Therapeutic Class Overview
Dipeptidyl Peptidase-4 (DPP-4) Inhibitors

Therapeutic Class

- **Overview/Summary:** The dipeptidyl peptidase-4 (DPP-4) inhibitors are one of two incretin-based therapies currently available for the management of type 2 diabetes. The DPP-4 inhibitors linagliptin, saxagliptin, and sitagliptin, are available as single-entity agents (linagliptin [Tradjenta®], saxagliptin [Onglyza®], and sitagliptin [Januvia®]) or in fixed-dose combination products with metformin (linagliptin/metformin [Jentadueto®], saxagliptin/metformin [Kombiglyze ER®], and sitagliptin/metformin [Janumet®, Janumet XR®]) or simvastatin (sitagliptin/simvastatin [Juvisync®]). Single-entity agents are available for use either as monotherapy or in combination with other antidiabetic agents. The fixed-dose combination products are available for use when treatment with both drug components is appropriate.[1-8] The DPP-4 inhibitors reversibly block the enzyme DPP-4, which is responsible for the rapid degradation of endogenous incretin hormones. These hormones are involved in the regulation of insulin and have multiple antidiabetic actions, including the enhancement of meal stimulated insulin secretion, decreased glucagon secretion, improvements in β cell function, and slowing of gastric emptying. Through their effect on these hormones, the DPP-4 inhibitors primarily target post-prandial glucose and have also been shown to decrease fasting plasma glucose. In general, this medication class is associated with a favorable side effect profile and also have a weight neutral effect compared to other antidiabetic agents commonly used in the management of type 2 diabetes.[9-11] Most of products within this medication class are available for once-daily dosing; however, the fixed-dose combination products containing metformin immediate-release require twice-daily dosing. In addition, due to specific components in the various fixed-dose combination products, additional warnings, precautions, and dosing requirements may be required in addition to those associated with single-entity DPP-4 inhibitors.[1-8] All DPP-4 inhibitor products are only available as branded agents.

Table 1. Current Medications Available in Therapeutic Class[1-8]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Single-Entity Agents			
Linagliptin (Tradjenta®)	Monotherapy or combination therapy as adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes	Tablet: 5 mg	-
Saxagliptin (Onglyza®)	Monotherapy or combination therapy as adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes	Tablet: 2.5 mg 5 mg	-
Sitagliptin (Januvia®)	Monotherapy or combination therapy as adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes	Tablet: 25 mg 50 mg 100 mg	-
Combination Products			
Linagliptin/ metformin (Jentadueto®)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes*	Tablet: 2.5/500 mg 2.5/850 mg 2.5/1,000 mg	-
Saxagliptin/ metformin	Adjunct to diet and exercise to improve glycemic control in adults	Tablet (saxagliptin/metformin ER): 5/500 mg	-

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
(Kombiglyze XR®)	with type 2 diabetes†	2.5/1,000 mg 5/1,000 mg	
Sitagliptin/ metformin (Janumet®, Janumet XR®)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes‡	Tablet (sitagliptin/metformin IR): 50/500 mg 50/1,000 mg Tablet (sitagliptin/metformin ER): 50/500 mg 50/1,000 mg 100/1,000 mg	-
Sitagliptin/ simvastatin (Juvisync®)	Patients for whom treatment with both sitagliptin and simvastatin is appropriate§	Tablet: 100/10 mg 100/20 mg 100/40 mg	-

ER=extended-release, IR=immediate-release
*When treatment with both linagliptin and metformin is appropriate.
†When treatment with both saxagliptin and metformin is appropriate.
‡When treatment with both sitagliptin and metformin or metformin extended-release is appropriate.
§Sitagliptin is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes. Simvastatin is indicated as an adjunctive therapy to diet to reduce the risk of total mortality by reducing coronary heart disease deaths and reduce the risk of non-fatal myocardial infarction, stroke, and the need for revascularization procedures in patients at high risk of coronary events; reduce elevated total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), apolipoprotein B, triglycerides (TG) and increase high density lipoprotein cholesterol in patients with primary hyperlipidemia (heterozygous familial and nonfamilial) and mixed dyslipidemia; reduce elevated TG in patients with hypertriglyceridemia and reduce TG and very low density lipoprotein cholesterol in patients with primary dysbetalipoproteinemia; and reduce TC and LDL-C in patients with primary homozygous familial hypercholesterolemia.

Evidence-based Medicine

- In general, the dipeptidyl peptidase-4 (DPP-4) inhibitors have been evaluated in clinical trials as add-on therapy to treatment regimens of established antidiabetic agents. Data consistently demonstrate that DPP-4 inhibitors are associated with positive effects on glycosylated hemoglobin (HbA_{1c}), fasting plasma glucose (FPG), and post-prandial glucose (PPG). In addition, glycemic goals were consistently achieved when an incretin mimetic was added to existing treatment regimens. Data also indicate that the DPP-4 inhibitors have a weight neutral effect and improvements in β cell function are not consistently achieved.[12-52]
- Head-to-head trials with other antidiabetic agents are limited and not consistent in terms of demonstrating "superiority".[38-42] Furthermore, combination therapy with a DPP-4 inhibitor and metformin consistently demonstrates "superiority" over monotherapy with either a DPP-4 inhibitor or metformin.[25,26,44,43]
- Sitagliptin has been compared head-to-head with other incretin-based therapies used in the management of type 2 diabetes in a limited number of clinical trials. As add-on therapy to metformin or as monotherapy in treatment-naïve patients, the incretin mimetics demonstrated "superiority" over sitagliptin in decreasing HbA_{1c}, FPG, PPG, and body weight. In addition, significantly more patients receiving incretin mimetics achieved glycemic goals compared to sitagliptin.[40-42]
- Of note, there have been no 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.[4-8]
- Overall, safety data demonstrate that DPP-4 inhibitors are well tolerated with a low incidence of hypoglycemia.[12-52]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
    - Type 2 diabetes:[53-57]
        - Metformin remains the cornerstone to most antidiabetic treatment regimens.[53-57]

