0.05). Solifenacin 10 and 20 mg and tolterodine produced significant improvements over placebo in the Contilife overall QOL score (P<0.05). The most frequently reported adverse event was dry mouth, followed by constipation and blurred vision. The frequency of dry mouth was highest among patients receiving solifenacin 20 mg (38%), tolterodine 2 mg (24%) and solifenacin 5 and 10 mg (14% each). Constipation was reported in 19% of patients taking solifenacin 20 mg.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Chapple et al.[86] (2004) Solifenacin 5 to 10 mg once daily vs tolterodine IR 2 mg twice daily vs placebo	DB, MC, RCT Patients ≥18 years of age with symptoms of OAB (including urgency, urge incontinence, or frequency) for ≥3 months (≥8 voids/24 hours, ≥3 episodes of urgency and/or ≥3 episodes of incontinence)	N=1,081 12 weeks	Primary: Urgency episodes, all incontinence episodes, urge incontinence episodes, voids/24 hours and voided volume/void Secondary: Not reported	Primary: There was a significant decrease in the mean number of urgency episodes/24 hours with solifenacin 5 and 10 mg (-52% and -55%, respectively) compared to placebo (-33%; both P<0.001). There was no significant difference in urgency episodes/24 hours between tolterodine (-38%) and placebo (P=0.0511). Direct comparison of solifenacin 5 and 10 mg with tolterodine resulted in estimated differences of - 0.791 and - 1.015 (95% CI, -1.434 to -0.148, and -1.659 to -0.370), respectively. There was a significant decrease in urge incontinence episodes/24 hours with solifenacin 5 mg (-1.41; P=0.002) and 10 mg (-1.36; P=0.0028) compared to placebo (-0.62). There was no significant difference in urge incontinence episodes/24 hours between tolterodine (-0.91) and placebo (P=0.2390). There was no significant difference in urge incontinence episodes/24 hours between solifenacin and tolterodine (5 mg, -0.487; 95% CI, -0.988 to 0.014 and 10 mg, -0.436; 95% CI, -0.921 to 0.048). There was a significant decrease in all incontinence episodes/24 hours with solifenacin 5 mg (-1.42; P=0.008) and 10 mg (-1.45; P=0.0038) compared to placebo (-0.76). There was no significant difference in all incontinence episodes/24 hours between tolterodine (-1.14) and placebo (P=0.1122). There was no significant difference in all incontinence episodes/24 hours between solifenacin and tolterodine (5 mg, -0.276; 95% CI, -0.761 to 0.208 and 10 mg, -0.316; 95% CI, -0.786 to 0.164). There was a significant decrease in mean number of voids/24 hours with solifenacin 5 mg (-2.19, -17%; P<0.001), solifenacin 10 mg (-2.61, -20%; P<0.001) and tolterodine (- 1.88, -15%; P=0.0145) compared to placebo (-1.20, - 8%). Direct comparison of solifenacin 5 and 10 mg with tolterodine resulted in estimated differences of -0.312 and -0.737 (95% CI -0.844 to 0.219, and -1.269 to -0.204). There was a significant increase in mean volume voided/void with solifenacin 5 mg (32.9 mL, +25.1%), solifenacin 10 mg (39.2 mL, +29.0%), and tolterodine (24.4 mL, +20.3%) compared to placebo (7.4 mL; all, P<0.001). There was no significant difference in mean volume

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				voided/void between solifenacin and tolterodine (5 mg, 8.4 mL; 95% CI, 0.496 to 16.34 and 10 mg, 14.8 mL; 95% CI, 6.855 to 22.72). The percentages of patients discontinuing treatment for an adverse event were 3.7% in the placebo group, 3.2% in the solifenacin 5 mg group, 2.6% in the solifenacin 10 mg group, and 1.9% in the tolterodine group. The incidence of dry mouth was lowest with solifenacin 5 mg (14%). Constipation was reported in 7.2 and 7.8% of patients treated with solifenacin 5 and 10 mg, respectively, in 2.6% of patients treated with tolterodine and in 1.9% of placebo patients. Blurred vision was reported in 3.6% of patients receiving solifenacin 5 mg, 5.6% receiving solifenacin 10 mg, 1.5% receiving tolterodine, and 2.6% receiving placebo. Secondary: Not reported
Yamaguchi et al.[87] (2011) Solifenacin 2.5 mg plus tamsulosin 0.2 mg once daily (TAM+SOL 2.5) vs solifenacin 5 mg plus tamsulosin 0.2 mg once daily (TAM+SOL 5) vs tamsulosin 0.2 mg once daily plus placebo (TAM+PBO)	DB, MC, PC, RCT Men ≥50 years of age with LUTS and residual OAB symptoms despite treatment with tamsulosin for ≥6 weeks, ≥2 urgency episodes per 24 hours in a 3-day bladder diary, Qmax ≥5 mL/s, and PVR volume <50 mL	N=638 12 weeks	Primary: Mean change in urgency episodes per 24 hours Secondary: Mean changes in micturitions, nocturia episodes, urgency incontinence episodes, IPSS, IPSS-QOL, and OABSS	Primary: The mean number of urgency episodes per 24 hours decreased by 2.2 and 2.4 episodes in the TAM+SOL 2.5 and TAM+SOL 5 groups, respectively. TAM+SOL 5 showed a significant improvement in urgency episodes compared to TAM+PBO (P=0.049). Secondary: The number of micturitions per 24 hours was reduced by 1.27 episodes in the TAM+SOL 2.5 group and by 1.06 episodes in TAM+SOL 5 groups, and both of these were significantly better than TAM+PBO (0.22 episodes; P<0.01). Compared to TAM+PBO, TAM+SOL 2.5 and TAM+SOL 5 did not significantly reduce the number of nocturia episodes and urgency incontinence. IPSS storage symptom score was significantly improved in both solifenacin groups compared to placebo. IPSS total score, voiding symptom score, post-micturition symptom score, or QOL were no significantly better compared to placebo.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				For OABSS, both solifenacin groups significantly improved the total score, daytime frequency score, urgency score, and urgency incontinence score compared to placebo. The most common adverse events were dry mouth (6.2% for TAM+SOL 2.5 vs 11.3% for TAM+SOL 5), constipation (3.8% for TAM+SOL 2.5 vs 10.3% for TAM+SOL 5), increase in PVR ≥50 mL (2.9% for TAM+SOL 2.5 vs 6.1% for TAM+SOL 5), abdominal discomfort (2.4% for TAM+SOL 2.5 vs 1.9% for TAM+SOL 5), and creatinine phosphokinase increase (1.9% for TAM+SOL 2.5 vs 2.3% for TAM+SOL 5). A total of four patients in TAM+SOL 5 had urinary retention requiring temporary cauterization.
Kreder et al.[88] (2002) Tolterodine ER 4 mg once daily	ES, OL Patients ≥18 years of age with urinary frequency (≥8 micturitions/24 hours), urge incontinence (≥5 incontinence episodes/week) and urgency for ≥6 months	N=1,077 12 months	Primary: Safety and tolerability Secondary: Efficacy	Primary: The most common adverse events were autonomic nervous system disorders (13.2%), gastrointestinal disorders (11.4%), general body disorders (14.5%), respiratory disorders (9.8%), urinary disorders (9.1%) and musculoskeletal disorders (6.0%). The most frequently report adverse event was dry mouth, which occurred in 12.9% of patients. Approximately 10% of patients withdrew from the study due to adverse events. The most common adverse events leading to withdrawal were dry mouth (1.8%), headache (0.8%), abdominal pain (0.8%), dizziness (0.7%), UTI (0.7%), dyspepsia (0.6%), constipation (0.6%), xerophthalmia (0.5%), and micturition disorders (0.5%). Secondary: The number of urge incontinence episodes/week was significantly decreased with tolterodine compared to baseline (median change, -83%). The number of micturitions/24 hours significantly decreased with tolterodine compared to baseline (median change, -21%). The change in volume voided/micturition significantly increased with tolterodine compared to baseline (median change, 25%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Approximately 75% of patients who received tolterodine perceived improvement after 12 months of therapy.
Takei et al.[89] (2005) Tolterodine ER 4 mg once daily	ES, OL Japanese patients ≥20 years of age with OAB symptoms including urinary urgency, urinary frequency (≥8 micturitions/24 hours) and urge incontinence (≥5 episodes/week) for ≥6 months	N=188 12 months	Primary: Safety and tolerability Secondary: Efficacy	Primary: The most common adverse event was dry mouth (33.5%). The incidence decreased during the course of the OL extension (24.5% during the first three months vs 4.3% during the six to 12-month periods). Approximately 23% of patients withdrew prematurely due to adverse events (10.0%), lack of efficacy (8.0%), consent withdrawal (3.7%), lost to follow-up (0.5%) and protocol violation (0.5%). Secondary: The number of incontinence episodes/week was decreased with tolterodine (mean change, -77.2%). The number of micturitions/24 hours significantly decreased with tolterodine (mean change, -21.3%; P<0.0001). The change in volume voided/micturition significantly increased with tolterodine (mean change, 19.6%; P<0.0001).
Choo et al.[90] (2008) Tolterodine ER 4 mg once daily	OL Patients ≥18 years of age with OAB who had urinary frequency (≥8 micturitions/24 hours) and urgency (≥2 episodes/24 hours) with or without urgency incontinence	N=60 12 weeks	Primary: Rate of PGA by a visual analogue scale Secondary: Changes in symptom severity, voiding diary and PPBC, and willingness to continue treatment	Primary: The median rate of PGA was: frequency (60%; 95% CI, 46.9 to 63.6), urgency (60%; 95% CI, 46.2 to 64.9), urge incontinence (80%; 95% CI, 34.2 to 80.0), nocturia (50%; 95% CI, 39.4 to 57.6) and tenesmus (30%; 95% CI, 25.4 to 52.2). Secondary: The median percentage reduction in symptom severity was as follows: frequency (45%; 95% CI, 36.2 to 54.4), urgency (55%; 95% CI, 40.1 to 60.4), urgency incontinence (71%; 95% CI, 39.2 to 76.8), nocturia (52%; 95% CI, 40.2 to 59.7) and tenesmus (26%; 95% CI, 16.9 to 50.4). Patients reported that the most troublesome symptoms were daytime frequency (50.0%), nocturia (17.9%), urgency incontinence (16.1%), urgency (10.7%) and tenesmus (5.4%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Frequency (-2.7), urgency (-4.2), urgency incontinence (-1.0), and nocturia (-0.7) were significantly reduced with tolterodine (all, P<0.01). The mean voided volume significantly increased with tolterodine (32 mL; P=0.05). Approximately 90% of patients experienced an improvement of at least one point in their bladder condition, and 62.5% reported improvements of at least two points on the PPBC questionnaire. A total of 73.2% of patients wished to continue treatment after receiving three months of treatment. The most common adverse events were dry mouth (21.7%), constipation or indigestion (10.0%), headache (5.0%), UTI (3.3%) and peripheral edema (1.7%).
Van Kerrebroeck et al.[91] (2001) Tolterodine ER 4 mg once daily vs tolterodine IR 2 mg twice daily vs placebo	DB, MC, PC, RCT Patients ≥18 years of age with urinary frequency (≥8 micturitions/24 hours) and urge incontinence (≥5 incontinence episodes/week) for ≥6 months	N=1,529 12 weeks	Primary: Incontinence episodes/week, number of micturition/24 hours, volume voided/micturition, and the number of pads used/24 hours Secondary: Not reported	Primary: The mean change in incontinence episodes/week was significantly better with tolterodine ER (-11.8; P=0.0001) and tolterodine IR (-10.6; P=0.0005) compared to placebo (-6.9). The median percentage reductions in incontinence episodes/week were: tolterodine ER, 71%; tolterodine IR, 60%; and placebo, 33%. Tolterodine ER was 18% more effective than tolterodine IR (P<0.05). The mean change in number of micturitions/24 hours was significantly better with tolterodine ER (-1.8; P=0.0047) and tolterodine IR (-1.7; P=0.0079) compared to placebo (-1.2). The mean change in volume voided/micturition was significantly greater with tolterodine ER (34 mL; P=0.0001) and tolterodine IR (29 mL; P=0.0001) compared to placebo (14 mL). The mean change in number of pads used/24 hours was significantly lower with tolterodine ER (-0.5; P=0.0145) and tolterodine IR (-0.5; P=0.0035) compared to placebo (-0.2). The most common adverse events in all treatment groups were dry mouth, constipation, and headache. With the exception of dry mouth, the incidence of adverse events was comparable between active treatment and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				placebo. The rate of dry mouth was 23, 30, and 8% for tolterodine ER, tolterodine IR, and placebo, respectively. Patients receiving tolterodine ER had 23% less dry mouth than those taking tolterodine IR (P=0.02). Discontinuation rates due to adverse events were similar in all the treatment groups (tolterodine ER, 5%; tolterodine IR, 5%; placebo, 6%). Secondary: Not reported
Swift et al.[92] (2003) Tolterodine ER 4 mg once daily vs tolterodine IR 2 mg twice daily vs placebo	DB, MC, PC, RCT (Subgroup analysis) Women ≥18 years of age with urinary frequency (≥8 micturitions/24 hours) and urge incontinence (≥5 incontinence episodes/week) for ≥6 months	N=1,235 12 weeks	Primary: Incontinence episodes/week, number of micturition/24 hours, volume voided/micturition, and the number of pads used/24 hours Secondary: Not reported	Primary: The mean change in incontinence episodes/week was significantly better with tolterodine ER (-11.8; P=0.001) and tolterodine IR (-10.1; P=0.001) compared to placebo (-7.2). The difference between tolterodine ER and tolterodine IR was significant (P=0.036). The median percentage reductions in incontinence episodes/week were: tolterodine ER, 71%; tolterodine IR, 57%; and placebo, 33%. The mean change in number of micturitions/24 hours was significantly better with tolterodine ER (-1.9; P=0.001) and tolterodine IR (-1.7; P=0.005) compared to placebo (-1.2). There was no significant difference between tolterodine ER and tolterodine IR. The mean change in volume voided/micturition was significantly greater with tolterodine ER (37.9 ml; P=0.001) and tolterodine IR (32.5 mL; P=0.001) compared to placebo (13.3 mL). There was no significant difference between tolterodine ER and tolterodine IR. The mean change in number of pads used/24 hours was significantly lower with tolterodine ER (-0.6; P=0.001) and tolterodine IR (-0.5; P=0.001) compared to placebo (-0.2). There was no significant difference between tolterodine ER and tolterodine IR. Dry mouth, constipation, headache and UTI were the most common adverse events in all treatment groups. With the exception of dry mouth, the incidence of adverse events was comparable between active treatment and placebo. There was no significant difference in dry mouth with tolterodine ER or tolterodine IR (P=0.06). Discontinuation rates due to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				adverse events were similar in all the treatment groups (tolterodine ER, 5%; tolterodine IR, 5%; placebo, 6%). Secondary: Not reported
Homma et al.[93] (2003) Tolterodine ER 4 mg once daily vs oxybutynin IR 3 mg three times daily vs placebo	AC, DB, PC, RCT, Patients ≥20 years of age with OAB and symptoms of urinary urgency, urinary frequency (≥8 micturitions/24 hours) and urge incontinence (≥5 episodes/week) for ≥6 months	N=608 12 weeks	Primary: Incontinence episodes/week Secondary: Voids/24 hours and mean volume voided/void, median number of incontinence pads used/24 hours, patient perception of bladder condition, patient perception of urgency, and QOL using the KHQ	Primary: The number of incontinence episodes/24 hours was significantly decreased with tolterodine (median -78.6%; P=0.0027) and oxybutynin (median -76.5%; P=0.0168) compared to placebo (-46.4%). There was no significant difference between tolterodine and oxybutynin (P=0.4469). Secondary: The number of voids/24 hours decreased with tolterodine (-2.0; P<0.001) and oxybutynin (-2.1; P=0.0114) compared to placebo (-1.1). There was no significant difference among the treatment groups (P=0.3132). The volume voided/void increased significantly with tolterodine (17.2 mL; P=0.0086) and oxybutynin (22.3 mL; P<0.001) compared to placebo (6.6 mL). The number of pads used/24 hours was not significantly different among the treatment groups. Approximately 72% of patients treated with tolterodine and 73% treated with oxybutynin perceived improvement after 12 weeks of treatment compared to 59% of patients treated with placebo. The difference between tolterodine and placebo was NS (P=0.515). There was no significant difference between tolterodine and oxybutynin (P=0.9394). Significantly more patients reporting at least some benefit with tolterodine (79%; P=0.0091; little benefit 36%; much benefit, 42%) and oxybutynin (81%; P<0.001; little benefit 29%; much benefit 53%) than with placebo (66%; little benefit 40%; much benefit 25%). There was no significant difference between tolterodine and oxybutynin in the assessment of treatment benefit (P=0.2240).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Treatment with tolterodine and oxybutynin resulted in significantly greater mean reductions in both the incontinence impact domain and role limitation domain scores (KHQ questionnaire) compared to placebo. There was no significant difference between the improvements with tolterodine and oxybutynin for either domain. Tolterodine and oxybutynin were associated with improvements in other KHO domains, including physical limitations, social limitations, personal relationships, sleep/energy, severity measures, and the severity of urinary symptoms compared to placebo. The differences in improvements between tolterodine and oxybutynin were NS for any of these domains. Dry mouth was the most common adverse event reported with tolterodine (33.5%), oxybutynin (53.7%) and placebo (9.8%). Dry mouth was more common in patients receiving oxybutynin than tolterodine (P<0.001). Other adverse events occurring in >5% of patients were constipation, abdominal pain/tenderness, dyspepsia, difficulty in voiding and headache. Eye disorders occurred in significantly more patients receiving oxybutynin than tolterodine (P<0.0383). The incidence of nervous system disorders was lower in the tolterodine group (8.4%) than in the oxybutynin group (12.7%) or placebo group (11.5%). More patients on oxybutynin withdrew due to adverse events compared to tolterodine (P<0.001).
Sussman et al.[94] (2002) Trial 1 Tolterodine ER 2 to 4 mg once daily Trial 2 Oxybutynin ER 5 to 10 mg once daily	OL, RCT Patients ≥18 years of age with OAB and symptoms of urinary frequency and urgency with or without urge incontinence	Trial 1 N=669 8 weeks Trial 2 N=620 8 weeks	Primary: Patient perception of bladder condition and patient assessment of treatment benefit Secondary: Physician assessment of treatment benefit	Primary: Seventy percent of patients in the tolterodine 4 mg group perceived an improvement in their bladder condition compared to 60% in the tolterodine 2 mg group, 59% in the oxybutynin 5 mg group, and 60% in the oxybutynin10 mg group (all P<0.01 vs tolterodine 4 mg). There was a greater percentage of patients who reported an improved bladder condition with tolterodine 4 mg compared to oxybutynin 10 mg (77 vs 65%; P<0.01) in those whose perception of bladder condition was moderate to severe at baseline. There was no significant difference in the perception of their bladder condition among treatment-naïve patients (P=0.11) and those who had received prior antimuscarinic therapy (P=0.11).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: There was no significant difference in patient assessment or physician's assessment of treatment benefit between tolterodine and oxybutynin. Dry mouth was dose-dependent in both trials (tolterodine 2 mg vs tolterodine 4 mg; P=0.09; oxybutynin 5 mg vs oxybutynin 10 mg; P=0.05). Patients treated with tolterodine 4 mg reported a significantly lower severity of dry mouth compared to oxybutynin 10 mg (P=0.03).
Chung et al.[95] (2010) Tolterodine ER 4 mg once daily and dutasteride 0.5 mg once daily	OL Men ≥45 years of age on dutasteride 0.5 mg for at least 6 months who failed alpha-blocker therapy, prostate >30 g, an IPSS ≥12, IPSS QOL item ≥3, ≥8 voids per 24 hours, ≥3 urgency episodes per 24 hours with or without urgency incontinence, and self-rated bladder condition on patient perception of bladder condition of hours at least "some moderate bother"	N=51 12 weeks	Primary: Change in frequency, nocturnal OAB micturition, IPSS, Qmax, change in PVR, adverse events, and episodes of urinary retention requiring a catheter Secondary: Not reported	Primary: Tolterodine ER significantly reduced frequency and urgency. Specifically, tolterodine reduced 24 hours micturition frequency (-3.2; P<0.02), OAB episodes (19.2%; P<0.03), severe OAB episodes (71.4%; P<0.05), and nighttime voiding (-0.9; P<0.003). Patients reported a reduction in 24 hours frequency from baseline 11.9 episodes to 10.2 episodes after three months of dutasteride, which further decreased to 8.7 after 12 weeks of tolterodine ER. IPSS decreased with the initial addition of dutasteride (19.3 to 14.3) and further decreased with the addition of tolterodine ER (7.1; P<0.001). There were no significant decreases in Qmax with the addition of tolterodine ER and tolterodine ER did not significantly increase PVR. Additionally, zero patients required catheterization. Four patients (7.5%) experienced dry mouth, one patient (2%) had constipation, and sexual function decreased in two patients (3.9%). Secondary: Not reported
Chung et al.[96] (2011) Tolterodine ER 4 mg once daily plus doxazosin 4 mg	OS, PRO, RCT Male patients ≥70 years of age with an IPSS score >8 and a storage subscore of	N=153 12 months	Primary: Improvement in IPSS subscores (voiding and storage) at 12 months	Primary: The mean IPSS-voiding (8.5 to 2.88 with tolterodine [P<0.001], 9.83 to 4.78 without tolterodine [P<0.001]), IPSS-storage (9.44 to 5.18 with tolterodine [P<0.001], 8.34 to 6.92 without tolterodine [P<0.001]), and IPSS-total (18.1 to 8.06 with tolterodine [P<0.001], 18.2 to 11.7 without