        - Patients with high glycosylated hemoglobin (HbA_{1c}) will most likely require combination or triple therapy in order to achieve glycemic goals.[53-57]
        - The dipeptidyl peptidase-4 (DPP-4) inhibitors are recommended as a potential second-line treatment option to be added to or used in combination with metformin in patients not achieving glycemic goals.[56]
            - In some clinical situations, the DPP-4 inhibitors may be used as monotherapy in patients with a lower HbA_{1c}; however, again metformin is usually the most appropriate initial choice for monotherapy.[55,56]
            - While the American Diabetes Association does not endorse the use of DPP-4 inhibitors in their treatment algorithm of well-validated antidiabetic agents, they state these agents may be appropriate choices in selected patients.[53,52]
            - A lower rate of hypoglycemia and an established efficacy and safety profile when used in combination with metformin are advantages associated with the DPP-4 inhibitors compared to other classes of antidiabetic agents.[56]
            - No one DPP-4 inhibitor is recommended or preferred over another.[53-57]
    - Hyperlipidemia:[58-63]
        - Therapeutic lifestyle changes remain an essential modality in the management of patients with hypercholesterolemia.
        - In general, hydroxymethylglutaryl coenzyme A reductase inhibitors (statins) are considered first-line therapy for decreasing low density lipoprotein cholesterol levels. If after six weeks, lipid goals are not achieved with statin monotherapy, a dosage increase or the addition of a bile acid sequestrant or nicotinic acid (niacin) should be considered.
        - Statins are recommended in patients with established coronary heart disease (CHD) or CHD risk equivalents. Choice of statin and dose should be based on cost and the amount of lipid lowering required for a specific patient.
        - Patients with risk factors for CHD but with no history of disease are likely to decrease their risk of CHD with lipid lowering therapy.
- Other Key Facts:
    - Most of the agents within the class are available for once-daily dosing; however, the fixed-dose combination products with metformin immediate-release are administered twice-daily (linagliptin/metformin [Jentadueto®] and sitagliptin/metformin [Janumet®]).[1-8]
    - No generic DPP-4 inhibitors are currently available.

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3. Januvia® [package insert]. Whitehouse Station (NJ): Merck & Co., Inc.; 2011 Nov.
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5. Kombiglyze XR® [package insert]. Princeton (NJ): Bristol-Myers Squibb Company; 2011 Nov.
6. Janumet® [package insert]. Whitehouse Station (NJ): Merck & Co., Inc.; 2011 Apr.
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Therapeutic Class Review
Dipeptidyl Peptidase-4 (DPP-4) Inhibitors

Overview/Summary

A significant advancement in the management of type 2 diabetes has been the development of incretin-based therapies. This novel therapeutic approach is important as type 2 diabetics have been shown to have an impaired incretin response.[1] Currently there are two classes of incretin-based therapies available; the dipeptidyl pepetidase-4 (DPP-4) inhibitors and the glucagon-like peptide-1 receptor agonists, or incretin mimetics. The DPP-4 inhibitors include linagliptin, saxagliptin, and sitagliptin, which are all available as single-entity products (linagliptin [Tradjenta®], saxagliptin [Onglyza®], and sitagliptin [Januvia®]) or in fixed-dose combination products (linagliptin/metformin [Jentadueto®], saxagliptin/metformin [Kombiglyze ER®], sitagliptin/metformin [Janumet®, Janumet XR®], and sitagliptin/simvastatin [Juvisync®]. The DPP-4 inhibitors are Food and Drug Administration-approved as adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes. Single-entity products are available for use either as monotherapy or in combination with other antidiabetic agents. The fixed-dose combination products are available for use when treatment with both drug components is appropriate.[2-9]

The DPP-4 inhibitors reversibly block the enzyme DPP-4, which is responsible for the rapid degradation of endogenous incretin hormones. These hormones are produced by the gastrointestinal tract in response to meals and are involved in the regulation of insulin. The antidiabetic actions of endogenous incretin hormones include the enhancement of meal stimulated insulin secretion, decreased glucagon secretion, improvements in β cell function, and slowing of gastric emptying. Through their effect on these hormones, the DPP-4 inhibitors primarily target post-prandial glucose (PPG) and have also been shown to decrease fasting plasma glucose (FPG).[10,11] In general, the DPP-4 inhibitors are associated with a favorable side effect profile and also have a weight neutral effect compared to other antidiabetic agents commonly used in the management of type 2 diabetes. Compared to sulfonylureas, the risk of hypoglycemia associated with the DPP-4 inhibitors is low due to the glucose-dependent nature of incretin hormone activity. In addition, the DPP-4 inhibitors have not been associated with the same increased risk of cardiovascular disease that has been observed with the use of thiazolidinediones (TZDs). In addition, as mentioned earlier the DPP-4 inhibitors improve the function of β cells and although TZDs and metformin treat insulin resistance, these agents do not address the progressive decline in β cell function that is observed in patients with type 2 diabetes.[10-12] Overall, this medication class is significantly more effective compared to placebo in reducing glycosylated hemoglobin (HbA_{1c}), FPG, and PPG, with no major effect on body weight. Head-to-head trials with other antidiabetic agents are limited and not consistent in terms of "superiority". Furthermore, combination therapy with a DPP-4 inhibitor and metformin consistently demonstrates "superiority" in improving glycemic outcomes over monotherapy with either a DPP-4 inhibitor or metformin.[13-53]

With regards to the specific DPP-4 inhibitor agents, all single-entity products are available for once-daily dosing. Two fixed-dose combination products contain metformin immediate-release (linagliptin/metformin [Jentadueto®] and sitagliptin/metformin [Janumet®]) which are available for twice-daily dosing. Two other fixed-dose combination products contain metformin extended-release (ER) (saxagliptin/metformin ER [Kombiglyze XR®] and sitagliptin/metformin ER [Janumet XR®]), and because of the metformin ER component, these products are available for once-daily dosing. The fixed-dose combination product combining sitagliptin and simvastatin (Juvisync®), a hydroxymethylglutaryl coenzyme A reductase inhibitor (statin), is also available for once-daily dosing. Single-entity linagliptin is the only agent within the class that does not require renal and hepatic dosing. Furthermore, because of the metformin component in certain fixed-dose combination products, caution is recommended with both renal and hepatic dysfunction. In addition, these products all have a boxed warning regarding the risk of lactic acidosis due to metformin accumulation. The fixed-dose combination product of sitagliptin/simvastatin has a pregnancy category of X and is associated with several drug interactions due to the simvastatin component.[2-9] Currently, none of the DPP-4 inhibitors are available generically.

According to current clinical guidelines for the management of type 2 diabetes, metformin remains the cornerstone of most antidiabetic treatment regimens. Additionally, patients with high HbA_{1c} will likely require combination or triple therapy in order to achieve glycemic goals.[55-59] The DPP-4 inhibitors are recommended as a potential second-line treatment option to be added to or used in combination with metformin in patients not achieving glycemic goals. In some clinical situations, the DPP-4 inhibitors may be used as monotherapy in patients with a lower HbA_{1c}; however, again metformin is usually the most appropriate initial choice for monotherapy.[57,58] While the American Diabetes Association does not endorse the use of DPP-4 inhibitors in their treatment algorithm of well-validated antidiabetic agents, they state these agents may be appropriate choices in selected patients.[55,56] Clinical guidelines note a lower rate of hypoglycemia and an established efficacy and safety profile when used in combination with metformin as advantages associated with the DPP-4 inhibitors compared to other classes of antidiabetic agents.[58] No one DPP-4 inhibitor is recommended or preferred over another.[55-59]

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Single-Entity Agents		
Linagliptin (Tradjenta®)	Dipeptidyl peptidase-4 inhibitors	-
Saxagliptin (Onglyza®)	Dipeptidyl peptidase-4 inhibitors	-
Sitagliptin (Januvia®)	Dipeptidyl peptidase-4 inhibitors	-
Combination Products		
Linagliptin/metformin (Jentadueto®)	Dipeptidyl peptidase-4 inhibitors/biguanide	-
Saxagliptin/metformin (Kombiglyze XR®)	Dipeptidyl peptidase-4 inhibitors/biguanide	-
Sitagliptin/metformin (Janumet®, Janumet XR®)	Dipeptidyl peptidase-4 inhibitors/biguanide	-
Sitagliptin/simvastatin (Juvisync®)	Dipeptidyl peptidase-4 inhibitors/ hydroxymethylglutaryl coenzyme A reductase inhibitor	-

Indications

Table 2. Food and Drug Administration-Approved Indications[2-9]

Generic name	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	Patients For Whom Treatment With Both Sitagliptin and Simvastatin is Appropriate
Single-Entity Agents			
Linagliptin		✔	
Saxagliptin		✔	
Sitagliptin		✔	
Combination Products			
Linagliptin/metformin	✔*		
Saxagliptin/metformin	✔†		
Sitagliptin/metformin	✔‡		
Sitagliptin/simvastatin			✔§

*When treatment with both linagliptin and metformin is appropriate.
†When treatment with both saxagliptin and metformin is appropriate.
‡When treatment with both sitagliptin and metformin or metformin extended-release is appropriate.
§Sitagliptin is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes. Simvastatin is indicated as an adjunctive therapy to diet to reduce the risk of total mortality by reducing coronary heart disease deaths and reduce the risk of non-fatal myocardial infarction, stroke, and the need for revascularization procedures in patients at high risk of coronary

events; reduce elevated total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), apolipoprotein B, triglycerides (TG) and increase high density lipoprotein cholesterol in patients with primary hyperlipidemia (heterozygous familial and nonfamilial) and mixed dyslipidemia; reduce elevated TG in patients with hypertriglyceridemia and reduce TG and very low density lipoprotein cholesterol in patients with primary dysbetalipoproteinemia; and reduce TC and LDL-C in patients with primary homozygous familial hypercholesterolemia.