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
and/or dutasteride 0.5 mg once daily vs doxazosin 4 mg and/or dutasteride 0.5 mg once daily	>5, QOL index score >3, total prostate volume >20 mL, Qmax <15 mL/second, and with urodynamic confirmed BPH/BOO		Secondary: Change in PVR volume, and QOL-I	tolterodine [P<0.001]) improved similarly in both groups by 12 months follow-up. The patients receiving tolterodine ER experienced a better reduction of IPSS-storage symptoms (4.26 vs 1.42; P<0.001). Secondary: The change of PVR in the patients who received tolterodine ER did not differ significantly from those who did not (15.2 vs 8.9 mL; P=0.69). QoL-I also improved in both groups, but change was not significantly different from each other (1.62 vs 1.46; P=0.551). Both groups demonstrated a significant improvement in Qmax compared to baseline, but there was not a significant difference between the two groups (P=0.275). Intolerable dry mouth, constipation, and dizziness were the most commonly reported adverse events and numerically occurred more in patients who received tolterodine ER.
Abrams et al.[97] (2001) Tolterodine IR 2 mg twice daily	ES, OL Patients ≥18 years of age with urinary frequency (≥8 micturitions/24 hours), urgency, and/or urge incontinence (≥1 incontinence episode/24 hours)	N=714 12 months	Primary: Number of micturitions/24 hours, number of urge incontinence episodes/24 hours, mean urine volume voided/micturition, safety Secondary: Not reported	Primary: The number of micturitions/24 hours significantly decreased with tolterodine (-2.4; P=0.0001; mean change, -20%). The number of urge incontinence episodes/24 hours significantly decreased with tolterodine (-1.3; P=0.0001; median change, -74%). The change in volume voided/micturition significantly increased with tolterodine (33 mL; P=0.0001; mean change, 18%). Approximately 69% of patients who received tolterodine perceived improvement after 12 months of therapy. The most frequently occurring adverse events were autonomic nervous system disorders (46%), general body disorders (22%), gastrointestinal disorders (22%) and urinary disorders (18%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The most frequently report adverse event was dry mouth, which occurred in 41% of patients (27% mild, 10% moderate, 3% severe). The most common adverse events leading to withdrawal were adverse events (15%), withdrawal of consent (13%), lost to follow-up (4%) and other (6%). A total of 34 (5%) patients withdrawing from the study due to dry mouth. Secondary: Not reported
Appell et al.[98] (2001) Tolterodine IR 2 mg twice daily	ES, OL Patients ≥18 years of age with OAB, increased urinary frequency (≥8 micturitions/24 hours) and urge incontinence (≥1 incontinence episode/24 hours) or urinary frequency	N=854 9 months	Primary: Safety and tolerability Secondary: Efficacy	Primary: The most frequently reported adverse events were autonomic nervous system disorders (31%), gastrointestinal disorders (24%) and general body disorders (26%). The most frequently report adverse event was dry mouth, which occurred in 28% of patients (19% mild, 7% moderate, 2% severe). Of those patients enrolled in the OL trial, 30% did not complete nine months of therapy. The most common reasons for withdrawal were adverse events (9%), lack of efficacy (6%), lot to follow-up (6%) and withdrawal of consent (4%). Secondary: The number of micturitions/24 hours significantly decreased with tolterodine (-2.5; P=0.0001; median change, -22%). The number of urge incontinence episodes/24 hours significantly decreased with tolterodine (-2.0; P=0.0001; median change, -76%). The change in volume voided/micturition significantly increased with tolterodine (40 mL; P=0.0001; median change, 22%). Approximately 65% of patients who received tolterodine perceived improvement after nine months of therapy. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Not reported
Kilic et al.[99] (2006) Tolterodine IR 1 mg twice daily vs oxybutynin IR 0.4 mg/kg three times daily	PRO, RCT Children with detrusor instability (most with symptoms of nocturnal enuresis associated with daytime incontinence, frequency, urgency, and/or small bladder volume)	N=60 ≥6 months	Primary: Urodynamic investigations before and after treatment, episodes of UUI, and adverse events Secondary: Not reported	Primary: The tolterodine group had a significant increase in the bladder capacity from 148.5 to 239.33 mL; P<0.001, an increase in compliance from 4.6 to 12.57; P<0.001, and a decrease in the maximum detrusor pressure from 79.43 to 40.4 cm H_20; P<0.001. In the oxybutynin group, a significant increase in bladder capacity from 154.67 to 255.23 mL; P<0.001, an increase in compliance from 5.13 to 13.07; P<0.001, and a decrease in the maximum detrusor pressure from 85.47 to 39.43 cm H_20; P<0.001, were found. Increase in the bladder capacity and compliance during cystometry and reduction in the maximal bladder pressure over the period were similar for tolterodine and oxybutynin groups. While there was not a statistically significant difference between the groups, both had a significant reduction in detrusor instability after six months (100 to 30.0% for tolterodine and 100 to 23.3% for oxybutynin). Clinical response was also similar between tolterodine and oxybutynin (73.3% for tolterodine and 80.0% for oxybutynin; P>0.05). Adverse events were significantly lower in the tolterodine group compared to the oxybutynin group (13 vs 27 events; P=0.027). Eight patients in the oxybutynin group were crossed over to tolterodine due to adverse effects. Secondary: Not reported
Appell et al.[100] (1997) Tolterodine IR 1 to 2 mg twice daily	DB, MC, PC, RCT (Pooled analysis) Patients ≥18 years of age with OAB, increased urinary frequency (≥8	N=1,120 (4 trials) 12 weeks	Primary: Number of micturitions/24 hours, number of incontinence episodes/24 hours, and mean urinary	Primary: The number of micturitions/24 hours significantly decreased with tolterodine 1 mg (P<0.001), tolterodine 2 mg (P<0.001), and oxybutynin (P<0.01) compared to placebo. There was no significant difference between tolterodine 2 mg and oxybutynin.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs oxybutynin IR 5 mg three times daily vs placebo	micturitions/24 hours) and urge incontinence (≥1 incontinence episode/24 hours) or urinary frequency		volume voided/micturition Secondary: Not reported	The number of incontinence episodes/24 hours significantly decreased with tolterodine (1 and 2 mg) and oxybutynin compared to placebo (P<0.05). There was no significant difference between tolterodine 2 mg and oxybutynin. The change in volume voided/micturition significantly increased with tolterodine (1 and 2 mg) and oxybutynin compared to placebo (P<0.001). Approximately 39% of patients who received placebo, 41% treated with tolterodine 1 mg, 52% treated with tolterodine 2 mg (P=0.003 vs placebo), and 50% treated with oxybutynin (P=0.017 vs placebo) perceived improvement after 12 weeks of treatment. Dry mouth was the most common adverse event (16% of the placebo group, 24% of the tolterodine 1 mg group, 40% of the tolterodine 2 mg group, and 78% of the oxybutynin group). The percentage of patients reporting dry mouth was significantly higher in the oxybutynin group than in the tolterodine or placebo groups (all, P<0.001). The percentage of patients reporting moderate or severe dry mouth was higher in the oxybutynin group (60%) compared to the tolterodine 1 mg group (4%), tolterodine 2 mg group (17%), and placebo group (6%; all, P<0.001). Other commonly reported adverse events included headache, dyspepsia, dizziness, and UTI. Dyspepsia was reported at a higher rate with oxybutynin (11%) than with tolterodine2 mg (6%; P=0.006). The proportion of patients who withdrew because of adverse events was higher in the oxybutynin group than in either of the tolterodine groups or the placebo group (all, P<0.001). Secondary: Not reported
Lee et al.[101] (2002) Tolterodine IR 2 mg twice daily	DB, MC, PG, RCT Patients ≥18 years of age with OAB and symptoms of urinary urgency and	N=228 8 weeks	Primary: Number of micturition/24 hours and incontinence episodes/24 hours	Primary: The number of micturitions/24 hours decreased with tolterodine (-2.6) and oxybutynin (-1.8) compared to baseline. There was no significant difference among the treatment groups (P=0.14).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs oxybutynin IR 5 mg twice daily	frequency (≥8 micturitions/24 hour) for ≥6 months		Secondary: Not reported	In patients who were incontinent at baseline, the number of incontinence episodes/24 hours decreased with tolterodine (-2.2) and oxybutynin (-1.4). There was no significant difference among the treatment groups (P=0.10). Overall, 45% of patients who received tolterodine and 46% of patients who received oxybutynin reported 'much' benefit. There was no significant difference among the groups. The most frequently reported adverse events were autonomic nervous system disorders, gastrointestinal disorders, and urinary disorders. Dry mouth was the most commonly reported adverse event and was significantly higher with oxybutynin than tolterodine (P=0.001). There was a higher frequency of moderate-to-severe dry mouth with oxybutynin (28%) than tolterodine (9%). Secondary: Not reported
Malone-Lee et al.[102] (2001) Tolterodine IR 2 mg twice daily vs oxybutynin IR 5 mg twice daily	DB, MC, RCT Patients ≥50 years of age with OAB, increased urinary frequency (≥8 micturitions/24 hours), and symptoms of urgency and/or urge incontinence (≥1 episode/24 hours)	N=379 10 weeks	Primary: Number of micturition/24 hours, incontinence episodes/24 hours and volume voided/micturition Secondary: Not reported	Primary: The number of micturitions/24 hours decreased with tolterodine (-1.7) and oxybutynin (-1.7). There was no significant difference among the treatment groups (P=0.97). The number of incontinence episodes/24 hours decreased with tolterodine (-1.3) and oxybutynin (-1.8). There was no significant difference among the treatment groups (P=0.065). The change in volume voided/micturition increased with tolterodine (33 mL) and oxybutynin (34 mL). There was no significant difference among the treatment groups (P=0.90). Approximately 45% of patients treated with tolterodine and 41% treated with oxybutynin perceived improvement after 12 weeks of treatment. There was no significant difference among the treatment groups. Autonomic nervous system disorders and gastrointestinal problems were the most commonly reported adverse events. A higher percentage of patients experienced dry mouth with oxybutynin (61%) than with