Pharmacokinetics

Table 3. Pharmacokinetics[60]

Generic Name	Bioavailability (%)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Single-Entity Agents				
Linagliptin	30	5 to <7	None	>100
Saxagliptin	Not reported	60	5-hydroxy saxagliptin	2.5 (3.1*)
Sitagliptin	87	87	None	12.4
Combination Products				
Linagliptin/metformin	30/50 to 60	5 to <7/90	None/none	>100/6.2
Saxagliptin/metformin	Not reported/ 50 to 60†	60/90	5-hydroxy saxagliptin/none	2.5 (3.1*)/ 6.2
Sitagliptin/metformin	87/50 to 60†	87/90	None/none	12.4/6.2
Sitagliptin/simvastatin	87/<5	87/13	None/ β-hydroxyacid form	12.4/ not reported

*Active metabolite.
†Immediate-release.

Clinical Trials

Clinical trials demonstrating the safety and efficacy of the dipeptidyl peptidase-4 (DPP-4) inhibitors in the management of type 2 diabetes are outlined in Table 4.[13-54] Of note, there have been no 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.[5-9]

Overall, linagliptin is more effective compared to placebo in decreasing glycosylated hemoglobin (HbA_{1c}) and fasting plasma glucose (FPG) as monotherapy or as add-on therapy to other antidiabetic agents in type 2 diabetics not achieving glycemic goals. In addition, more patients achieved glycemic goals (HbA_{1c} <7.0%) with linagliptin compared to placebo.[13-17] Similar results were achieved with saxagliptin when compared to placebo.[18-24] In a single head-to-head trial, saxagliptin (5 mg once-daily) demonstrated non-inferiority to sitagliptin (100 mg once-daily) in decreasing HbA_{1c}. However, a significantly greater proportion of patients achieved an HbA_{1c} ≤6.5% and achieved significant decreases in FPG with sitagliptin compared to saxagliptin.[25] In addition, combination therapy with saxagliptin and metformin was "superior" to monotherapy with either agent in observed decreases in HbA_{1c}, FPG, and post-prandial glucose (PPG), and a significantly greater proportion of patients achieved glycemic goals with combination therapy.[26,27] Similar results were also achieved with sitagliptin when compared to placebo, and again, combination therapy with sitagliptin and metformin demonstrated "superiority" over monotherapy with either agent.[28-40,44,45] Of note, while the DPP-4 inhibitors have consistently demonstrated efficacy in decreasing HbA_{1c}, FPG, and PPG, and in achieving glycemic goals, observed decreases in body weight and improvements in β cell function with these agents are not consistent in terms of "superiority" compared to baseline values, placebo, or other antidiabetic agents.[13-40]

Sitagliptin has been compared head-to-head with other incretin-based therapies used in the management of type 2 diabetes in a limited number of clinical trials. As add-on therapy to metformin, the incretin mimetics demonstrated "superiority" over sitagliptin in decreasing HbA_{1c}, FPG, PPG, and body weight. In addition, significantly more patients receiving incretin mimetics achieved glycemic goals compared to patients receiving sitagliptin.[41,42] In a trial evaluating exenatide extended-release, metformin, pioglitazone,

and sitagliptin, all as monotherapy in drug-naïve type 2 diabetics, extended extended-release demonstrated “superiority” over sitagliptin for these outcomes.[43]

In general, meta-analyses and Cochrane Reviews evaluating incretin-based therapies, including the DPP-4 inhibitors, support the results observed in randomized-controlled trials evaluating these agents.[47-53] A meta-analysis revealed that DPP-4 inhibitors are not associated with an increased risk of cardiovascular events compared to placebo or other antidiabetic agents.[48]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Forst et al[13] Linagliptin 1, 5, or 10 mg/day vs placebo vs glimepiride (OL) 1 to 3 mg/day Patients were also receiving metformin.	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 control on metformin alone (HbA_{1c} 7.5 to 10.0%)	N=333 12 weeks	Primary: Change in baseline HbA_{1c} 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	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 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.
Del Prato et al[14] Linagliptin 5 mg/day	DB, MC, PC, PG, RCT Type 2 diabetics	N=503 24 weeks	Primary: Change in baseline HbA_{1c}	Primary: Adjusted mean differences of the change in HbA_{1c} significantly favored linagliptin compared to placebo (-0.69%; *P*<0.0001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo	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)		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 baseline FPG, and two-hour PPG, safety	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). 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[15] 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, who had inadequate	N=701 24 weeks	Primary: Change in baseline HbA_{1c} Secondary: Change in baseline FPG, two-hour PPG,	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).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
All patients also received metformin ≥1,500 mg/day.	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		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 required rescue medication; safety	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). 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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				signs.
Owens et al[16] Linagliptin 5 mg QD vs placebo Patients were also receiving metformin and a sulfonylurea.	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 metformin ≥1,500 mg/day and the maximum tolerated dose of a sulfonylurea	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 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	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). 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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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.
Gomis et al[17] Linagliptin 5 mg/day plus pioglitazone 30 mg/day vs pioglitazone 30 mg/day	DB, DD, MC, 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 pioglitazone (-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 pioglitazone (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 pioglitazone (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 pioglitazone (*P*<0.0001 at each visit). Combination therapy significantly decreased FPG compared to pioglitazone (-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). 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).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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 pioglitazone, respectively. Laboratory analyses did not reveal any clinically significant findings.
Hollander et al[18] Saxagliptin 2.5 and 5 mg QD vs placebo All patients also received a TZD.	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	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). 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.
Chacra et al[19] Saxagliptin 2.5 and 5 mg QD vs	DB, MC, RCT Type 2 diabetics 18 to 77 years of age with inadequate glycemic control	N=768 24 weeks	Primary: Change in baseline HbA_{1c} Secondary: Change in baseline FPG and	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).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo All patients also received glyburide 7.5 mg/day.	(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		PPG $AUC_{0\text{-}3hr}$, proportion of patients achieving an HbA_{1c} <7.0%, safety	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 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 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.
Chacra et al[20] Saxagliptin 2.5 and 5 mg QD vs placebo All patients also received glyburide 7.5 mg/day.	DB, ES, 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,	N=768 52 weeks (76 weeks total)	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: Decreases in HbA_{1c} with saxagliptin 2.5 and 5 mg compared to placebo were -0.11 and -0.03 vs -0.69% after 76 weeks, respectively (*P*<0.0001 for both). Secondary: There were minimal decreases in FPG at week 76 with saxagliptin 2.5 mg (-1 mg/dL; 95% CI, -6.1 to 8.5), saxagliptin 5 mg (-8 mg/dL; 95% CI, 0.4 to 15.4), and placebo (-4 mg/dL; 95% CI, -6.4 to 14.8), respectively. The PPG $AUC_{0\text{-}3hr}$ decreases were maintained during the extension trial. A greater proportion of patients receiving saxagliptin achieved an HbA_{1c} <7.0% compared to placebo (11.0 and 9.6 vs 5.3%; *P* value not reported). Similar

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	fasting C-peptide ≥1 ng/mL, and BMI ≤40 kg/m^2			results were observed with HbA_{1c} ≤6.5% (4.1 and 5.2 vs 1.5%; *P* value not reported).
Rosenstock et al (abstract)[21] Saxagliptin 2.5, 5, 10 mg QD vs placebo Trial was conducted with a separate OL cohort with patients receiving saxagliptin 10 mg QD (treatment-naïve type 2 diabetics with inadequate glycemic control [HbA_{1c} >10.0 to ≤12.0%]).	OL, PC, RCT Treatment-naïve type 2 diabetics with inadequate glycemic control, and an HbA_{1c} ≥7.0 and ≤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.
DeFronzo et al[22] Saxagliptin 2.5, 5, and 10 mg QD vs placebo All patients also received metformin 1,500 to 2,500 mg/day.	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)	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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	≥8 weeks, fasting C-peptide concentration ≥1 ng/mL, and BMI ≤40 kg/m^2			all).
Rosenstock et al[23] Saxagliptin 2.5, 5, 10, 20, and 40 mg QD (low-dose cohort) vs saxagliptin 100 mg QD (high-dose cohort) 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 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).
Stenlöf et al[24] Saxagliptin 5 mg QD vs	DB, MC, PC, RCT Type 2 diabetics with inadequate glycemic control (HbA_{1c} 7.0 to	N=93 4 weeks	Primary: Change in baseline 24-hour mean weighted glucose	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

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placebo All patients also received metformin ER ≥1,500 mg/day.	10.0%), and currently receiving stable doses of metformin IR or metformin ER (≥1,500 mg/day) as monotherapy for ≥8 weeks		Secondary: Change in baseline four-hour mean weighted PPG, two-hour PPG (both assessed after the evening meal), three-day average mean daily glucose, and two-day average FPG	placebo (-30.7 vs 0.4 mg/dL; *P*<0.0001). Similar results were observed with 2-hour mean weighted PPG (-38.2 vs -2.8 mg/dL; *P*=0.0010). 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).
Scheen et al[25] 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, the small improvement in β cell function did not differ between the two treatments.

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Jadzinsky et al[26] Saxagliptin 5 and 10 mg QD plus metformin 500 mg/day vs saxagliptin 10 mg QD vs metformin 500 mg/day	AC, DB, MC, RCT Type 2 diabetics 18 to 77 years of age, HbA_{1c} ≥8.0 to ≤12.0%, fasting C-peptide concentration ≥1.0 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 requiring rescue for failing to achieve prespecified glycemic targets or discontinuing for lack of efficacy at 24 weeks	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). 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).
Pfutzner et al[27] Saxagliptin 5 and 10 mg QD plus metformin 500 mg/day vs	AC, DB, ES, MC, RCT Type 2 diabetics 18 to 77 years of age, HbA_{1c} ≥8.0 to ≤12.0%, fasting C-peptide	N=1,306 52 weeks (76 weeks total)	Primary: Change in baseline HbA_{1c} Secondary: Change in baseline body weight, proportion	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:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
saxagliptin 10 mg QD vs metformin 500 mg/day	concentration ≥1 ng/mL, and BMI ≤40 kg/m^2		of patients achieving an HbA_{1c} <7.0 and ≤6.5%	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 sitagliptin and metformin (51.5 and 50.5 vs 25 and 34.7%, respectively, *P* values not reported). Similar results were observed with HbA_{1c} <6.5% (*P* values not reported).
Scott et al[28] Sitagliptin 5, 12.5, 25, and 50 mg BID vs placebo vs glipizide 5 to 20 mg/day	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
Hanefeld et al[29] Sitagliptin 25 and 50 mg QD vs sitagliptin 50 mg BID	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:	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;