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				tolterodine (37%). Severe dry mouth was more common in the oxybutynin group (15%) than in the tolterodine group (4%). The proportion of patients who withdrew because of adverse events was similar in the oxybutynin group (15%) and in the tolterodine group (15%). Secondary: Not reported
Abrams et al.[103] (1998) Tolterodine IR 2 mg twice daily vs oxybutynin IR 5 mg three times daily vs placebo	DB, MC, PC, RCT Patients ≥18 years of age with OAB, increased urinary frequency (≥8 micturitions/24 hours), and symptoms of urgency and/or urge incontinence (≥1 episode/24 hours) for ≥6 months	N=293 12 weeks	Primary: Number of micturition/24 hours, incontinence episodes/24 hours and volume voided/micturition Secondary: Not reported	Primary: The mean change in number of micturitions/24 hours was significantly lower with tolterodine (-2.7; P=0.0022) compared to placebo (-1.6). There was no difference between oxybutynin (-2.3) and placebo (P=0.068). There was also no significant difference between tolterodine and oxybutynin (95% CI, -1.1 to 0.1). The number of incontinence episodes/24 hours significantly decreased with oxybutynin (-1.7; P=0.023) compared to placebo (-0.9). There was no difference between tolterodine (-1.3) and placebo (P=0.22). There was also no significant difference between tolterodine and oxybutynin (95% CI, -0.2 to 1.0). The change in volume voided/micturition significantly increased with tolterodine (38 mL) and oxybutynin (47 mL) compared to placebo (6 mL; P<0.001). Approximately 47% of patients who received placebo, 50% treated with tolterodine, and 49% treated with oxybutynin perceived improvement after 12 weeks of treatment. There was no significant difference among the groups. Dry mouth was the most common adverse event. It was reported at a significantly higher rate with both tolterodine (50%) and oxybutynin (86%) than placebo (21%; P<0.001). It was also more common with oxybutynin than tolterodine (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The proportion of patients who withdrew because of adverse events was higher in the oxybutynin group (17%) than in the tolterodine (8%) or placebo (12%) groups. Secondary: Not reported
Drutz et al.[104] (1999) Tolterodine IR 2 mg twice daily vs oxybutynin IR 5 mg three times daily vs placebo	DB, MC, PC, RCT Patients ≥18 years of age with OAB, increased urinary frequency (≥8 micturitions/24 hours), and symptoms of urgency and/or urge incontinence (≥1 episode/24 hours)	N=277 12 weeks	Primary: Number of micturition/24 hours, incontinence episodes/24 hours and volume voided/micturition Secondary: Not reported	Primary: The number of micturitions/24 hours significantly decreased with tolterodine (-2.0; P=0.036) compared to placebo (-1.1). There was no difference between oxybutynin (-2.0) and placebo (P=0.066). There was also no significant difference between tolterodine and oxybutynin (95% CI, -0.8 to 0.8). The number of incontinence episodes/24 hours was not significantly different with tolterodine (-1.7; P=0.063) or oxybutynin (-1.7; P=0.10) compared to placebo (-1.0). There was no significant difference between tolterodine and oxybutynin (95% CI, -0.7 to 0.7). The change in volume voided/micturition significantly increased with tolterodine (34 mL; P=0.0075) and oxybutynin (50 mL; P=0.0001) compared to placebo (12 mL). Dry mouth was the most common adverse event (15% of the placebo group, 30% of the tolterodine group, and 69% of the oxybutynin group). The percentage of patients reporting dry mouth was significantly higher in the oxybutynin group than in the tolterodine group (P<0.001). The percentage of patients reporting moderate or severe dry mouth was higher in the oxybutynin group (44%) compared to the tolterodine group (9%), and placebo group (7%). Other more commonly reported adverse events with oxybutynin were headache (10%) and dizziness (11%). Headache occurred in 15% of patients receiving tolterodine. The proportion of patients who withdrew because of adverse events was higher in the oxybutynin group (31%) than in the tolterodine (13%) or placebo (14%) groups. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Not reported
Leung et al.[105] (2002) Tolterodine IR 2 mg twice daily vs oxybutynin IR 5 mg three times daily	DB, MC, RCT Women ≥18 years of age with OAB, increased urinary frequency (≥8 micturitions/24 hours), and symptoms of urgency and/or urge incontinence (≥1 episode/24 hours)	N=106 10 weeks	Primary: Tolerability Secondary: Efficacy	Primary: The median drug compliance rate was 87.5% with oxybutynin and 75% in with tolterodine (P=0.778). Adverse events occurred in 49.1% of patients treated with oxybutynin and 60.4% of patients treated with tolterodine (P=0.329). The proportion of patients who withdrew was 15.1% with oxybutynin and 17.0% with tolterodine (P=1.0). Secondary: There was no significant difference in frequency of micturition (P=0.965), urgency episodes (P=0.672), incontinence episodes (P=0.993), or pad use (P=0.665) among the treatment groups.
Giannitsas et al.[106] (2004) Tolterodine IR 2 mg twice daily for 6 weeks vs oxybutynin IR 5 mg three times daily for 6 weeks	OL, RCT, XO Patients ≥18 years of age with OAB who were categorized according to the characteristics of the first overactive detrusor contraction during filling cystometrogram: high volume–low pressure (grade-group I), high volume–high pressure (grade-group II), low volume–low pressure (grade-group III) and low	N=128 12 weeks	Primary: Volume voided/micturition, number of micturition/24 hours, incontinence episodes/24 hours, and other urodynamic parameters in the total population and individual severity groups Secondary: Not reported	Primary: <u>Total Study Population</u> The mean volume voided/micturition was significantly increased with tolterodine (40.6 mL) and oxybutynin (43.8 mL) and there was no significant difference among the treatment groups. The mean change in number of micturitions/24 hours was -0.9 with tolterodine and -0.8 with oxybutynin (which reached statistical significance only with tolterodine). There was an increase in the 24 hour volume of urine with both treatments; however it was only statistically significant with oxybutynin. Overactivity index was significantly decreased with tolterodine and oxybutynin; there was no significant difference among the treatment groups. There was a significant increase in bladder volume at first desire to void with tolterodine and oxybutynin, which was significantly higher with oxybutynin. The volume at first overactive detrusor contraction and maximum cystometric capacity were significantly increased with tolterodine and oxybutynin; there was no significant difference among the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	volume–high pressure (grade-group IV)			treatment groups. There was no significant change in pressure of first overactive contraction with tolterodine or oxybutynin. Low volume–High pressure Overactivity (Group IV) The mean volume voided/micturition was significantly increased with tolterodine (39.7 mL) and oxybutynin (54.2 mL) and there was no significant difference among the treatment groups. The mean change in number of micturitions/24 hours was -0.9 with tolterodine and -1.0 with oxybutynin; there was no significant difference among the treatment groups. There was an increase in the 24 hour volume of urine with both treatments; however it was only statistically significant with oxybutynin. Overactivity index was significantly decreased with oxybutynin. Volume at first desire to void was significantly increased with oxybutynin and volume at first overactive contraction was significantly increased with tolterodine. There was no significant change in pressure of first overactive contraction with tolterodine or oxybutynin. Low volume–Low pressure Overactivity (Group III) The mean volume voided/micturition was significantly increased with tolterodine (48.8 mL) and oxybutynin (43.1 mL) and there was no significant difference among the treatment groups. There were no significant changes in the rest of voiding diary parameters in this group. Overactivity index was significantly reduced with tolterodine only. Volume at first desire to void was increased significantly with tolterodine and oxybutynin; there was no significant difference among the treatment groups. There were no significant changes for pressure of first overactive contraction and cystometric capacity with tolterodine or oxybutynin. High volume–High pressure Overactivity (Group II) Changes in clinical parameters did not reach statistical significance.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Overactivity index was reduced by tolterodine and oxybutynin; there was no significant difference among the treatment groups. Oxybutynin achieved an increase in volume at first desire to void and volume at first overactive contraction. There were no significant changes in max cystometric capacity and pressure of first overactive contraction. High volume–Low pressure Overactivity (Group I) The small number of patients in this group did not allow for statistical analyses to be performed. Secondary: Not reported
Harvey et al.[107] (2001) Tolterodine IR 1 to 2 mg twice daily vs oxybutynin IR 2.5 to 5 mg three times daily	MA Patients ≥18 years of age with OAB, increased urinary frequency (≥8 micturitions/24 hours), and symptoms of urgency and/or urge incontinence (≥1 episode/24 hours)	4 trials 12 weeks	Primary: Incontinent episodes/24 hours, quantity of pad used/24-hour period, micturitions/24 hours, and voided volume/micturition Secondary: Adverse events	Primary: The mean change in number of micturitions/24 hours was not significantly different between tolterodine and oxybutynin (WMD, 0.00; 95% CI, -0.38 to 0.38). The number of incontinence episodes/24 hours significantly favored oxybutynin compared to tolterodine (WMD, 0.41; 95% CI, 0.04 to 0.77). The change in volume voided/micturition significantly favored oxybutynin (–8.24 mL; 95% CI, –14.11 to –2.38). This translates to an average increase in the volume voided/micturition of more than 8 mL among patients using oxybutynin compared to patients using tolterodine. Secondary: Dry mouth was significantly lower with tolterodine than oxybutynin (RR, 0.54; 95% CI, 0.48 to 0.61), including moderate to severe dry mouth (RR, 0.33; 95% CI, 0.24 to 0.45). There were fewer patients who withdrew from studies due to dry mouth with tolterodine compared to oxybutynin (RR, 0.63; 95% CI, 0.46 to 0.88).
Staskin et al.[108] (2020) EMPOWUR Vibegron 75 mg QD	DB, MC, RCT Patients 18 years of age or older with a history of OAB,	N=1,518 12 weeks	Primary: Change from baseline to week 12 in the average daily number of	Primary: At 12 weeks the LS mean change from baseline in micturition frequency among 492 patients in the vibegron group was -1.8 episodes per day, compared with -1.3 among 475 patients in the placebo group, a LS mean difference of -0.5 (95% CI, -0.8 to -0.2; P<0.001). For tolterodine the LS

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo QD vs tolterodine extended release 4 mg QD	diagnosed by a physician three or more months before screening		micturitions and change from baseline to week 12 in the average daily number of UUI episodes Secondary: Change from baseline to week 12 in the average daily number of urgency episodes, average volume voided per micturition and proportion of wet OAB cases with 75% or greater reduction in the average daily number of UUI episodes.	mean 12-week change among 378 patients was -1.6, a LS mean difference of -0.3 from placebo (95% CI, -0.6 to 0.1; P=0.0988). At 12 weeks the LS mean change from baseline in UUI episode frequency among 383 patients in the vibegron group was -2.0 episodes per day, compared with -1.4 among 372 patients in the placebo group, a LS mean difference of -0.6 (95% CI, -0.9 to -0.3; P<0.0001). For tolterodine the LS mean 12-week change among 286 patients was -1.8, a LS mean difference of -0.4 from placebo (95% CI, -0.7 to -0.1; P=0.0123). Secondary: At 12 weeks the LS mean change from baseline in frequency of urgency episodes among 492 patients in the vibegron group was -2.7 episodes per day, compared with -2.0 among 475 patients in the placebo group, a LS mean difference of -0.7 (95% CI, -1.1, -0.2; P=0.0020). For tolterodine the LS mean 12-week change among 378 patients was -2.5, a LS mean difference of -0.4 from placebo (95% CI, -0.9 to 0.0; P=0.0648). At 12 weeks the LS mean change in volume voided per micturition was 23.5 mL among 490 patients in the vibegron group vs 2.2 mL among 478 patients in the placebo group, a LS mean difference of 21.2 (95% CI, 14.3 to 28.1; P<0.0001). For tolterodine the LS mean change was 15.5 among 375 patients and LS mean difference of 13.3 from placebo (95% CI, 5.9 to 20.7; P<0.001). At 12 weeks the proportion of wet OAB cases with 75% or greater reduction from baseline in UUI episodes per day was 52.4% in the vibegron group vs 36.8% in the placebo group (P<0.0001). For tolterodine the proportion was 47.6%.
Staskin et al.[109] (2020) EMPOWUR extension study Vibegron 75 mg QD	DB, MC, RCT Patients 18 years of age or older with a history of OAB, diagnosed by a physician three or	N=505 52 weeks	Primary: Adverse events Secondary: Change from baseline at week 52 in average daily	Primary: A total of 12 patients (2.4%) discontinued owing to adverse events. The most common adverse events with vibegron/tolterodine (>5% in either group) were hypertension (8.8%/8.6%), urinary tract infection (6.6%/7.3%), headache (5.5%/3.9%), nasopharyngitis (4.8%/5.2%) and dry mouth (1.8%/5.2%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs tolterodine extended release 4 mg QD	more months before screening		number of micturitions and urgency episodes (all patients), and urge and total urinary incontinence episodes (patients with overactive bladder wet) based on 7-day diary data	Secondary: Improvements in efficacy end points were maintained for patients receiving vibegron for 52 weeks; least squares mean change from baseline to week 52 in micturitions was –2.4 for vibegron vs –2.0 for tolterodine; in urge urinary incontinence episodes –2.2 vs –1.7 (P<0.05); in urgency episodes –3.4 vs –3.2; and in total incontinence episodes –2.5 vs –1.9 (P<0.05). Among patients with overactive bladder wet 61.0% receiving vibegron experienced ≥75% reduction in urge urinary incontinence episodes after 52 weeks of treatment vs 54.4% with tolterodine, while 40.8% vs 34.2% experienced a 100% reduction.
Staskin et al.[110] (2004) Trospium 20 mg twice daily vs placebo	DB, MC, PC, RCT Patients with OAB	N=658 12 weeks	Primary: Central nervous system adverse effects and daytime sleepiness using the SSS Secondary: Not reported	Primary: After 12 weeks of treatment, 2.5% of patients receiving placebo and 1.5% of patients receiving trospium exhibited a clinically significant increase (3 points or greater) from baseline in their SSS scores. There was no significant difference between the treatment groups. In a subgroup analysis based on age (<65 and ≥65 years of age; <75 and ≥75 years of age), there was no significant difference in SSS scores among the treatment groups. Approximately 5.8% of patients receiving trospium and 5.2% of patients receiving placebo reported at least one central nervous system adverse event. Somnolence was reported by 0.3% of patients receiving trospium and 0.6% of patients receiving placebo. Sedation was reported by 0.3% of patients receiving placebo and no patients reported sedation with trospium. Secondary: Not reported
Halaska et al.[111] (2003) Trospium (TCl) 20 mg twice daily vs	AC, DB, MC, RCT Patients ≥18 years of age with urge syndrome, urge incontinence, urge incontinence as one	N=358 52 weeks	Primary: Safety and efficacy Secondary: Not reported	Primary: Blood chemistry, nitrogenous metabolites, uric acid, and sodium and potassium were not adversely affected by either treatment. Systolic and diastolic blood pressure were unaffected by the treatments. A pulse rate of >100 beats/min was noted in 27 patients treated with TCl (10.1%) as compared to six patients in the OXY group (6.7%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
oxybutynin IR (OXY) 5 mg twice daily	component of mixed incontinence, or urge incontinence due to a neurological condition (detrusor hyperreflexia)			In the TCl group at 26 and 52 weeks of treatment, 49 and 63% of the trial physicians assessed tolerability as very good, respectively. In the OXY group, the assessment by the trial physicians at the same points showed very good tolerability in 36 and 42% of patients, respectively. Appraisal by the patients led to similar results. Adverse events were observed in 64.8% of patients in the TCl group and 76.7% of patients in the OXY group. Dry mouth was the most common adverse event and was reported by 33% of patients treated with TCl and 50% of those treated with OXY. UTI was reported by 12% of patients receiving TCl and 11% of patients receiving OXY. For the adverse events taken as a whole, the differences between TCl and OXY were significant with regards to time to event (P<0.01). There was also a significant difference between the two treatment groups in favor of TCl for the overall total of adverse events having probable or possible connections with the trial medication (P=0.02), for all gastrointestinal adverse events with this classification (P=0.02) and for dryness of the mouth (P<0.01). When the number of adverse events is viewed in relation to the total number of patients treated and the duration of treatment, the risk of occurrence of an adverse event/patient/week is 0.027 for TCl and 0.045 for OXY (RR, 0.6 in favor of TCl). Patients treated with TCl showed increases in maximum cystometric bladder capacity of 92 mL at 26 weeks and 115 mL at 52 weeks. The OXY group showed increases of 117 and 119.4 mL respectively. The changes from baseline were significant in both treatment arms (P=0.001). There was no significant difference between the treatment groups. The increase in volume at the first unstable contraction was 46.0 mL with TCl and 36.7 mL with OXY. There was no significant difference between the treatment groups. There was no significant difference between the treatment groups in the volume at the first sensation to void, as well as of other urodynamic parameters.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The frequency of micturition in the TCl group decreased by 1.2 micturitions/day at two weeks, 2.9 micturitions/day at 26 weeks and 3.5 micturitions/day at 52 weeks. In frequency of micturitions in the OXY group decreased by 1.5 micturitions/day at two weeks, 3.4 micturitions/day at 26 weeks and 4.2 micturitions/day at 52 weeks. Episodes of urgency in the TCl group decreased by 1.6 at two weeks, 3.2 at six weeks and 3.5 at 52 weeks. In the OXY group, episodes of urgency decreased by 1.7 at 2 weeks, 3.2 at 26 weeks and 3.6 at 52 weeks. After 52 weeks of treatment, 29 and 17% of the physicians considered the therapeutic outcome for the TCl and OXY groups as ‘‘cure’’, respectively. The results were similar with regards to patient assessments. Secondary: Not reported
Madersbacher et al.[112] (1995) Trospium (TCl) 20 mg twice daily vs oxybutynin IR (Oxy) 5 mg three times daily	DB, MC, RCT Patients with detrusor hyperreflexia	N=95 2 weeks	Primary: Maximum bladder capacity and maximum voiding detrusor pressure during micturition Secondary: Bladder compliance, residual urine, adverse events	Primary: Maximum bladder capacity in the TCl group increased significantly by 96.6 mL (P<0.001). In the Oxy group, maximum bladder capacity increased by 163.0 mL (P<0.001). There was no significant difference between the treatment groups (P=0.057). Maximum detrusor pressure during micturition decreased by 35.4 cmH_20 (P<0.001) in the TCl group and 38 cmH_20 (P<0.001) in the Oxy group. There was no significant difference between the treatment groups (P=0.63). Secondary: Bladder compliance increased by 16.96 mL/cm H_20 (P<0.001) in the TCl group and by 22.56 mL/cmH_20 in the Oxy group (P<0.001). There was no significant difference between the treatment groups (P=0.43). Residual urine increased by 76.45 mL in the TC1 group and 114.08 in the Oxy group. There was no significant difference between the treatment groups (P=0.19).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				There was no significant difference between the treatment groups with regards to the frequency of hyper-reflexive waves (P=0.16). There were no significant changes in blood pressure among the treatment groups. The rate of adverse events was similar in both groups. Dry mouth occurred in 54% of patients in the TCl group and 56% of patients in the Oxy group. The severity grading showed that dryness of the mouth deteriorated to 'severe' in 4% of patients receiving TC1 and 23% of patients receiving Oxy. Withdrawal from the trial occurred more frequently in patients taking Oxy (16%) than in those taking TCl (6%). The Oxy patients withdrew earlier (after an average of 7.1 days) than the TCl patients (after an average of 14.3 days).
Zinner et al.[113] (2011) Trospium ER 60 mg once daily	ES, OL Patients ≥18 years of age with symptoms of OAB for ≥6 months who met the following criteria: urinary frequency ≥30 toilet voids per 3 days, ≥1 severe urgency severity rating per 3 days, and ≥3 UUI episodes per 3 days	N=944 48 weeks	Primary: Changes in the mean number of toilet voids per day and UUI episodes per day Secondary: Urgency severity associated with toilet voids, voided volume per void, daily urgency frequency associated with toilet voids, OAB-PGA, KHQ, and OAB-q	Primary: There were reductions from baseline in the number of daily toilet voids and UUI episodes in both the placebo-to-trospium and trospium-to-trospium groups. The mean change in number of toilet voids per day was -3.2 (-24.5%) in the placebo-to-trospium group and -3.4 (-25.5%) in the trospium-to-trospium group at week 48. The median change in the number of UUI episodes per day was -2.3 in both groups (-85.7%). Secondary: Urgency severity associated with toilet voids, voided volume per void, and daily urgency frequency associated with toilet voids all improved in both groups. Significant improvements in OAB-PGA findings were present with both groups. Patients in the placebo-to-trospium and trospium-to-trospium groups reported improvements from baseline in individual questions addressing toilet void frequency (84.1 and 85.1%, respectively), UUI (79.9 and 82.6%, respectively), and urgency severity (79.2 and 81.6%, respectively). Overall OAB symptoms improved in approximately 84% of patients. KHQ and OAB-q demonstrated improvements with both groups at week 48.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Overall, 552 patients (58.5%) experienced ≥1 treatment emergent adverse events, of which 197 were considered at least possibly related to study medication. Dry mouth (n=60) and constipation (n=59) were the most common adverse events reported.
Bolduc et al.[114] (2009) Combination antimuscarinic therapy (oxybutynin 10 to 30 mg, tolterodine ER 4 mg, and/or solifenacin 5 to 10 mg)	OL, PRO Children with OAB, persistent incontinence and a partial urodynamic response to an optimal dose of a well-tolerated, ER antimuscarinic drug	N=33 ≥6 months	Primary: Efficacy for continence Secondary: Safety and tolerability	Primary: Continence improved in all cases. A total of 17 (52%), 14 (42%), and two patients (6%) rated 100% improvement (complete dryness), a >90% decrease in incontinence episodes and a 50 to 89% decrease, respectively. MVV in three-day diaries improved from 165 to 330 mL. Cystometric bladder capacity improved from 192 to 380 mL without any deterioration in compliance and maximum detrusor contraction pressure decreased from 77 to 18 cm H_20 (P<0.01). Secondary: Overall, 12 patients (36%) reported no adverse effects, 16 (48%) reported mild adverse effects (dry mouth, constipation, blurred vision, and headache), and 5 (15%) had a moderate adverse effect (dry mouth). No patients discontinued therapy due to adverse effects.
Chapple et al.[115] (2008) Darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine, trospium	MA Patients ≥18 years of age with OAB	73 trials ≥2 weeks	Primary: Incontinence episodes/day, number of micturitions/day, urgency episodes/day, volume voided/micturition, proportion of patients returning to continence, proportion of patients undergoing global improvements in their storage LUTS	Primary: Antimuscarinic agents were significantly more effective than placebo with regards to the mean change in the number of incontinence episodes/day. Pooled differences in mean changes ranged from 0.4 to 1.1 incontinence episodes per day. Tolterodine 2 mg IR was not more effective than placebo; however, the 4 mg ER/IR formulations were more effective than placebo. There were no significant differences among the antimuscarinic agents with the exception of fesoterodine 8 mg/day. One study found that this agent was more effective than tolterodine ER 4 mg/day (P=0.03). Antimuscarinic agents were significantly more effective than placebo with regards to the mean change in the number of micturitions/day. Pooled differences in mean changes ranged from 0.5 to 1.3 episodes per day. Three trials favoring solifenacin 10 mg/day over tolterodine IR 4 mg/day (P=0.01). Four trials favored solifenacin 10 mg/day over solifenacin 5 mg/day (P=0.02). Otherwise, there were no significant differences among the antimuscarinic agents.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Secondary: Tolerability, safety, and HRQOL	Fesoterodine, propiverine, solifenacin, and tolterodine were significantly more effective than placebo with regards to the mean change in the number of urgency episodes/day (when this outcome was reported). Pooled differences in mean changes ranged from 0.64 to 1.56 episodes per day. Some trial data favored solifenacin 10 mg/day over tolterodine IR 4 mg/day (P<0.01) and solifenacin 5 mg/day over tolterodine IR 4 mg/day (P=0.01). Otherwise, there were no significant differences among the antimuscarinic agents. Antimuscarinic agents were significantly more effective than placebo with regards to the mean change in the volume voided/micturition (when this outcome was reported). Differences in pooled mean changes were 13 to 40 ml. Solifenacin 10 mg/day was favored over tolterodine IR 4 mg/day (P<0.01); solifenacin 10 mg/day was favored over solifenacin 5 mg/day (P<0.01); fesoterodine 8 mg/day was favored over tolterodine ER 4 mg/day (P=0.03); and oxybutynin IR 15 mg/day was favored over tolterodine IR 4 mg/day (P<0.01). The proportions of patients who had improvements in their bladder condition was significantly higher for fesoterodine 4 and 8 mg/day than for placebo (P=0.01and P=0.01, respectively). Otherwise, there were no significant differences among the antimuscarinic agents. Secondary: Compared to placebo, treatment with oxybutynin IR (15 and 7.5 to 10 mg/day) was associated with significantly higher risk of withdrawal due to any cause (P=0.04 and P<0.01, respectively). Otherwise, there was no significant difference in the proportions of patients who withdrew for any causes between active treatments and placebo. Oxybutynin IR 7.5 to 10 mg/day was associated with a significantly greater risk of withdrawal due to any cause than oxybutynin ER 5 mg/day (P=0.03); oxybutynin IR 7.5 to 10 mg/day was associated with a greater risk of withdrawal than tolterodine ER 4 mg/day (P<0.01) and tolterodine IR 4 mg/day (P=0.04); oxybutynin IR 15 mg/day was associated with a greater risk of withdrawal than tolterodine IR 4 mg/day P<0.01) and oxybutynin ER 15 mg/day (P=0.04).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Tolterodine ER 4 mg/day was associated with a significantly lower risk of withdrawal due to an adverse event than placebo (P=0.02). Formulations associated with a significantly higher risk of withdrawal due to adverse events than placebo were as follows: oxybutynin IR 7.5 to 10 mg/day (P=0.01), oxybutynin IR 15 mg/day (P<0.01), and solifenacin 10 mg/day (P=0.04). Tolterodine ER 4 mg/day was associated with lower risk of withdrawal due to an adverse event compared to oxybutynin transdermal delivery system 3.9 mg/day (P=0.01) and oxybutynin IR 15 mg/day (P<0.01); tolterodine IR 4 mg/day was associated with a lower risk than oxybutynin IR 15 mg/day (P<0.01); and oxybutynin ER 5 mg/day was associated with a lower risk than oxybutynin ER 15 mg/day (P=0.04). Otherwise, there were no significant differences among the antimuscarinic agents. Every antimuscarinic agent was associated with a significantly greater risk of adverse events than placebo, except tolterodine IR 2 mg/day (P=0.97) and oxybutynin transdermal delivery system 3.9 mg/day (P=0.07). The pooled RR for any adverse event in comparison to placebo varied between 1.13 and 2.00. The risk of adverse events was significantly lower with tolterodine IR 2 mg/day than with oxybutynin ER 5 mg/day (P<0.01) and lower with tolterodine IR 4 mg/day than with oxybutynin IR 7.5 to 10 mg/day (P<0.01) and oxybutynin IR 15 mg/day (P<0.01). There was a higher risk of adverse events with fesoterodine 8 mg/day than with fesoterodine 4 mg/day (P=0.04) and tolterodine ER 4 mg/day (P=0.04). There was a higher risk of adverse events with oxybutynin IR 7.5 to 10 mg/day than with trospium 40 mg/day (P=0.02). Dry mouth was the most frequently reported adverse event and occurred in 29.6% of patients receiving antimuscarinic therapy compared to 7.9% of patients receiving placebo. The following adverse events were reported at statistically significantly higher levels in first-named active treatments than in second-named active treatments: blurred vision (solifenacin 10 mg/day vs solifenacin 5 mg/day, solifenacin 10 mg/day vs tolterodine IR 4 mg/day); constipation (solifenacin 5 mg/day vs tolterodine ER and IR 4 mg/day, darifenacin 15 mg/day vs tolterodine IR 4 mg/day); fatigue (tolterodine ER 4 mg/day vs fesoterodine 4 or 8 mg/day); nausea