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs sitagliptin 100 mg QD vs placebo			Adverse events, body weight	*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.
Brazg et al[30] Sitagliptin 50 mg BID vs placebo All patients also received metformin ≥1,500 mg/day. Patients received 1 drug regimen for 4 weeks then XO to the comparator group for 4 weeks.	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. 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.
Nonaka et al[31] 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	N=151 12 weeks	Primary: Change in baseline HbA_{1c}, FPG, PPG, body weight; adverse effects	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 placebo (*P*<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	≤240 mg/dL		Secondary: Not reported	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). 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
Raz et al[32] Sitagliptin 100 mg QD vs placebo All patients also received metformin ≥1,500 mg/day	DB, MC, PC, PG, RCT Type 2 diabetics 18 to 78 years of age, HbA_{1c} of 7.0 to 10.0% that were 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

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				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.
Charbonnel et al[33] Sitagliptin 100 mg QD vs placebo All patients also received metformin ≥1,500 mg/day. Pioglitazone was used as rescue therapy if defined glycemic goals were not met.	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% (47.0an vs 18.3%; *P*<0.001) and <6.5% (17.2 vs 4.9%; *P*<0.001) compared to 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).
Rosenstock et al[34] Sitagliptin 100 mg QD	DB, MC, PC, PG, RCT Type 2 diabetics	N=353 24 weeks	Primary: Change in baseline HbA_{1c}	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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo All patients were also receiving pioglitazone 30 or 45 mg QD.	≥18 years of age with inadequate glycemic control (HbA_{1c} ≥7.0 to ≤10.0%) on pioglitazone monotherapy		Secondary: Change in baseline FPG, fasting insulin, proinsulin, and lipid profiles; safety and tolerability	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). 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.
Hermansen et al[35] Sitagliptin 100 mg QD vs placebo All patients also received glimepiride with or without metformin.	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 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

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				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).
Scott et al[36] Sitagliptin 100 mg QD vs placebo vs rosiglitazone 8 mg QD All patients also received metformin.	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)

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				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 (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

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				measurements significantly increased with rosiglitazone (*P* values not reported).
Raz et al[37] Sitagliptin 100 and 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.
Aschner et al[38] Sitagliptin 100 and 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	Sample 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 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.
Derosa et al[39] Metformin 850 mg BID vs sitagliptin 100 mg QD All patients were also receiving pioglitazone.	DB, MC, RCT Type 2 diabetics ≥18 years of age, uncontrolled (HbA_{1c} >7.5%) with diet, exercise, and pioglitazone 30 mg/day	N=151 12 months	Primary: Change in baseline body weight and BMI at three, six, nine, and 12 months Secondary: Change in baseline HbA_{1c}, FPG, PPG, fasting plasma insulin, insulin resistance and β cell function, fasting plasma proinsulin, proinsulin:fasting plasma insulin ratio, adiponectin,	Primary: There was no difference in BMI or body weight at months three, six, nine, and 12 with sitagliptin. Metformin significantly decreased body weight and BMI at month 12 compared to baseline and sitagliptin (both *P*<0.05). Secondary: Both treatments significantly improved HbA_{1c} at months nine and 12 (*P*<0.05 and *P*<0.01), with no differences between the two treatments (*P* values not reported). Both treatments significantly decreased FPG at months nine and 12 (*P*<0.05 and *P*<0.01), with no differences between the two treatments (*P* values not reported). Both treatments significantly decreased PPG at months nine and 12 (*P*<0.05 and *P*<0.01), with no differences between the two treatments (*P* values not reported). Both treatments significantly decreased fasting plasma insulin (sitagliptin month 12; *P*<0.05 and metformin months nine and 12; *P*<0.05 and *P*<0.01,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			resistin, and TNF-α and high-sensitivity CRP at months three, six, nine, and 12	respectively), and at month 12 the decrease was significantly greater with metformin compared to sitagliptin (*P*<0.05). Both treatments significantly increased HOMA-B (sitagliptin months nine and 12; *P*<0.05 and *P*<0.01, and metformin month 12; *P*<0.05), with no differences between the two treatments. Both treatments significantly decreased fasting plasma proinsulin (sitagliptin Month 12; *P*<0.05 and metformin months nine and 12; *P*<0.05 and *P*<0.01), and at month 12 the decrease was significantly greater with metformin compared to sitagliptin (*P*<0.05). Both treatments significantly decreased proinsulin:fasting plasma insulin ratio (sitagliptin month 12; *P*<0.05 and metformin months six, nine, and 12; *P*<0.05, *P*<0.02, and *P*<0.01), and at month 12 the decrease was greater with metformin compared to sitagliptin (*P*<0.05). Both treatments significantly decreased HOMA-IR (sitagliptin month 12; *P*<0.05 and metformin months nine and 12; *P*<0.05 and *P*<0.01), and at month 12 the decrease was significantly greater with metformin compared to sitagliptin (*P*<0.05). Metformin significantly increased adiponectin at month 12 compared to baseline and sitagliptin (*P*<0.05 for both). Metformin significantly decreased resistin at month 12 compared to baseline and sitagliptin (*P*<0.05 for both). Metformin significantly decreased TNF-α at month 12 compared to baseline and sitagliptin (*P*<0.05 for both). Both treatments significantly decreased high-sensitivity CRP at month 12 (*P*<0.05 for both), with no difference between the two treatments (*P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Nauck et al[40] Sitagliptin 100 mg QD vs glipizide 5 to 20 mg QD All patients were also receiving metformin ≥1,500 mg/day.	AC, DB, MC, non-inferiority, PG, RCT Type 2 diabetics 18 to 78 years of age, inadequately controlled (HbA_{1c} ≥6.5 to ≤10.0%) on metformin monotherapy	N=1,172 52 weeks	Primary: Change in baseline HbA_{1c} Secondary: Change in baseline FPG, body weight, and fasting insulin, proinsulin; safety and tolerability	Primary: Both treatments decreased HbA_{1c} by -0.67% (95% CI, -0.75 to -0.59). The upper limit of the two-sided 95% CI for the between group difference of 0.08% was less than the pre-specified non-inferiority margin of 0.3%. A similar proportion of patients achieved an HbA_{1c} <7.0% with each treatment (63 vs 59%; treatment difference, 3.9%; 95% CI, -2.8 to 10.7). Sitagliptin demonstrated non-inferiority to glipizide. Secondary: Decreases in FPG were not different between the two treatments (-0.56 [95% CI, -0.81 to -0.30] vs -0.42 mmol/L [95% CI, -0.67 to -0.17]). Body weight significantly decreased with sitagliptin (-1.5 kg; 95% CI, -2.0 to -0.9), and significantly increased with glipizide (1.1 kg; 95% CI, 0.5 to 1.6; treatment difference, -2.5 kg; 95% CI, -3.1 to -2.0; *P*<0.001). There was a decrease in fasting proinsulin with sitagliptin compared to an increase with glipizide (*P* value not reported). Glipizide was associated with a significantly higher incidence of hypoglycemia compared to sitagliptin (32 vs 5%; *P*<0.001). No meaningful differences in overall serious clinical adverse events were observed between the two treatments.
Bergenstal et al[41] 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, 6-point self-monitored glucose concentrations,	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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
pioglitazone 45 mg QD All patients received existing metformin therapy.			body weight, fasting lipid profile, fasting insulin profile, BP, cardiovascular risk markers, patient-reported QOL, safety	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 6-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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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.
Pratley et al[42] Liraglutide 1.2 and 1.8 mg SC QD vs sitagliptin 100 mg QD All patients received existing metformin therapy.	MC, OL, PG, RCT Type 2 diabetic patients 18 to 80 years of age with an HbA_{1c} 7.5 to 10.0%, BMI ≤45 kg/m^2, and had been treated with metformin (≥1,500 mg/day) for ≥3 months	N=665 26 weeks	Primary: Change in baseline HbA_{1c} Secondary: Proportion of patients reaching HbA_{1c} targets <7.0 or ≤6.5%; FPG; PPG; body weight; β cell function; fasting lipid profile; cardiovascular risk markers; BP;	Primary: In the "superiority" comparison, significantly greater lowering of HbA_{1c} (8.5% at baseline) was achieved with liraglutide 1.8 mg (-1.50%; 95% CI, -1.63 to -1.37) and 1.2 mg (-1.24%; 95% CI, -1.37 to -1.11) compared to sitagliptin (-0.90%; 95% CI, -1.03 to -0.77). Treatment differences for liraglutide 1.8 mg vs sitagliptin were -0.60% (95% CI, -0.77 to -0.43; *P*<0.0001) and -0.34% (95% CI, -0.51 to -0.16; *P*<0.0001) for liraglutide 1.2 mg vs sitagliptin. Secondary: Significantly more patients achieved HbA_{1c} targets (<7.0 and ≤6.5%) with liraglutide compared to sitagliptin (<7.0%: liraglutide 1.8 mg: OR, 4.50; 95% CI, 2.90 to 6.71; liraglutide 1.2 mg: OR, 2.75; 95% CI, 1.78 to 4.25; and ≤6.5%: liraglutide 1.8 mg: OR, 4.25; 95% CI, 2.55 to 7.08; liraglutide 1.2 mg: OR, 2.11; 95% CI, 1.24 to 3.59; *P* values not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			heart rate; physical measures; treatment satisfaction; adverse events; composite endpoint of proportion of patients with a HbA_{1c} <7.0%, no hypoglycemia, and weight change of ≤0 kg	After 26 weeks, decreases in FPG were significantly greater with liraglutide compared to sitagliptin (liraglutide 1.8 mg, -2.14 mmol/L [95% CI, -2.43 to -1.84], liraglutide 1.2 mg, -1.87 [95% CI, -2.16 to -1.57], and sitagliptin, -0.83 [95% CI, -1.13 to -0.54]; *P* values not reported). Treatment differences were -1.31 mmol/L (95% CI, -1.70 to -0.91; *P* value not reported) for liraglutide 1.8 mg compared sitagliptin and -1.04 mmol/L (95% CI, -1.43 to -0.64; *P* value not reported) for liraglutide 1.2 mg compared to sitagliptin. Mean reductions in the AUC for PPG is not reported because data were difficult to interpret. The decrease in body weight after 26 weeks was significantly greater with liraglutide compared to sitagliptin (liraglutide 1.8 mg, -3.38 kg [95% CI, -3.70 to -2.84], liraglutide 1.2 mg, -2.86 kg [95% CI, -1.50 to -0.42], and sitagliptin, -0.96 kg [95% CI, -1.50 to -0.42]; *P* values not reported). Treatment differences were -2.42 kg (95% CI, -3.14 to -1.70; *P* value not reported) for liraglutide 1.8 mg compared to sitagliptin and -1.90 kg (95% CI, -2.61 to -1.18; *P* value not reported) for liraglutide 1.2 mg compared to sitagliptin. Liraglutide was associated with significant improvements in HOMA-B, C-peptide concentration, and proinsulin:insulin ratio compared to sitagliptin, but no treatment-related differences were observed for HOMA-IR or fasting insulin concentration. Changes in the lipid profile between liraglutide and sitagliptin were not different, apart from the decrease in TC which was significantly greater with liraglutide 1.8 mg compared to sitagliptin (*P* value not reported). Data on cardiovascular markers were not reported. Both liraglutide and sitagliptin had a small effect on SBP and DBP; lowering of DBP with sitagliptin seemed to be significant compared to liraglutide 1.8 mg, but not compared to liraglutide 1.2 mg (*P* values not reported). Heart rate increased with liraglutide, and decreased slightly with sitagliptin;