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				(oxybutynin IR 15 mg/day vs oxybutynin ER 15 mg/day); and vomiting (tolterodine ER 4 mg/day vs oxybutynin ER 7.5 to 10 mg/day). Significant differences in HRQOL were reported for darifenacin, fesoterodine, oxybutynin transdermal delivery system, solifenacin, tolterodine ER and IR, and trospium compared to placebo.
Hay-Smith et al.[116] (2009) Darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine, trospium	MA Patients with OAB with or without a urodynamic diagnosis of detrusor overactivity	N=11,332 (49 trials) Variable duration	Primary: QOL, patient's observations, symptoms, objective measurements, adverse events Secondary: Not reported	Primary: <u>Oxybutynin vs tolterodine (10 studies)</u> There was no significant difference between the groups in the proportion of people reporting cure/improvement (47% with tolterodine vs 44% with oxybutynin; RR, 1.06; 95% CI 0.89 to 1.26). There was no significant difference between IR tolterodine and ER oxybutynin with regards to the change in the number of leakage episodes/24 hours (WMD, -0.15; 95% CI, -0.47 to 0.16). There was no significant difference between IR tolterodine and ER oxybutynin with regards to the change in micturitions/24 hours (WMD, -0.25; 95% CI, -0.61 to 0.10). There were fewer withdrawals with tolterodine therapy (7%) compared to treatment with oxybutynin (12%; RR, 0.57; 95% CI, 0.43 to 0.75). Dry mouth was significantly lower with tolterodine than oxybutynin (RR, 0.60; 95% CI, 0.54 to 0.66). <u>Oxybutynin vs trospium (four studies)</u> Two trials reported on maximum cystometric capacity and residual volume and there was no significant difference between the groups. Dry mouth was significantly lower with trospium than oxybutynin (RR, 0.74; 95% CI, 0.59 to 0.93). <u>ER vs IR oxybutynin (four trials)</u> There was no significant difference in patient's perception of improvement (one trial).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				There was no significant difference between the groups in the number of leakage episodes/24 hours. There was a lower maximum cystometric capacity and larger volume at first contraction in the ER formulations; however, only volume at first contraction was significant. There was no significant difference in residual volume measured using ultrasound. There was no significant difference in withdrawals due to adverse events between IR and ER groups. Dry mouth was significantly lower with the ER preparations (RR, 0.77; 95% CI, 0.66 to 0.91). <u>ER vs IR tolterodine (one trial)</u> There was no significant difference between the ER and IR formulations with regards to leakage episodes or micturitions/24 hours. There was no significant difference in withdrawals due to adverse events. There were fewer reports of dry mouth for those using the ER preparation. <u>ER oxybutynin vs IR tolterodine (one trial)</u> There was no significant difference in the number of leakage episodes/24 hours. There was a significant difference in favor of oxybutynin for the number of micturitions/24 hours. There was no significant difference in the number of withdrawals due to adverse events among the treatment groups. There was no significant difference in the rate of dry mouth among the treatment groups. <u>ER tolterodine vs IR oxybutynin (one trial)</u> The risk of dry mouth was less for those taking ER tolterodine compared to oxybutynin IR. <u>Tolterodine ER vs oxybutynin ER (two trials)</u> There was no significant difference in change in leakage episodes or micturitions/24 hours (one trial).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				There was no statistically significant difference between the groups in withdrawals due to adverse events. There was no significant difference in the rate of dry mouth among the treatment groups; however, there was clinical heterogeneity noted among the studies. One study found significantly fewer reports of dry mouth with oral ER tolterodine than oral ER oxybutynin. There was no difference in risk of dry mouth between oral ER tolterodine and transdermal ER oxybutynin. Secondary: Not reported
Maman et al.[117] (2014) Darifenacin, fesoterodine, mirabegron, oxybutynin, solifenacin, tolterodine, trospium	MA Patients ≥18 years of age with a diagnosis of OAB, may be referred to as detrusor overactivity or urinary urgency	N=27,309 (44 trials) Variable duration	Primary: Efficacy outcomes including micturition frequency, incontinence and urgency urinary incontinence; safety outcomes including dry mouth, constipation and blurred vision Secondary: Not reported	Primary: The results from 26 studies (22,040 patients) showed that the effect of mirabegron 50 mg did not differ significantly in terms of micturition frequency from other treatments, except solifenacin 10 mg, which was more effective (mean difference vs mirabegron 50 mg of -0.584). The estimated mean difference of tolterodine compared to mirabegron was not significant (0.157 micturition episodes per day). The results from 17 studies (13,101 patients) showed improvement with mirabegron 50 mg in the daily number of incontinence episodes per 24 hours from baseline to end of study was not significantly different from improvements with tolterodine 4 mg, oxybutynin 10 mg, darifenacin 7.5 mg and 15 mg and fesoterodine 4 mg and 8 mg. Mirabegron 50 mg was statistically superior to placebo with a mean difference estimated at 0.493 incontinence episodes per day. The results of 18 studies (16,044 patients) showed that mirabegron 50 mg was significantly less efficacious than solifenacin 10 mg in terms of urgency urinary incontinence (mean difference vs mirabegron 50 mg of -0.422 urgency incontinence episodes per day) and did not differ significantly from other antimuscarinics. All 44 trials (27,309 patients) reported a similar incidence of dry mouth with mirabegron 50 mg to placebo (OR, 1.344). All antimuscarinics were

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				associated with a significantly higher risk of dry mouth compared with mirabegron 50 mg. The OR for the occurrence of dry mouth with antimuscarinics compared with mirabegron 50 mg ranged from 5.213 with solifenacin 5 mg to 40.702 with oxybutynin IR 15 mg. Data of 41 studies (25,257 patients) reported incidence of constipation associated with mirabegron 50 mg was comparable with placebo (OR, 0.732). Other antimuscarinics except darifenacin 15 mg, fesoterodine 8 mg, solifenacin 5 mg, solifenacin 10 mg and trospium 60 mg had similar incidences of constipation. The 25 studies (14,348 patients) available reported blurred vision being relatively rare and no significant difference in risk of developing blurred vision was found between treatments arms. Secondary: Not reported

Drug regimen abbreviations: ER=extended-release, IR=immediate-release, LA=long acting, SR=sustained-release, XL=extended release
Study abbreviations: AC=active control, CI=confidence interval, DD=double-dummy, DB=double-blind, ES=extension study, MA=meta-analysis, MC=multicenter, NS=not significant, OL=open-label, OR=odds ratio, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RR=relative risk, XO=crossover
Miscellaneous abbreviations: BPH=benign prostatic hyperplasia, BOO=bladder outlet obstruction, HRQOL=health-related quality of life, ICIQ-SF=International Consultation on Incontinence Questionnaire–Short Form, IIQ=incontinence impact questioner, IPSS=international prostate symptoms score, IPSS-QOL=international prostate symptoms score quality of life, KHQ=King's Health Questionnaire, LUTS=lower urinary tract symptoms, MVV=mean voided volume per void, OAB=overactive bladder, OAB-PGA=Overactive Bladder Patient Global Assessment questionnaire, OAB-q=Overactive Bladder Questionnaire, OABSS=Overactive Bladder Symptom Scores, PPBC=Patient Perception of Bladder Condition Questionnaire, PGA=patient global assessment, PRO=patient reported outcome, PVR=postvoid residual, Qmax=maximum flow rate, QOL=quality of life, QOL-I=Quality of Life Index, SMD=standard mean difference, SSS=Stanford Sleepiness Scale, TSQ=Treatment Satisfaction Questionnaire, UDI=urogenital distress inventory, UPS=Urgency Perception Scale, URI=upper respiratory infection, USS=Urinary Sensation Scale, UTI=urinary tract infection, UUI=urgency urinary incontinence, VAS=visual analog scale, VVPM=volume voided per micturition, 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 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 9. Relative Cost of the Genitourinary Smooth Muscle Relaxants: Antimuscarinics

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Darifenacin	extended-release tablet	N/A	N/A	$
Fesoterodine	extended-release tablet	Toviaz®*	$$$$$	$
Flavoxate	tablet	N/A	N/A	$$$
Oxybutynin	extended-release tablet, syrup, tablet, transdermal gel, transdermal patch	Ditropan XL®*, Gelnique®, Oxytrol®	$$$$$	$
Solifenacin	oral suspension, tablet	Vesicare®*	$$$$$	$
Tolterodine	extended-release capsule, tablet	Detrol®*, Detrol LA®*	$$$$$	$
Trospium	extended-release capsule, tablet	N/A	N/A	$$

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

X.Conclusions

Urinary incontinence and overactive bladder cause both physical and psychological morbidity, as well as adversely impact quality of life.[1] Initial treatment options include lifestyle modifications (weight loss and dietary changes) and behavioral therapy (bladder training, physical therapy, and toileting assistance). Pharmacologic therapy is typically trialed if initial treatment is ineffective.[3] Antimuscarinic drugs increase bladder capacity,

decrease urgency, and are useful for the treatment of urge incontinence.[3] All agents are available in a generic formulation.

Several guidelines provide recommendations on the use of the genitourinary smooth muscle relaxants for the treatment of urinary incontinence and overactive bladder. Antimuscarinic agents are the primary treatment for patients with overactive bladder symptoms (with or without urge incontinence), in addition to lifestyle modifications and behavioral therapy.[17-23] In general, the guidelines do not identify a single preferred agent for initial therapy. However, several recent guidelines provide general recommendations.[18-20,23] For example, two guidelines from the American Urological Association and the European Association of Urology favor the use of extended-release preparations.[18,20] In addition, guidelines from the National Institute of Health and Clinical Excellence recommend immediate-release oxybutynin, immediate-release tolterodine, or once-daily darifenacin as initial therapy.[17] Several guidelines also recommend the use of transdermal oxybutynin if anticholinergic side effects are experienced with initial therapy.[18-20,23]

In clinical trials, the genitourinary smooth muscle relaxants have been shown to modestly improve urinary symptoms, including frequency, urgency, nocturia, and incontinence episodes.[24-117] The majority of the studies were six to 12 weeks in duration; however, a few long-term (up to 36 months), open-label, non-comparative studies have also been conducted. There were relatively few active-controlled studies found in the medical literature with flavoxate, darifenacin, fesoterodine, solifenacin, or trospium. The majority of the active-controlled studies compared oxybutynin and tolterodine. Several studies have demonstrated similar efficacy with the genitourinary smooth muscle relaxants for most, but not all, of the outcomes assessed. In general, studies directly comparing immediate-release and extended-release formulations of the same drug found no differences in efficacy.[53-57,63,92] Studies directly comparing immediate-release formulations of different drugs, as well as studies directly comparing extended-release formulations of different drugs, also demonstrated similar efficacy.[26,29,37,42,60-61,80,83,99-106,111-112] Few studies have demonstrated greater efficacy with one genitourinary smooth muscle relaxant over another.[24,38,43,49,59-60,77,82,86,94] The use of the genitourinary smooth muscle relaxants for the treatment of urinary incontinence and overactive bladder has also been associated with an improvement in quality of life.[37,41,54,76,85-86,93]

Adverse events occur frequently with the genitourinary smooth muscle relaxants due to their antimuscarinic effects, which often leads to discontinuation of therapy. The most common adverse events include dry mouth, blurred vision, abdominal discomfort, drowsiness, nausea, and dizziness. These agents may also cause confusion or memory impairment in the elderly.[3] The incidence of adverse events varies among the agents and depends upon the formulation used (extended-release, immediate-release, or transdermal). Adverse events tend to be higher with the immediate-release formulations compared to extended-release formulations. In general, dry mouth occurs at a higher rate with oral oxybutynin than with the other agents.[6,7]

There is insufficient evidence to support that one brand genitourinary smooth muscle relaxant: antimuscarinic 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 genitourinary smooth muscle relaxants: antimuscarinics 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 genitourinary smooth muscle relaxant: antimuscarinic 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 Genitourinary Smooth Muscle Relaxants
AHFS Class 861208 – Selective Beta-3-Adrenergic Agonists
November 8, 2023

I. Overview

Urinary incontinence is the involuntary leakage of urine, which may be classified as urgency, stress, overflow, or mixed incontinence.[1] Urgency incontinence is accompanied by a sense of urgency, while stress incontinence generally occurs with effort, exertion, sneezing, or coughing. Overflow incontinence is associated with dribbling and/or continuous leakage due to incomplete bladder emptying.[1] Overactive bladder is a functional disorder characterized by urinary urgency, daytime frequency (>8 voids during the daytime), nocturia (>1 void at night), with or without incontinence.[2] Urinary incontinence and overactive bladder may be due to lower urinary tract dysfunction or secondary to non-genitourinary disorders. The most common cause of overactive bladder is overactivity of the bladder's detrusor muscle. Symptoms may be assessed by patient history, the use of validated questionnaires, and/or bladder diaries. Clinical testing (e.g., bladder stress test, postvoid residual volume testing, urine flow rate, and urodynamic testing) may help identify the pathology, but are not always necessary for diagnosis or initiation of therapy.[1] Urinary incontinence and overactive bladder cause both physical and psychological morbidity, as well as adversely impact quality of life.[1] Initial treatment options include lifestyle modifications (weight loss and dietary changes) and behavioral therapy (bladder training, physical therapy, and toileting assistance).[3] Pharmacologic therapy is typically trialed if initial treatment is ineffective.[3] Neurogenic lower urinary tract disorder is caused by a lesion at any level of the nervous system.[4,5] The lesion interferes with the normal nerve pathways associated with urination. Early diagnosis and treatment of neurogenic lower urinary tract disorder is essential for both congenital and acquired disorders as irreversible changes may occur.[5]

Mirabegron is the first beta-3 adrenergic receptor agonist to be approved for the treatment of overactive bladder, and vibegron is the second. Beta-3 adrenergic receptor agonists relax the detrusor smooth muscle during the storage phase of the urinary bladder fill-void cycle which increases bladder capacity. Because they act via the beta-3 adrenergic receptor rather than through muscarinic cholinergic receptors, these agents may have an improved tolerability profile compared to other urinary antispasmodics.[6-9]

The selective beta-3-adrenergic agonists that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. No agents are available in a generic formulation. This class was last reviewed in November 2021.

Table 1. Genitourinary Smooth Muscle Relaxants: Beta-3 Agonists Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Mirabegron	extended-release tablet, suspension	Myrbetriq®	none
Vibegron	tablet	Gemtesa®	none

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

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the genitourinary smooth muscle relaxants are summarized in Table 2.

Table 2. Treatment Guidelines Using the Genitourinary Smooth Muscle Relaxants: Beta-3 Agonists

Clinical Guideline	Recommendation(s)
National Institute for Health and Clinical Excellence:	<u>Behavioral therapy</u> • Bladder training should be offered for a minimum of six weeks as first-line treatment to women with urge or mixed urinary incontinence.

Clinical Guideline	Recommendation(s)
Urinary Incontinence and Pelvic Organ Prolapse in Women: Management (2019)[10] Last updated Jun 2019	• If women do not achieve satisfactory benefit from bladder training, the combination of an overactive bladder medicine with bladder training should be considered if frequency is a troublesome symptom. • Do not offer transcutaneous sacral nerve stimulation, transcutaneous posterior tibial nerve stimulation, or percutaneous posterior tibial nerve stimulation to women with urinary incontinence. <u>Pharmacologic therapy</u> • Before starting treatment with a medicine for overactive bladder, the following should be explained to the woman: the likelihood of the medicine being successful; the common adverse effects associated with the medicine; that some adverse effects of anticholinergic medicines, such as dry mouth and constipation, may indicate that the medicine is starting to have an effect; that she may not see substantial benefits until she has been taking the medicine for at least four weeks and that her symptoms may continue to improve over time; and that the long-term effects of anticholinergic medicines for overactive bladder on cognitive function are uncertain. • When offering anticholinergic medicines to treat overactive bladder, the following should be taken into consideration of the woman's: coexisting conditions (such as poor bladder emptying, cognitive impairment or dementia); current use of other medicines that affect total anticholinergic load; and risk of adverse effects, including cognitive impairment. • Flavoxate, propantheline and imipramine should not be offered for the treatment of urinary incontinence or overactive bladder in women. • Immediate-release oxybutynin should not be offered to older women who may be at higher risk of a sudden deterioration in their physical or mental health. • Anticholinergic medicine with the lowest acquisition cost should be offered to treat overactive bladder or mixed urinary incontinence in women. • If the first medicine for overactive bladder or mixed urinary incontinence is not effective or well-tolerated, another medicine with a low acquisition cost should be offered. • A transdermal overactive bladder treatment should be offered to women unable to tolerate oral medicines. • The use of desmopressin may be considered to reduce nocturia in women with urinary incontinence or overactive bladder who find it a troublesome symptom. • Duloxetine is not recommended as a first-line treatment for women with predominant stress urinary incontinence. Duloxetine should not routinely be used as a second-line treatment for women with stress urinary incontinence, although it may be offered as second-line therapy if women prefer pharmacological to surgical treatment or are not suitable for surgical treatment. • Systemic hormone replacement therapy is not recommended for the treatment of urinary incontinence. • Intravaginal estrogens are recommended for the treatment of overactive bladder symptoms in postmenopausal women with vaginal atrophy. • Mirabegron is recommended as an option for treating the symptoms of overactive bladder only for people in whom antimuscarinic drugs are contraindicated or clinically ineffective, or have unacceptable side effects. ○ People currently receiving mirabegron that is not recommended for them should be able to continue treatment until they and their clinician consider it appropriate to stop. <u>Complementary therapy</u> • Complementary therapies are not recommended for the treatment of urinary incontinence or overactive bladder.

Clinical Guideline	Recommendation(s)
European Association of Urology: **Non-neurogenic Female LUTS (2023)**[11]	Antimuscarinic drugs • Anticholinergic drugs are effective in improving overactive bladder (OAB) symptoms, decreasing urge urinary incontinence (UUI) episodes, decreasing daily urgency and frequency episodes and increasing mean voided volumes, compared with placebo. • Anticholinergic drugs caused higher adverse events than placebo including dry mouth, cognitive impairment, and constipation. • Once daily (extended release) formulations are associated with lower rates of adverse events compared to immediate release preparations. • Transdermal oxybutynin (patch) is associated with lower rates of dry mouth than oral anticholinergic drugs but has a higher rate of withdrawal due to skin reaction. • Higher doses of anticholinergic drugs are more effective to improve OAB symptoms but exhibit a higher risk of adverse effects. • No anticholinergic drug is clearly superior to another for cure or improvement of OAB/UUI. • The combination of antimuscarinics plus another treatment modality was more effective than antimuscarinics alone in improving OAB. • Adherence to anticholinergic treatment is low and decreases over time because of lack of efficacy, adverse events and/or cost. • Adherence to anticholinergic treatment is low and decreases over time because of lack of efficacy, adverse events and/or cost. • Most patients will stop anticholinergic agents within the first three months. • Recommendations: Offer anticholinergic drugs to woman with OAB who fail conservative treatment; Consider extended-release formulations of anticholinergic drugs whenever possible; If an anticholinergic treatment proves ineffective, consider dose escalation, offering an alternative anticholinergic formulation, or the use of mirabegron (alone or in combination with an anticholinergic); Encourage early review (of efficacy and adverse effects) of patients on anticholinergic medication for OAB. Beta-3 agonists • Mirabegron and vibegron are better than placebo for improvement of OAB/UUI symptoms. • Adverse event rates with mirabegron and vibegron are similar to placebo. • Beta-3 agonists are as effective as antimuscarinics in the management of OAB but with lower dry mouth rates. • Patients inadequately treated with solifenacin 5 mg may benefit more from the addition of mirabegron than dose escalation of solifenacin. • Recommendations: Offer beta-3 agonists as an alternative to anticholinergics to women with overactive bladder who fail conservative treatment; Offer mirabegron as an additional therapy in patients who are inadequately treated with solifenacin 5 mg. Anticholinergics and beta-3 agonists in the elderly • Anticholinergic drugs are effective in elderly patients suffering from OAB/UUI. • Mirabegron has been shown to be efficacious and safe in elderly women suffering from OAB. • In older women the cognitive impact of drugs which have anticholinergic effects is cumulative and increases with length of exposure. • Oxybutynin may worsen cognitive function in elderly women. • Darifenacin, fesoterodine, solifenacin and trospium have not been shown to cause cognitive dysfunction in elderly women in short-term studies. • Long-term anticholinergic treatment should be used with caution in elderly women, especially those who are at risk of, or have pre-existing cognitive dysfunction.

Clinical Guideline	Recommendation(s)
	• Assess anticholinergic burden and associated co-morbidities in patients being considered for anticholinergic therapy for overactive bladder syndrome. Pharmacological management of mixed urinary incontinence • Treat the most bothersome symptom first in patients with mixed urinary incontinence (MUI). • Offer anticholinergic drugs or beta-3 agonists to patients with urgency-predominant MUI. • Offer duloxetine (where licensed) to selected patients with stress-predominant MUI unresponsive to other conservative treatments and who want to avoid invasive treatment, counselling carefully about the risk of adverse events. Pharmacological management of nocturia • Offer desmopressin treatment for nocturia secondary to nocturnal polyuria to women, following appropriate counselling regarding the potential benefits and associated risks (including hyponatremia). • Carefully monitor serum sodium concentration in elderly patients treated with desmopressin. Avoid prescribing desmopressin to patients with a baseline serum sodium concentration below normal range. • Offer anticholinergic treatment for nocturia to women with urge urinary incontinence or other LUTS, following appropriate counselling regarding the potential benefits and associated risks. • Inform women with nocturia that combination of behavioral therapy and anticholinergic drugs is unlikely to provide increased efficacy compared with either modality alone. • Offer combination of anticholinergics and desmopressin to women with overactive bladder and nocturia secondary to nocturnal polyuria, following appropriate counselling regarding the potential benefits and associated risks. • Offer vaginal oestrogen treatment to women with nocturia, following appropriate counselling regarding the potential benefits and associated risks. • Offer timed diuretic treatment to women with nocturia secondary to polyuria, following appropriate counselling regarding the potential benefits and associated risks.
European Association of Urology: **Non-neurogenic Male LUTS (2023)**[12]	Pharmacological treatment • Offer α1-blockers to men with moderate-to-severe lower urinary tract symptoms (LUTS). • α1-blockers are effective in reducing urinary symptoms (International Prostate Symptom Score: IPSS) and increasing the peak urinary flow rate (Qmax) compared with placebo. • Alfuzosin, terazosin and doxazosin showed a statistically significant increased risk of developing vascular-related events compared with placebo. • Alfuzosin, doxazosin, tamsulosin or terazosin exposure has been associated with an increased risk of intra-operative floppy iris syndrome (IFIS). • Ejaculatory dysfunction is significantly more common with α1-blockers than with placebo, particularly with more selective α1-blockers such as tamsulosin and silodosin. • Use 5α-reductase inhibitors in men who have moderate-to-severe LUTS and an increased risk of disease progression (e.g., prostate volume > 40 mL). • Counsel patients about the slow onset of action of 5α-reductase inhibitors. • Use muscarinic receptor antagonists in men with moderate-to-severe LUTS who mainly have bladder storage symptoms. • Do not use antimuscarinic overactive bladder medications in men with a post-void residual volume > 150 mL.

Clinical Guideline	Recommendation(s)
	• Use beta-3 agonists in men with moderate-to-severe LUTS who mainly have bladder storage symptoms. • Use phosphodiesterase type 5 inhibitors in men with moderate-to-severe LUTS with or without erectile dysfunction. • Offer combination treatment with an α1-blocker and a 5α-reductase inhibitor to men with moderate-to-severe LUTS and an increased risk of disease progression (e.g., prostate volume > 40 mL). • Use combination treatment of a α1-blocker with a muscarinic receptor antagonist in patients with moderate-to-severe LUTS if relief of storage symptoms has been insufficient with monotherapy with either drug. Do not prescribe combination treatment in men with a post-void residual volume > 150 mL. • Use combination treatment of a α1-blocker with mirabegron in patients with persistent storage LUTS after treatment with α1-blocker monotherapy. • Offer antimuscarinic drugs or mirabegron to adults with urge urinary incontinence who failed conservative treatment. • Offer duloxetine to men with stress urinary incontinence. Inform patients about the possible adverse events of duloxetine and that its use is off label for this indication in Europe.
American Urological Association: **Diagnosis and Treatment of Overactive Bladder (Non-Neurogenic) in Adults: American Urological Association/ Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction Guideline (2012); Amended (2014, 2019)**[13]	Diagnosis • Overactive bladder is a symptom complex that is not generally life threatening. • The clinician should engage in a diagnostic process to document symptoms and signs that characterize overactive bladder and exclude other disorders that could be the cause of the patient's symptoms. • After assessment has been performed to exclude conditions requiring treatment and counseling, no treatment is an acceptable choice. First line treatment • Behavioral therapies (e.g., bladder training, bladder control strategies, pelvic floor muscle training, fluid management) should be offered as first line therapy. • Behavioral therapies can also be combined with pharmacologic management. Second line treatment • Clinicians should offer oral antimuscarinics or oral beta-3-adrenoceptor agonists as second line therapy. • If extended-release and immediate-release formulations are available, the extended-release should be preferred over the immediate-release given formulation due to lower rates of dry mouth. Transdermal oxybutynin is also an option. • If a patient experiences inadequate symptom control and/or unacceptable adverse drug events with one agent, then a dose modification or a different antimuscarinic medication or β3-adrenoceptor agonist may be tried. • May consider combination therapy with an anti-muscarinic and β3-adrenoceptor agonist for patients refractory to monotherapy with either anti-muscarinics or β3-adrenoceptor agonists. • Anti-muscarinics should be avoided in patients with narrow-angle glaucoma unless approved by the treating ophthalmologist and should also be used with extreme caution in patients with impaired gastric emptying or a history of urinary retention. • Manage constipation and dry mouth before abandoning effective anti-muscarinic therapy. Management may include bowel management, fluid management, dose modification or alternative anti-muscarinics. • Use caution in prescribing anti-muscarinics in patients who are using other medications with anti-cholinergic properties.

Clinical Guideline	Recommendation(s)
	• Use caution in prescribing anti-muscarinics or β3-adrenoceptor agonists in the frail patient. • Patients who are refractory to behavioral and pharmacologic therapy should be evaluated by an appropriate specialist if they desire additional therapy. <u>Third line treatment</u> • Clinicians may offer intradetrusor onabotulinumtoxinA as a third-line option in the carefully selected patients who has been refractory to first and second line overactive bladder treatments. The patient must be able and willing to return for frequent post-void residual evaluation and able and willing to perform self-catheterization if necessary. • Clinicians can also offer peripheral tibial nerve stimulation as third-line treatment. • Clinicians may offer sacral neuromodulation as third line treatment in a carefully selected patient population characterized by server refractory overactive bladder symptoms or patients who are not candidates for second-line therapy and are willing to undergo a surgical procedure. • Patients should persist with new treatments for an adequate trial in order to determine whether the therapy is efficacious and tolerable. Combination therapeutic approaches should be assembled methodically, with the addition of new therapies occurring only when the relative efficacy of the preceding therapy is known. Therapies that do not demonstrate efficacy after an adequate trial should be ceased.
National Institute for Health and Clinical Excellence: **Urinary Incontinence in Neurological Disease (2012)**[14]	<u>Behavioral treatment</u> • For patients with neurogenic lower urinary tract dysfunction, behavioral management programs should be considered (e.g., timed voiding, bladder retraining or habit retraining). • When choosing a behavioral management program, take into account that prompted voiding and habit retraining are particularly suitable for people with cognitive impairment. <u>Antimuscarinics</u> • Antimuscarinic drugs should be offered to patients with spinal cord disease (e.g., spinal cord injury or multiple sclerosis) who have symptoms of overactive bladder such as increased frequency, urgency and incontinence. • In patients with conditions affecting the brain (e.g., cerebral palsy, head injury or stroke) with symptoms of an overactive bladder, antimuscarinic drugs should be considered. • Antimuscarinic drug treatment should be considered in patients with urodynamic investigations showing impaired bladder storage. • Residual urine volume should be monitored in patients not using intermittent or indwelling catheterization after beginning treatment. • Antimuscarinic treatment can reduce bladder emptying, which may increase the risk of urinary tract infections and may precipitate or exacerbate constipation. Antimuscarinics known to cross the blood-brain barrier (e.g. oxybutynin) have the potential to cause central nervous system related adverse effects (e.g., confusion). <u>Botulinum toxin A</u> • Bladder wall injection with botulinum toxin A should be offered to adult patients with spinal cord diseases (e.g., spinal cord injury or multiple sclerosis) and symptoms of overactive bladder and an inadequate response to or poorly tolerated antimuscarinic drugs. • Bladder wall injection with botulinum toxin A may be considered for children and young people with spinal cord disease and symptoms of overactive bladder for who antimuscarinic drugs were ineffective or poorly tolerated.

Clinical Guideline	Recommendation(s)
	• Bladder wall injection with botulinum toxin A may be considered in adults with spinal cord disease with urodynamic investigations showing impaired bladder storage for whom antimuscarinic drugs were ineffective or poorly tolerated. • Consider bladder wall injection with botulinum toxin A for children and young people with spinal cord disease with urodynamic investigations showing impaired bladder storage and for whom antimuscarinic drugs were ineffective or poorly tolerated. • A catheterization regimen is needed in most people with neurogenic lower urinary tract dysfunction after botulinum toxin A treatment. The patient must be able and willing to manage such a regimen should urinary retention develop after the treatment. • Monitor residual urine volume in patients who are not using a catheterization regimen during treatment with botulinum toxin A. • Monitor upper urinary tract in patients at risk of renal complications (e.g., those with high intravesical pressures on filling cystometry) during treatment. • People should be offered repeated botulinum toxin A injections and have prompt access to repeat injections when symptoms return.
International Scientific Committee: **Evaluation and Treatment of Urinary Incontinence, Pelvic Organ Prolapse, and Fecal Incontinence (2018)**[15]	<u>Initial management of urinary incontinence in children</u> • For children with mono-symptomatic nocturnal enuresis, initial treatment should include: o Parental and child counselling and motivation o Review of bladder diary with attention to night-time polyuria o Age appropriate education and demystification or explanation o Counselling, timed voiding, behavior modification and bowel management when necessary o Antimuscarinics may be used if the child has overactive bladder symptoms <u>Initial management of urinary incontinence in men</u> • For men with stress, urgency or mixed urgency/stress incontinence, initial treatment should include: o Lifestyle interventions. o Supervised pelvic floor muscle training for men with post-radical prostatectomy stress urinary incontinence. o Scheduled voiding regimes for overactive bladder. o Antimuscarinic/beta 3 agonist drugs for overactive bladder symptoms with or without urgency incontinence if the patient has no evidence of significant post-void residual urine. o Alpha adrenergic antagonists (α-blockers) can be added if it is thought that there may also be bladder outlet obstruction. <u>Initial management of urinary incontinence in women</u> • For women with stress, urgency or mixed urgency/stress incontinence, initial treatment should include: o Advice on caffeine reduction for overactive bladder and weight reduction. o Supervised pelvic floor muscle training and vaginal cones training for women with stress incontinence. o Supervised bladder training for overactive bladder. o If estrogen deficiency and/or urinary tract infection is found, the patient should be treated at initial assessment and then reassessed after a suitable interval. o Antimuscarinics/beta 3 agonist for overactive bladder symptoms with or without urgency incontinence. o Duloxetine may be considered for stress urinary incontinence.

Clinical Guideline	Recommendation(s)

	Initial management of neurogenic urinary incontinence
	• Conservative treatment modalities (often in combination):
	  ○ Intermittent catheterization.
	  ○ Behavioral treatment.
	  ○ Timed voiding.
	  ○ Continence products.
	  ○ Antimuscarinics.
	  ○ Alpha-1-adrenergic blockers.
	  ○ Oral cannabinoid agonists (MS)
	  ○ Beta-3-agonist alone or as an add-on to antimuscarinics
	  ○ Bladder expression.
	  ○ Triggered voiding.
	  ○ Indwelling catheter.
	
	Management of urinary incontinence in frail older persons
	• Initial treatment should be individualized and influenced by goals of care, treatment preferences, and estimated remaining life expectancy, as well as the most likely clinical diagnosis.
	• In some frail elders the only possible outcome may be contained urinary incontinence (managed with pads), especially for persons with minimal mobility (require assistance of >2 persons to transfer), advanced dementia (unable to state their name), and/or nocturnal urinary incontinence.
	• Conservative and behavioral therapy for urinary incontinence include lifestyle changes, bladder training for more fit alert patients, and prompted voiding for frailer, more impaired patients.
	• For select cognitively intact patients, pelvic muscle exercises may be considered. Antimuscarinics may be added to conservative therapy of urgency urinary incontinence.
	• Alpha-blockers may be cautiously considered in frail men with suspected prostatic outlet obstruction. All drugs should be started at the lowest dose and titrated with regular review until either care goals are met or adverse effects are intolerable.
	• DDAVP (vasopressin) has a high risk of severe hyponatremia in frail persons and should not be used outside specialist centers or without very careful monitoring and long term follow-up.

American College of Obstetricians and Gynecologists: **Practice Bulletin: Urinary Incontinence in Women (2015)**[16] Reaffirmed 2022	• Behavioral therapy (e.g., bladder training and prompted voiding) and pelvic floor muscle exercises improve symptoms of stress, urgency, and mixed urinary incontinence and may be recommended as an initial, noninvasive treatment in many women. • Moderate weight loss can improve urinary incontinence symptoms in overweight and obese women. • Pelvic floor muscle exercises appear to be an effective treatment for adult women with stress, urgency, or mixed incontinence and can be recommended as a noninvasive treatment for many women. • Current evidenced-based medical treatments typically are reserved for urgency urinary incontinence. Medical therapies for treatment of stress urinary incontinence are less effective and generally are not recommended. Available medical treatments for urgency urinary incontinence include antimuscarinic agents (also known as anticholinergic agents), β-agonists, onabotulinumtoxinA, and estrogen. • The antimuscarinic medications have been shown to have a small beneficial effect as therapy for urgency incontinence. Numerous antimuscarinic agents are available, including darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine, and trospium, that have similar efficacy and safety profiles; however, conclusions

Clinical Guideline	Recommendation(s)
	regarding comparative effectiveness and safety are limited by the lack of high-quality evidence from head-to-head trials between specific agents. • Antimuscarinic medications also were associated with significant discontinuation rates because of bothersome adverse effects, with dry mouth as the most frequently reported adverse event. • Compared with antimuscarinic treatment, intravesical onabotulinumtoxinA results in similar reduction of incontinence episodes, and more patients report complete resolution of incontinence. Thus, intradetrusor onabotulinumtoxinA may be a treatment option for overactive bladder in appropriate patients, and consideration of its use requires shared decision making between the patient and physician. • Systemic estrogen therapy, with or without progesterone, does not appear to be effective in the prevention or treatment of urinary incontinence; several large trials of hormone therapy have found an increased occurrence of stress incontinence in users of hormone therapy (estrogen alone or combined with progesterone). Locally administered (vaginal) estrogen, however, may be of some benefit in decreasing urinary incontinence.
European Association of Urology/European Society for Pediatric Urology: **Guidelines on Pediatric Urology: Management of Neurogenic Bladder in Children (2023)**[4]	Medical therapy • Antimuscarinic/anticholinergic medication reduces/prevents detrusor overactivity and lowers intravesical pressure. • Oxybutynin is the most frequently used in children with neurogenic bladder with a success rate of up to 93%. Dose-dependent side-effects (such as dry mouth, facial flushing, blurred vision heat intolerance etc.) limit its use. • Tolterodine, solifenacin, fesoterodine, trospium chloride and propiverine and their combinations can also be used in children. • Early prophylactic treatment with anticholinergics showed a lower rate of renal deterioration as well as a lower rate of progression to bladder augmentation. • Beta-3 agonists like mirabegron as an adjuvant treatment has been shown to be effective and safe in some recent studies of children (> five years) and adolescents. • Alpha-adrenergic antagonists may facilitate emptying in children with neurogenic bladder. Botulinum toxin injections • In neurogenic bladders that are refractory to anticholinergics, the off-label use of suburothelial or intramuscular injection of onabotulinum toxin A into the detrusor muscle is a treatment option. • Onabotulinum toxin A seems to be more effective in bladders with obvious detrusor muscle over-activity, whereas non-compliant bladders without obvious contractions are unlikely to respond. • Urethral sphincter onabotulinum toxin A injection has been shown to be effective in decreasing urethral resistance and improve voiding. The evidence is still too low to recommend its routine use in decreasing outlet resistance, but it could be considered as an alternative in refractory cases.
European Association of Urology: **Guidelines on Neuro-Urology (2022)**[5]	• Use antimuscarinic therapy as the first-line medical treatment for neurogenic detrusor overactivity. Long-term efficacy and safety of antimuscarinic therapy for neurogenic detrusor overactivity (NDO) is well documented. • Prescribe α-blockers to decrease bladder outlet resistance. • Do not prescribe parasympathomimetics for underactive detrusor. • Mirabegron does not improve urodynamic outcomes in NDO patients. • Maximize outcomes for NDO by considering combination therapy.

III.Indications

The Food and Drug Administration (FDA)-approved indications for the genitourinary smooth muscle relaxants 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 Genitourinary Smooth Muscle Relaxants: Beta-3 Agonists[8,9]

Indication	Mirabegron	Vibegron
Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency	✔	✔
Treatment of neurogenic detrusor overactivity in pediatric patients aged three years and older	✔	

IV.Pharmacokinetics

The pharmacokinetic parameters of the genitourinary smooth muscle relaxants are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Genitourinary Smooth Muscle Relaxants: Beta-3 Agonists[7]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Mirabegron	29 to 35	71	Liver	Renal (6 to 12)	50
Vibegron	Not reported	50	Not reported	Renal (20), Feces (59)	30.8

V.Drug Interactions

Major drug interactions with the genitourinary smooth muscle relaxants are listed in Table 5.

Table 5. Major Drug Interactions with the Genitourinary Smooth Muscle Relaxants: Beta-3 Agonists[7]

Generic Name(s)	Interaction	Mechanism
Mirabegron	Propafenone	Concurrent use of mirabegron and propafenone may result in increased propafenone exposure due to inhibition of CYP2D6- and CYP3A4-mediated propafenone metabolism by mirabegron.
Mirabegron	Sirolimus	Concurrent use of mirabegron and sirolimus may result in increased exposure of sirolimus.
Mirabegron	Thioridazine	Coadministration may have additive effects on the prolongation of the QT interval.
Vibegron	Digoxin	Concurrent use of digoxin and vibegron may result in increased digoxin exposure.

VI.Adverse Drug Events

The most common adverse drug events reported with the genitourinary smooth muscle relaxants are listed in Table 6.

Table 6. Adverse Drug Events (%) Reported with the Genitourinary Smooth Muscle Relaxants: Beta-3 Agonists[6]

Adverse Events	Mirabegron	Vibegron
Cardiovascular		

Adverse Events	Mirabegron	Vibegron
Hypertension	8 to 11	-
Tachycardia	1 to 2	-
Central nervous system		
Dizziness	1 to 3	-
Headache	2 to 4	4
Gastrointestinal		
Abdominal pain	1	-
Constipation	1 to 3	<2
Diarrhea	2	2
Nausea	-	2
Xerostomia	3 to 4	<2
Genitourinary		
Cystitis	2	-
Urinary retention	-	<2
Urinary tract infection	3 to 6	-
Vaginitis	✔	-
Respiratory		
Nasopharyngitis	4	3
Sinusitis	3	-
Other		
Arthralgia	2	-
Hot flash	-	<2
Influenza	3	-
Pain	3	-
Upper respiratory tract infection	-	2

✔ Percent not specified.
- Event not reported or incidence <1%.

VII. Dosing and Administration

The usual dosing regimens for the genitourinary smooth muscle relaxants are listed in Table 7.

Table 7. Usual Dosing Regimens for the Genitourinary Smooth Muscle Relaxants: Beta-3 Agonists[6]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Mirabegron	Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and frequency: (ER: 25 to 50 mg once daily	Treatment of neurogenic detrusor overactivity in pediatric patients aged 3 years and older: ER: 25 to 50 mg once daily for patients weighing ≥35 kg (refer to package insert for additional weight-based dosing information)	Tablet (ER): 25 mg 50 mg Suspension (ER): 8 mg/mL
Vibegron	Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and frequency: Tablet: 75 mg once daily	The safety and effectiveness in pediatric patients have not been established.	Tablet: 75 mg

ER=extended-release

VIII.Effectiveness

Clinical studies evaluating the safety and efficacy of the genitourinary smooth muscle relaxants are summarized in Table 8.

Table 8. Comparative Clinical Trials with the Genitourinary Smooth Muscle Relaxants: Beta-3 Agonists

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Nitti et al.[17] (2013) Mirabegron 100 mg once daily vs mirabegron 50 mg once daily vs placebo	DB, MC, PC, PG, RCT Patients ≥18 years of age, with OAB symptoms for ≥3 months and with an average baseline micturition frequency of ≥8 micturitions/24 hours and ≥3 urgency episodes with or without incontinence during the 3-day micturition diary period	N=1,328 12 weeks	Primary: Change from baseline to end of treatment in the mean number of incontinence episodes per 24 hours, change from baseline to end of treatment in the mean number of micturitions per 24 hours Secondary: Change from baseline to end of treatment in the mean VVPM, change from baseline to week four in the mean number of incontinence episodes per 24 hours, change from baseline to week four in the mean number of micturitions per 24 hours, change from baseline to final	Primary: Change from baseline to end of treatment in the mean number of incontinence episodes per 24 hours was -1.63 in the mirabegron 100 mg group, -1.47 in the mirabegron 50 mg group and -1.13 in the placebo group. When compared to placebo the change from baseline was statistically significant in both the mirabegron 100 mg (P<0.05) and 50 group (P<0.05). Change from baseline to end of treatment in the mean number of micturitions per 24 hours was -1.75 in the mirabegron 100 mg group, -1.66 in the mirabegron 50 mg group, and -1.05 in the placebo group. When compared to placebo the change from baseline was statistically significant in both the mirabegron 100 mg (P<0.05) and 50 group (P<0.05). Secondary: Change from baseline to end of treatment in the mean VVPM was 18.0 mL in the mirabegron 100 mg group, 18.2 mL in the mirabegron 50 mg group, and 7 mL in the placebo group. When compared to placebo the change from baseline was statistically significant in the mirabegron 100 mg (P<0.05) and 50 group (P<0.05). Change from baseline to week 4 in the mean number of incontinence episodes per 24 hours was -1.18 in the mirabegron 100 mg group, -1.20 in the mirabegron 50 mg group, and -0.72 in the placebo group. When compared to placebo the change from baseline was statistically significant in the mirabegron 100 mg (P<0.05) and 50 group (P<0.05). Change from baseline to week 4 in the mean number of micturitions per 24 hours was -1.37 in the mirabegron 100 mg group, -1.19 in the mirabegron 50 mg group, and -0.77 in the placebo group. When compared to placebo the change from baseline was statistically significant in the mirabegron 100 mg (P<0.05) and 50 group (P<0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			visit in mean level of urgency, change from baseline to final visit in mean number of urgency incontinence episodes per 24 hours, change from baseline to final visit in grade 3 or 4 urgency episodes per 24 hours, change from baseline to final visit in mean number of nocturia episodes, safety	Change from baseline to final visit in mean level of urgency was -0.21 in the mirabegron 100 mg group, -0.19 in the mirabegron 50 mg group, and -0.08 in the placebo group. When compared to placebo the change from baseline was statistically significant in the mirabegron 100 mg (P<0.05) and 50 group (P<0.05). Change from baseline to final visit in mean number of urgency incontinence episodes per 24 hours was -1.45 in the mirabegron 100 mg group, -1.32 in the mirabegron 50 mg group and -0.89 in the placebo group. When compared to placebo the change from baseline was statistically significant in the mirabegron 100 mg (P<0.05) and 50 group (P<0.05). Change from baseline to final visit in grade 3 or 4 urgency episodes per 24 hours was -1.76 in the mirabegron 100 mg group, -1.57 in the mirabegron 50 mg group, and -0.82 in the placebo group. When compared to placebo the change from baseline was statistically significant in the mirabegron 100 mg (P<0.05) and 50 group (P<0.05). Change from baseline to final visit in mean number of nocturia episodes was -0.57 in the mirabegron 100 mg and mirabegron 50 mg group compared to -0.38 in the placebo group. When compared to placebo the change from baseline was statistically significant in the mirabegron 100 mg (P<0.05) and 50 group (P<0.05). Mirabegron was well tolerated and the incidence of adverse events was similar across all groups. Adverse events reported in the placebo group, mirabegron 50 mg group and mirabegron 100 mg respectively were hypertension (6.6 vs 6.1 vs 4.9%), UTI (1.8 vs 2.7 vs 3.7), headache (2.0 vs 3.2 vs 3.0%), nasopharyngitis (2.9 vs 3.4 vs 2.5%), URI (2.6 vs 2.7 vs 2.1%), diarrhea (1.3 vs 2.3 vs 2.3%), sinusitis (2.2 vs 2.0 vs 2.1%), dry mouth (1.5 vs 0.5 vs 2.1%), constipation (1.8 vs 1.4 vs 1.6%). Serious adverse events were reported in 2.0, 2.5 and 3.2% of patients in the placebo group, mirabegron 50 mg group and mirabegron 100 mg respectively. Treatment discontinuation due to adverse events was

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				reported in 3.8, 4.1 and 4.4% of patients in the placebo group, mirabegron 50 mg group and mirabegron 100 mg respectively.
Shin DG et al.[18] (2018) MIRACLE Mirabegron 50 mg or placebo (Mirabegron 50 mg given to both groups during extension phase)	DB, PC, PG, MC, RCT Male patients ≥20 years of age with symptoms of OAB persistent for at least 12 weeks, an average of 8 or more 24 hour micturition episodes according to a 3-day voiding diary and those with a score of 2 or greater in the urgency score section (Q3) of the OABSS	N=464 12 weeks plus 14 weeks extension	Primary: Change in the mean number of 24 hour micturition episodes from baseline to 12 weeks Secondary: Changes in the following mean scores from baseline to 12 and 26 weeks of medication: Q3, urgency incontinence score (Q4), total sum of the OABSS score, urgency score (Q4), storage subscore (sum of Q2, Q4, and Q7), and QOL score on the IPSS test	Primary: The mean number of 24 hour micturition episodes significantly reduced by -1.61±2.20 in the mirabegron group and by -1.45±2.54 in the placebo group (P<0.001 in both). The overall reduction in the mean number of 24 hour micturition episodes itself was not significantly different between the two groups (P=0.06). Secondary: Significantly greater changes from baseline to 12 weeks were observed in total OABSS, OABSS urgency incontinence score (Q4), IPSS storage subscore (Q2 + Q4 + Q7), and IPSS urgency score (Q4) in the mirabegron group (P=0.01 for all). However, when mirabegron 50 mg was given to both groups from the 12 to the 26 week point, the changes in all of the investigated parameters from baseline to 26 weeks were similar between the groups. Additionally, the mirabegron group had a significantly larger proportion of patients with a mean of <8 episodes of micturition per 24 hours at the 12 week point than did the placebo group (42.90% vs 27.27%, respectively; P=0.001).
Liao CH et al.[19] (2019) Mirabegron 25 mg daily for 12 weeks (M25 group) vs	AC, RCT Patients who previously received antimuscarinic agents and if a drug-free period longer than two weeks was recorded prior to	N=242 12 weeks	Primary: Percentage of patients without urgency or with a reduction of ≥2 in daily urgency episodes after treatment Secondary:	Primary: Both groups showed similar numbers of patients who reached the primary endpoint after treatment (M25: 64.6%; M50: 64.9%; P=0.554). Secondary: All OABSS in both groups improved significantly at four and 12 weeks. Patients in the M50 group had significantly more patients with a reduction of ≥2 in daily urgency episodes (60.9%) than the M25 group (34.5%) for those with residual daily urgency episodes ≥2 after 25 mg mirabegron for four weeks (P=0.034). The M50 group also had a higher number of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mirabegron 25 mg daily for 4 weeks + 50 mg daily for eight weeks (M50 group)	initiating the mirabegron therapy		OABSS and other voiding parameters	patients with a reduction of ≥1 in UUI (87.5% vs. 37.5%; P=0.021) for those with residual daily UUI episodes ≥1. The OABSS, patient perception of intensity of urgency scale, IPSS storage subscore, patient perception of bladder condition, and QOL index in both groups improved significantly at four and 12 weeks after treatment. However, both groups showed no significant difference in the changes of parameters from baseline to 12 weeks. According to the voiding diary, episodes of daytime micturition, nocturia, urgency, and UUI improved after 12 weeks in both groups, but dose escalation to 50 mg further improved the daily urgency and UUI episodes from four to 12 weeks after the initial mirabegron 25 mg treatment. Patients who remained on mirabegron 25 mg had similar urgency and UUI episodes from week four to12.
Herschorn et al.[20] (2020) PILLAR Mirabegron 25 mg daily (optional dose escalation to 50 mg/day at week 4 or 8) vs placebo	DB, MC, RCT Patients ≥65 years of age with wet OAB (urgency, urinary frequency and urinary incontinence) who recorded ≥1 incontinence episode and ≥3 urgency episodes, and an average of ≥8 micturitions/24 h over a 3-day diary	N=888 12 weeks	Primary: Safety Secondary: Not reported	Primary: Treatment-emergent adverse events (TEAEs), the majority mild or moderate in severity, were reported in 39.4% of placebo patients and 44.2 and 49.8% of those who received mirabegron 25 mg or 50 mg, respectively. The most common TEAEs in mirabegron-treated patients were urinary tract infection, headache, and diarrhea. The incidence of TEAEs was slightly higher in mirabegron patients aged ≥75 years than in those aged <75 years. There were no clinically meaningful differences in changes in vital signs from baseline to end of treatment for any treatment group, and no differences were observed between mirabegron and placebo treatment groups. Secondary: Not reported
Wagg et al.[21] (2020) PILLAR Mirabegron 25 mg daily (optional dose escalation to 50	DB, MC, RCT Patients ≥65 years of age with wet OAB for at least 3 months (urgency, urinary frequency and urinary	N=888 12 weeks	Primary: Coprimary endpoints: change from baseline to end of treatment (EOT) in the mean numbers of micturitions/24h	Primary: Statistically significant adjusted mean improvements were observed for the mirabegron group versus the placebo group for the coprimary endpoints of change from baseline to EOT in the mean number of micturitions/24 h (difference, –0.7; 95% CI, –1.0 to –0.3) and mean number of incontinence episodes/24 h (difference, –0.6; 95% CI, –0.8 to –0.3).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg/day at week 4 or 8) vs placebo	incontinence) who recorded ≥1 incontinence episode and ≥3 urgency episodes, and an average of ≥8 micturitions/24 h over a 3-day diary		and incontinence episodes/24h Secondary: Change from baseline to EOT in the mean volume voided/micturition, mean number of urgency episodes/24h, and mean number of urgency incontinence episodes/24h	Secondary: Statistically significant improvements were observed for mirabegron versus placebo in change from baseline to EOT in the mean number of micturitions/24h (P<0.001), mean number of incontinence episodes/24h (P<0.001), mean volume voided/micturition (P=0.002), mean number of urgency episodes/24h (P<0.001), and mean number of urgency incontinence episodes/24h (P<0.001).
Kaplan et al.[22] (2020) PLUS Mirabegron 25 mg daily (dose escalation to 50 mg/day at week 4) vs placebo	DB, MC, RCT Men ≥40 years of age who have been receiving 0.4 mg tamsulosin daily for 2 or more months for the treatment of previously diagnosed benign prostatic hyperplasia associated lower urinary tract symptoms based on the clinical judgment of the investigator, had symptoms of OAB (8 or more micturitions per day and 2 or more	N=715 12 weeks	Primary: Change in mean number of micturitions per day from baseline to end of treatment Secondary: Changes from baseline in mean volume voided per micturition, number of urgency episodes per day (grade 3/4), total urgency and frequency score (TUFS) and total International Prostate Symptom Score (I-PSS); safety	Primary: Tamsulosin plus mirabegron was statistically superior to tamsulosin plus placebo in reducing the mean number of micturitions per day (-2.00 vs -1.62; adjusted difference, -0.39; 95% CI, -0.76 to -0.02; P=0.039). Secondary: Statistically superior results were noted for tamsulosin plus mirabegron in mean volume voided per micturition (P=0.007), urgency episodes per day (P=0.004), and total urgency and frequency score (P=0.004) (not International Prostate Symptom Score; P=0.81). Higher overall treatment emergent adverse event rates were observed with tamsulosin plus placebo, although higher rates of drug related treatment emergent adverse events were noted with tamsulosin plus mirabegron. Urinary retention rates were higher in the tamsulosin plus mirabegron group.

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	urgency episodes per day), and had a prostate specific antigen <4 ng/ml or 4 to <10 ng/ml with a negative biopsy within 2 years			
Herschorn et al.[23] (2017) SYNERGY Solifenacin 5 mg plus mirabegron 25 mg (combined S5 + M25 group) vs solifenacin 5 mg plus mirabegron 50 mg (combined S5 + M50 group) vs solifenacin 5 mg vs mirabegron 25 mg vs mirabegron 50 mg vs	DB, MC, RCT Patients aged ≥18 years with wet OAB (urgency, urinary frequency and urinary incontinence) for ≥3 months who recorded on average ≥8 micturitions/24 h, ≥1 urgency episode/24 h, and ≥3 urinary incontinence episodes over the 7-day micturition diary	N=3,398 18 weeks (4-week placebo run-in, 12-week DB treatment period, 2-week placebo run-out period)	Primary: Change from baseline to end of treatment in the mean number of urinary incontinence episodes/24 h and micturitions/24 h, assessed using a 7-day electronic micturition diary Secondary: Change from baseline in the mean volume voided/micturition, change from baseline in mean number of urinary incontinence episodes/24 h, micturitions/24 h, urgency episodes/24 h, UUI episodes/24 h and nocturia episodes/24 h; the percentage of	Primary: Although the combined S5 + M50 group significantly reduced urinary incontinence episodes compared to solifenacin 5 mg, with a mean (SE) adjusted difference of −0.20 (0.12) urinary incontinence episodes/24 hours (95% CI, −0.44 to 0.04, P=0.033), statistical “superiority” versus mirabegron 50 mg was not demonstrated (mean adjusted difference, −0.23 UI episodes/24 hours; 95% CI, −0.47 to 0.01; P=0.052). Therefore, the primary objective for the combined S5 + M50 therapy was not met. Because the null hypothesis for this test was not rejected, the subsequent hypotheses for mean number of micturitions/24 h and the MVV/micturition could not be tested. Also, no hypothesis testing could be performed for the combined S5 + M25 group. Urinary incontinence episodes decreased vs baseline for all treatment arms. The mean adjusted change from baseline to end of treatment was greater in the combined therapy groups vs monotherapies and placebo. Secondary: For micturitions/24 hours, adjusted change from baseline was greater in the combined therapy groups vs monotherapies (combined S5 + M50 group, nominal P values 0.006 and <0.001 versus solifenacin 5 mg and mirabegron 50 mg, respectively; combined S5 + M25 group, nominal P values 0.040 and 0.001 versus solifenacin 5 mg and mirabegron 25 mg, respectively). All active treatment groups had greater improvements in the mean numbers of micturitions/24 hours versus placebo, with effect sizes for the combined therapy groups (combined S5 + M25 group: -0.85 micturitions/24 h; combined S5 + M50 group: -0.95 micturitions/24 h) higher than with mirabegron monotherapy (25 mg: -0.36; 50 mg: -0.39 micturitions/24 h) and solifenacin 5 mg (-0.56 micturitions/24 h). The combined S5 + M50 group was statistically significantly improved

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo			patients (responders) achieving zero urinary incontinence episodes/24 h in the last 7 days prior to each visit, micturition frequency normalization (<8 episodes/24 h), and the number of UUI episodes and nocturia episodes in the 7-day diary; safety	compared to both monotherapies at end of treatment for UUI episodes, urgency episodes, and nocturia, with effect sizes that appeared to be additive. The combined S5 + M25 group demonstrated statistically significant improvement compared to mirabegron 25 mg for the same variables, except for nocturia. In responder analyses at the end of treatment, odds ratios in favor of both combined therapies vs monotherapies were shown for the proportion of patients with zero urinary incontinence episodes and those achieving micturition frequency normalization. There was a slightly increased frequency of treatment-emergent adverse events in the combined therapy groups vs monotherapies and placebo. Most of the treatment-emergent adverse events were mild or moderate in severity. There were slightly higher frequencies of dry mouth, constipation, and dyspepsia in the combined therapy groups versus monotherapies.
Drake et al.[24] (2016) BESIDE Solifenacin 5 mg and mirabegron 50 mg (combination) vs solifenacin 5 mg vs solifenacin 10 mg	DB, MC, RCT Adult OAB patients remaining incontinent despite daily solifenacin 5mg during 4-wk single-blind run-in	N=2,174 12 weeks	Primary: Change from baseline to end of treatment in the mean number of incontinence episodes/24 hours Secondary: Change from baseline to end of treatment in the mean number of micturitions/24 hours, number of incontinence episodes; safety	Primary: The adjusted change from baseline to end of treatment in the mean number of incontinence episodes per 24 hours was greater with combination (−1.80) versus solifenacin 5 mg (−1.53; P=0.001) and versus solifenacin 10 mg (−1.67; P=0.008). Secondary: At end of treatment, reductions in mean daily micturitions and in three-day incontinence episodes were significantly greater with combination versus solifenacin 5 mg (P<0.001). Combination was noninferior to solifenacin 10 mg for both key secondary end points and superior to solifenacin 10 mg for the reduction in micturition frequency. Significant differences in favor of the combination were evident as early as week four versus solifenacin 5 mg and week eight versus solifenacin 10 mg. The incidence of treatment-emergent adverse events was lowest with solifenacin 5 mg (33.1%), highest with solifenacin 10 mg (39.4%), and 35.9% with combination; dry mouth and constipation were the most common treatment-emergent adverse events. Incidence of dry mouth was

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				lower with combination (5.9%) versus solifenacin 10 mg (9.5%) and similar to solifenacin 5 mg (5.6%).
Gratzke et al.[25] (2019) SYNERGY II Solifenacin succinate 5 mg plus mirabegron 50 mg combination therapy vs solifenacin 5 mg monotherapy vs mirabegron 50 mg monotherapy	DB, MC, PG, RCT Patients completed either BESIDE or SYNERGY study or male or female and ≥18 years of age with symptoms of wet OAB (urinary frequency and urgency with incontinence) for ≥3 months	N=1,829 12 months	Primary: Safety, measured as treatment emergent adverse events Secondary: Change from baseline to the end of treatment in the mean number of incontinence episodes per 24 hours and micturitions per 24 hours	Primary: Overall, 856 patients (47%) experienced ≥1 treatment emergent adverse events. Treatment emergent adverse events frequency was slightly higher in the combination group (combination, 49%; mirabegron, 41%; solifenacin, 44%). Across all groups, the majority of the treatment emergent adverse events were mild or moderate in severity (mild, 24%, moderate, 19%, severe, 4%). There were no clinically relevant differences across groups in the frequency of treatment emergent adverse events leading to permanent treatment discontinuation (difference vs combination -0.2% for mirabegron and 0.4% for solifenacin). Serious treatment emergent adverse events were reported by 67 patients (3.7%); one was considered possibly treatment-related (mirabegron group, atrial fibrillation). Dry mouth was the most common treatment emergent adverse events (combination, 6.1%; solifenacin, 5.9%; mirabegron, 3.9%). Secondary: Combination therapy was statistically superior to both monotherapies in terms of change from baseline to end of treatment in the mean number of incontinence episodes per 24 hours (adjusted mean difference: mirabegron, -0.5; 95% CI, -0.7 to -0.2; P<0.001; solifenacin, -0.1; 95% CI, -0.4 to 0.1; P=0.002) and the mean number of micturitions per 24 hours (adjusted mean difference: mirabegron, -0.5; 95% CI, -0.8 to -0.2; P<0.001; solifenacin, -0.4; 95% CI, -0.7 to -0.1; P=0.004).
Inoue M et al.[26] (2019) Solifenacin 5 mg once daily for 4 weeks followed by mirabegron 50 mg once daily for 4 weeks (group S) vs	PRO, RCT, XO Female patients ≥20 years, an OABSS of 3 or higher and urgency once or more per week	N=47 8 weeks	Primary: Efficacy outcomes including change in OABSS, IPSS and VAS Secondary: Not reported	Primary: The IPSS was significantly improved after the subjects received solifenacin (P value not reported). After they received mirabegron, the IPSS was also improved, but not significantly. The OABSS was significantly improved in both groups after treatment. There were no significant differences between the two groups. In group M, the OABSS after eight weeks was significantly improved compared to that after four weeks. On the other hand, in group S, it was not significantly improved.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mirabegron 50 mg once daily for 4 weeks followed by solifenacin 5 mg once daily for 4 weeks (group M)				In group M, the VAS values for urgency and incontinence were significantly improved after treatment. In addition, the VAS values for urgency and incontinence after eight weeks were significantly improved compared to those after four weeks. In group S, on the other hand, they were not significantly improved.
Chapple et al.[27] (2013) Mirabegron 100 mg once daily vs mirabegron 50 mg once daily vs tolterodine ER 4 mg once daily	DB, MC, RCT Patients ≥18 years of age with OAB symptoms for ≥3 months and with an average baseline micturition frequency of ≥8 micturitions/24 hours and ≥3 urgency episodes with or without incontinence during the 3-day micturition diary period	N=2,444 12 months	Primary: Incidence and severity of treatment-emergent adverse events, vital signs and laboratory tests Secondary: Change from baseline in micturition frequency and urgency frequency at one, three, six, nine and 12 months; OAB-q, PPBC and VAS scores, proportion of treatment responders (≥50% decrease from baseline in the incontinence episodes/24 hours or those with zero incontinence episodes at final visit)	Primary: The incidence of treatment-emergent adverse events was similar among patients treated with mirabegron 50 mg (59.7%), 100 mg (61.3%) or tolterodine ER (62.6%). Most events were categorized as mild or moderate in severity. The most frequent treatment-related adverse events included hypertension, dry mouth, constipation, and headache, occurring at a similar incidence across all treatment groups, except for dry mouth, which was highest in the tolterodine group. Discontinuations resulting from adverse events were similar between treatment groups, with 6.4, 5.9 and 6.0% of patients treated with mirabegron 50 mg, 100 mg and tolterodine ER 4 mg, discontinuing treatment, respectively. Urinary retention occurred in one patient each in the mirabegron 50 mg and 100 mg group compared to three patients treated with tolterodine ER. Urinary retention requiring catheterization was reported in one patient receiving mirabegron 100 mg and tolterodine ER. There was a higher incidence of cardiac arrhythmias with tolterodine ER 4 mg (6.0%) compared to mirabegron 50 mg (3.9%) and 100 mg (4.1%). Mean changes from baseline in systolic blood pressure with mirabegron 50 mg, 100 mg and tolterodine were 0.2, 0.4 and -0.5 mm Hg for morning measurements and -0.3, 0.1 and 0.0 mm Hg for evening measurements, respectively. The mean changes in diastolic blood pressure were -0.3, 0.4, and 0.1 mm Hg, respectively for morning measurements and 0.0, 0.1 and 0.6 mm Hg, respectively for evening measurements. There was a higher incidence of neoplasm (benign, malignant and unspecified including cysts and polyps) in the mirabegron 100 mg group

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				(1.3%) compared to the 50 mg group (0.1%) and tolterodine ER 4 mg (0.5%). Secondary: There were similar improvements between treatments with regard to the mean number of micturitions/24 hours (-1.27 for mirabegron 50 mg, -1.41 for mirabegron 100 mg and -1.39 for tolterodine ER 4 mg; P values not reported). Improvements in the mean number of incontinence episodes/24 hours (-1.01 for mirabegron 50 mg, -1.24 for mirabegron 100 mg and -1.26 for tolterodine ER 4 mg) and MVV (17.5 mL for mirabegron 50 mg, 21.5 mL for mirabegron 100 mg and 18.1 mL for tolterodine ER 4 mg) were similar among treatment groups (P values not reported). At the final visit, the proportion of treatment responders (≥50% reduction from baseline in the mean number of incontinence episodes/24 hours was 63.7, 66.3 and 66.8% for patients treated with mirabegron 50 mg, 100 mg and tolterodine ER, respectively; P values not reported). The proportion of patients who reported zero incontinence episodes at the final visit was 43.4, 45.8 and 45.1%, respectively; P values not reported). Both doses of mirabegron showed numerical improvements on the other secondary efficacy variables including OAB-q symptom bother and QOL, treatment satisfaction, number of nocturia episodes and PPBC.
Khullar et al.[28] (2013) SCORPIO Mirabegron 100 mg once daily vs mirabegron 50 mg once daily vs	AC, DB, MC, PC, PG, RCT Patients ≥18 years of age, with OAB symptoms for ≥3 months and an average baseline micturition frequency of ≥8 micturitions/24 hours and ≥3 urgency episodes with or without	N=1,978 12 weeks	Primary: Change from baseline to end of treatment in the mean number of incontinence episodes/24 hrs, change from baseline to end of treatment in the mean number of micturitions/24 hrs Secondary:	Primary: Change from baseline to end of treatment in the mean number of incontinence episodes per 24 hours was -1.46 in the mirabegron 100 mg group, -1.57 in the mirabegron 50 mg group, -1.27 in the tolterodine SR group and -1.17 in the placebo group. When compared to placebo the change from baseline was statistically significant in the mirabegron 100 mg (P<0.05) and 50 group (P<0.05) but not in the tolterodine SR group (P value not reported). Change from baseline to end of treatment in the mean number of micturitions per 24 hours was -1.77 in the mirabegron 100 mg group, -1.93 in the mirabegron 50 mg group, -1.59 in the tolterodine SR group and -1.34 in the placebo group. When compared to placebo the change from baseline was statistically significant in the mirabegron 100 mg (P<0.05)

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tolterodine SR 4 mg once daily vs placebo	incontinence during the 3-day micturition diary period		Change from baseline to end of treatment in the mean VVPM, change from baseline to week four in the mean number of incontinence episodes/24 hrs, change from baseline to week 4 in the mean number of micturitions/24 hrs, change from baseline to final visit in mean level of urgency, change from baseline to final visit in mean number of urgency incontinence episodes/24 hrs, change from baseline to final visit in grade 3 or 4 urgency episodes/ 24 hrs, change from baseline to final visit in mean number of nocturia episodes, safety	and 50 group (P<0.05) but not in the tolterodine SR group (P value not reported). Secondary: Change from baseline to end of treatment in the mean VVPM was 25.6 mL in the mirabegron 100 mg group, 24.2 mL in the mirabegron 50 mg group, 25.0 mL in the tolterodine SR group and 12.3 mL in the placebo group. When compared to placebo the change from baseline was statistically significant in the mirabegron 100 mg (P<0.05) and 50 group (P<0.05) and tolterodine SR group (P<0.05). Change from baseline to week four in the mean number of incontinence episodes per 24 hours was -1.03 in the mirabegron 100 mg group, -1.04 in the mirabegron 50 mg group, -1.00 in the tolterodine SR group and -0.65 in the placebo group. When compared to placebo the change from baseline was statistically significant in the mirabegron 100 mg (P<0.05) and 50 group (P<0.05) and tolterodine SR group (P<0.05). Change from baseline to week four in the mean number of micturitions per 24 hours was -1.29 in the mirabegron 100 mg group, -1.16 in the mirabegron 50 mg group, -1.10 in the tolterodine SR group and -0.77 in the placebo group. When compared to placebo the change from baseline was statistically significant in the mirabegron 100 mg (P<0.05) and 50 group (P<0.05) and tolterodine SR group (P<0.05). Change from baseline to final visit in mean level of urgency was -0.30 in the mirabegron 100 mg group, -0.31 in the mirabegron 50 mg group, -0.29 in the tolterodine SR group and -0.22 in the placebo group (P values not reported). Change from baseline to final visit in mean number of urgency incontinence episodes per 24 hours was -1.33 in the mirabegron 100 mg group, -1.46 in the mirabegron 50 mg group, -1.18 in the tolterodine SR group and -1.11 in the placebo group (P values not reported). Change from baseline to final visit in grade 3 or 4 urgency episodes per 24 hours was -1.96 in the mirabegron 100 mg group, -2.25 in the mirabegron

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				50 mg group, -2.07 in the tolterodine SR group and -1.65 in the placebo group (P values not reported). Change from baseline to final visit in mean number of nocturia episodes was -0.56 in the mirabegron 100 mg group, -0.41 in the mirabegron 50 mg group, -0.50 in the tolterodine SR group and -0.45 in the placebo group (P values not reported). Mirabegron and tolterodine SR were well tolerated and the incidence of adverse events was similar across all groups. Adverse events reported in ≥2% of the placebo, mirabegron 50 mg group, mirabegron 100 mg and tolterodine SR group respectively included hypertension (7.7 vs 5.9 vs 5.4 vs 8.1%), nasopharyngitis (1.6 vs 2.8 vs 2.8 vs 2.8%), dry mouth (2.6 vs 2.8 vs 2.8 vs 10.1%), headache (2.8 vs 3.7 vs 1.8 vs 3.6%), influenza (1.6 vs 2.2 vs 2.0 vs 1.4%), UTI (1.4 vs 1.4 vs 1.8 vs 2.0%), constipation (1.4 vs 1.6 vs 1.6 vs 2.0%).
Yamaguchi et al.[29] (2014) mirabegron 50 mg once daily vs placebo once daily vs tolterodine 4 mg once daily (as an active comparator)	AC, DB, PC, RCT Patients ≥20 years of age experiencing OAB symptoms for ≥24 weeks	N=1139 12 weeks	Primary: Change in the mean number of micturitions/24 h from baseline Secondary: Micturition variables related to urgency and/or incontinence and quality-of-life domain scores on KHQ, adverse events	Primary: Mirabegron 50 mg was associated with a significantly greater change from baseline in the mean number of micturitions/24 h compared with placebo (P<0.001). Secondary: The mean [SD] change from baseline to final assessment for the secondary efficacy variables showed significant improvements for mirabegron vs placebo for number of urgency episodes/24 h (–1.85 [2.555] vs –1.37 [3.191]; P=0.025); number of incontinence episodes/24 h (–1.12 [1.475] vs –0.66 [1.861]; P=0.003); number of urgency incontinence episodes/24 h (–1.01 [1.338] vs –0.60 [1.745]; P=0.008); and volume voided/micturition (24.300 [35.4767] vs 9.715 [29.0864] mL; P<0.001); but not for number of nocturia episodes (–0.44 [0.933] vs –0.36 [1.062]; P=0.277). The percentage of subjects with zero incontinence episodes at the final assessment in the placebo, mirabegron, and tolterodine groups was 39.4, 50.8, and 48.8%, respectively. Treatment with mirabegron for 12 weeks was associated with significant improvements compared with placebo in seven of the nine quality-of-life domain scores in the KHQ. The overall incidence of treatment-related AEs was similar in the mirabegron (24.5%) and placebo (24.0%) groups, but higher in the tolterodine group (34.9%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Chapple et al.[30] (2015) Mirabegron 50 mg once daily vs placebo	Pooled post hoc analysis Patients with OAB and incontinent at baseline	N=1740 (3 trials) 12 weeks	Primary: Mean change from baseline to final visit (end of treatment) in mean number of incontinence episodes/24 h and mean number of micturitions/24 h Secondary: Mean number of urgency incontinence episodes/24 h, mean number of urgency episodes/ 24 h, and level of urgency	Primary: Mirabegron 50 mg resulted in statistically significant improvements from baseline to final visit relative to placebo in mean number of incontinence episodes per 24 h and mean number of micturitions per 24 h (P<0.001). Secondary: Mirabegron 50 mg resulted in statistically significant improvements from baseline to final visit relative to placebo in mean number of urgency episodes per 24 h and mean volume voided per micturition (P<0.001).
Maman et al.[31] (2014) Darifenacin, fesoterodine, mirabegron, oxybutynin, solifenacin, tolterodine, trospium	MA Patients ≥18 years of age with a diagnosis of OAB, may be referred to as detrusor overactivity or urinary urgency	N=27,309 (44 trials) Variable duration	Primary: Efficacy outcomes including micturition frequency, incontinence and urgency urinary incontinence; safety outcomes including dry mouth, constipation and blurred vision Secondary: Not reported	Primary: The results from 26 studies (22,040 patients) showed that the effect of mirabegron 50 mg did not differ significantly in terms of micturition frequency from other treatments, except solifenacin 10 mg, which was more effective (mean difference vs mirabegron 50 mg of -0.584). The estimated mean difference of tolterodine compared to mirabegron was not significant (0.157 micturition episodes per day). The results from 17 studies (13,101 patients) showed improvement with mirabegron 50 mg in the daily number of incontinence episodes per 24 hours from baseline to end of study was not significantly different from improvements with tolterodine 4 mg, oxybutynin 10 mg, darifenacin 7.5 mg and 15 mg and fesoterodine 4 mg and 8 mg. Mirabegron 50 mg was statistically superior to placebo with a mean difference estimated at 0.493 incontinence episodes per day.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The results of 18 studies (16,044 patients) showed that mirabegron 50 mg was significantly less efficacious than solifenacin 10 mg in terms of urgency urinary incontinence (mean difference vs mirabegron 50 mg of -0.422 urgency incontinence episodes per day) and did not differ significantly from other antimuscarinics. All 44 trials (27,309 patients) reported a similar incidence of dry mouth with mirabegron 50 mg to placebo (OR, 1.344). All antimuscarinics were associated with a significantly higher risk of dry mouth compared with mirabegron 50 mg. The OR for the occurrence of dry mouth with antimuscarinics compared with mirabegron 50 mg ranged from 5.213 with solifenacin 5 mg to 40.702 with oxybutynin IR 15 mg. Data of 41 studies (25,257 patients) reported incidence of constipation associated with mirabegron 50 mg was comparable with placebo (OR, 0.732). Other antimuscarinics except darifenacin 15 mg, fesoterodine 8 mg, solifenacin 5 mg, solifenacin 10 mg and trospium 60 mg had similar incidences of constipation. The 25 studies (14,348 patients) available reported blurred vision being relatively rare and no significant difference in risk of developing blurred vision was found between treatments arms. Secondary: Not reported
Staskin et al.[32] (2020) EMPOWUR Vibegron 75 mg QD vs placebo QD vs	DB, MC, RCT Patients 18 years of age or older with a history of OAB, diagnosed by a physician three or more months before screening	N=1,518 12 weeks	Primary: Change from baseline to week 12 in the average daily number of micturitions and change from baseline to week 12 in the average daily number of UUI episodes	Primary: At 12 weeks the LS mean change from baseline in micturition frequency among 492 patients in the vibegron group was -1.8 episodes per day, compared with -1.3 among 475 patients in the placebo group, a LS mean difference of -0.5 (95% CI, -0.8 to -0.2; P<0.001). For tolterodine the LS mean 12-week change among 378 patients was -1.6, a LS mean difference of -0.3 from placebo (95% CI, -0.6 to 0.1; P=0.0988). At 12 weeks the LS mean change from baseline in UUI episode frequency among 383 patients in the vibegron group was -2.0 episodes per day, compared with -1.4 among 372 patients in the placebo group, a LS mean difference of -0.6 (95% CI, -0.9 to -0.3; P<0.0001). For tolterodine the LS

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tolterodine extended release 4 mg QD			Secondary: Change from baseline to week 12 in the average daily number of urgency episodes, average volume voided per micturition and proportion of wet OAB cases with 75% or greater reduction in the average daily number of UUI episodes.	mean 12-week change among 286 patients was -1.8, a LS mean difference of -0.4 from placebo (95% CI, -0.7 to -0.1; P=0.0123). Secondary: At 12 weeks the LS mean change from baseline in frequency of urgency episodes among 492 patients in the vibegron group was -2.7 episodes per day, compared with -2.0 among 475 patients in the placebo group, a LS mean difference of -0.7 (95% CI, -1.1, -0.2; P=0.0020). For tolterodine the LS mean 12-week change among 378 patients was -2.5, a LS mean difference of -0.4 from placebo (95% CI, -0.9 to 0.0; P=0.0648). At 12 weeks the LS mean change in volume voided per micturition was 23.5 mL among 490 patients in the vibegron group vs 2.2 mL among 478 patients in the placebo group, a LS mean difference of 21.2 (95% CI, 14.3 to 28.1; P<0.0001). For tolterodine the LS mean change was 15.5 among 375 patients and LS mean difference of 13.3 from placebo (95% CI, 5.9 to 20.7; P<0.001). At 12 weeks the proportion of wet OAB cases with 75% or greater reduction from baseline in UUI episodes per day was 52.4% in the vibegron group vs 36.8% in the placebo group (P<0.0001). For tolterodine the proportion was 47.6%.
Staskin et al.[33] (2020) EMPOWUR extension study Vibegron 75 mg QD vs tolterodine extended release 4 mg QD	DB, MC, RCT Patients 18 years of age or older with a history of OAB, diagnosed by a physician three or more months before screening	N=505 52 weeks	Primary: Adverse events Secondary: Change from baseline at week 52 in average daily number of micturitions and urgency episodes (all patients), and urge and total urinary incontinence	Primary: A total of 12 patients (2.4%) discontinued owing to adverse events. The most common adverse events with vibegron/tolterodine (>5% in either group) were hypertension (8.8%/8.6%), urinary tract infection (6.6%/7.3%), headache (5.5%/3.9%), nasopharyngitis (4.8%/5.2%) and dry mouth (1.8%/5.2%). Secondary: Improvements in efficacy end points were maintained for patients receiving vibegron for 52 weeks; least squares mean change from baseline to week 52 in micturitions was –2.4 for vibegron vs –2.0 for tolterodine; in urge urinary incontinence episodes –2.2 vs –1.7 (P<0.05); in urgency episodes –3.4 vs –3.2; and in total incontinence episodes –2.5 vs –1.9 (P<0.05). Among patients with overactive bladder wet 61.0% receiving

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			episodes (patients with overactive bladder wet) based on 7-day diary data	vibegron experienced ≥75% reduction in urge urinary incontinence episodes after 52 weeks of treatment vs 54.4% with tolterodine, while 40.8% vs 34.2% experienced a 100% reduction.

Drug regimen abbreviations: ER=extended-release, IR=immediate-release, LA=long acting, SR=sustained-release, XL=extended release
Study abbreviations: AC=active control, CI=confidence interval, DD=double-dummy, DB=double-blind, ES=extension study, MA=meta-analysis, MC=multicenter, NS=not significant, OL=open-label, OR=odds ratio, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RR=relative risk, XO=crossover
Miscellaneous abbreviations: BPH=benign prostatic hyperplasia, BOO=bladder outlet obstruction, HRQOL=health-related quality of life, ICIQ-SF=International Consultation on Incontinence Questionnaire–Short Form, IIQ=incontinence impact questioner, IPSS=international prostate symptoms score, IPSS-QOL=international prostate symptoms score quality of life, KHQ=King's Health Questionnaire, LUTS=lower urinary tract symptoms, MVV=mean voided volume per void, OAB=overactive bladder, OAB-PGA=Overactive Bladder Patient Global Assessment questionnaire, OAB-q=Overactive Bladder Questionnaire, OABSS=Overactive Bladder Symptom Scores, PPBC=Patient Perception of Bladder Condition Questionnaire, PGA=patient global assessment, PRO=patient reported outcome, PVR=postvoid residual, Qmax=maximum flow rate, QOL=quality of life, QOL-I=Quality of Life Index, SMD=standard mean difference, SSS=Stanford Sleepiness Scale, TSQ=Treatment Satisfaction Questionnaire, UDI=urogenital distress inventory, UPS=Urgency Perception Scale, URI=upper respiratory infection, USS=Urinary Sensation Scale, UTI=urinary tract infection, UUI=urgency urinary incontinence, VAS=visual analog scale, VVPM=volume voided per micturition, 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 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 9. Relative Cost of the Genitourinary Smooth Muscle Relaxants: Beta-3 Agonists

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Mirabegron	extended-release tablet, suspension	Myrbetriq®	$$$$$	N/A
Vibegron	tablet	Gemtesa®	$$$$$	N/A

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

X.Conclusions

Urinary incontinence and overactive bladder cause both physical and psychological morbidity, as well as adversely impact quality of life.[1] Initial treatment options include lifestyle modifications (weight loss and dietary changes) and behavioral therapy (bladder training, physical therapy, and toileting assistance). Pharmacologic therapy is typically trialed if initial treatment is ineffective.[3] Antimuscarinic drugs increase bladder capacity, decrease urgency, and are useful for the treatment of urge incontinence.[3] Beta-3 adrenergic receptor agonists increase bladder capacity via relaxation of the detrusor smooth muscle. This novel mechanism may improve tolerability compared to antimuscarinic agents.[3,8,9]

Mirabegron and vibegron are β-3 adrenergic receptor agonists. Based on this mechanism of action, a potential advantage of mirabegron compared to the other agents is the low incidence of any anticholinergic adverse events; however, the agent is associated with an increased incidence of hypertension.[8,9] In clinical studies, mirabegron

demonstrated safety and efficacy in reducing overactive bladder symptoms with an adverse event profile similar to placebo.[17-18,23-25,27-31] The FDA approval of vibegron dug was based on the 12-week, double-blind, placebo- and active- controlled, phase III EMPOWUR randomized controlled trial including 1,518 patients with OAB. At 12 weeks micturitions decreased by an adjusted mean of 1.8 episodes per day for the vibegron group compared to 1.3 for the placebo group (P<0.001) and 1.6 for the tolterodine group. Among incontinent patients urge urinary incontinence episodes decreased by an adjusted mean 2.0 episodes per day for the vibegron group compared to 1.4 for the placebo group (P<0.0001) and 1.8 for the tolterodine group.[32]

The consensus recommendations for overactive bladder are from the 2014/2019 American Urological Association guideline, which indicates that first line treatment consists of behavioral therapies (e.g., bladder training, bladder control strategies). Antimuscarinic agents or β-3 adrenergic receptor agonists are recommended as second line and no specific agent is indicated as a preferred.[13] The European Association of Urology's Guidelines (2023) recommend offering beta-3 agonists as an alternative to anticholinergics to women with overactive bladder who fail conservative treatment or as an additional therapy in patients who are inadequately treated with solifenacin. They also state that beta-3 agonists are better than placebo and as efficacious as antimuscarinics for improvement of urgency urinary incontinence symptoms, with adverse event rates similar to placebo.[11] Guidelines do not give preference to one beta-3 agonist over another.[10-16]

There is insufficient evidence to support that one brand genitourinary smooth muscle relaxant: beta-3 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 genitourinary smooth muscle relaxants: beta-3 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 genitourinary smooth muscle relaxant: beta-3 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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