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				differences were small but significant with both doses of liraglutide compared to sitagliptin (*P* values not reported). Liraglutide was associated with significantly greater reductions in waist circumference compared to sitagliptin, but no treatment-related differences of waist:hip ratio were observed (*P* values not reported). Improvements were observed in all DTSQ items for all treatments. The increase in patients' treatment satisfaction from baseline was significantly greater with liraglutide 1.8 mg compared to sitagliptin (treatment difference, 1.39; 95% CI, 0.13 to 2.64; *P* value not reported), but the increase with liraglutide 1.2 mg compared to sitagliptin was not significant (*P* value not reported). Most treatment-emergent adverse events were reported with liraglutide. Two deaths occurred, neither of which was judged as likely to be related to the study drug. The most common adverse events were gastrointestinal symptoms, especially with liraglutide, and infections and infestations, which occurred with similar frequency with all treatments. Forty six, 37, and 14% of liraglutide 1.8 mg-, liraglutide 1.2 mg-, and sitagliptin-treated patients achieved the composite secondary endpoint. Measurements scheduled to be taken after baseline were missing for some patients. The ORs vs sitagliptin were 5.46 (95% CI, 3.37 to 8.85; *P*<0.0001) for liraglutide 1.8 mg and 3.45 (95% CI, 2.12 to 5.61; *P*<0.0001) for liraglutide 1.2 mg.
Russell-Jones et al[43] DRUATION-4 Exenatide ER 2 mg SC once weekly vs metformin 2,000 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	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, 7-	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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs pioglitazone 45 mg/day vs sitagliptin 100 mg/day	type 2 diabetics with HbA_{1c} 7.1 to 11.0%, BMI 23 to 45 kg/m^2, and stable weight		point self-monitored glucose concentrations, weight, lipid profile, insulin profile, safety and tolerability, patient-reported QOL	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. 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-

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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 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).
Rigby et al[44] (abstract) Colesevelam 3.75 g QD vs rosiglitazone 4 mg QD vs sitagliptin 100 mg QD All patients were also receiving metformin.	MC, OL, RCT Type 2 diabetics inadequately controlled (HbA_{1c} 7.0 to 10.0%) on stable doses of metformin (1,500 to 2,550 mg/day for ≥3 months)	N=169 16 weeks	Primary: Change in baseline HbA_{1c} Secondary: Not reported	Primary: All treatments significantly decreased HbA_{1c} (colesevelam, -0.3%; *P*<0.031, rosiglitazone, -0.6%; *P*<0.001, sitagliptin, -0.4%; *P*<0.009). Colesevelam significantly decreased LDL-C (-11.6%; *P* value not reported), and rosiglitazone and sitagliptin significantly increased LDL-C (7.8% and 7.7%; *P* values not reported). Secondary: Not reported
Goldstein et al[45] Sitagliptin 50 mg BID plus	DB, MC, PC, PG, RCT	N=1,091 24 weeks	Primary: Change in baseline HbA_{1c}	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).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
metformin 500 and 1,000 mg BID vs sitagliptin 100 mg QD vs metformin 500 and 1,000 mg BID vs placebo	Type 2 diabetics 18 to 78 years of age and an HbA_{1c} of 7.5 to 11.0%		Secondary: Change in baseline FPG, fasting serum insulin, fasting serum proinsulin, lipid profiles, β cell function, insulin resistance; adverse events	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[46] Sitagliptin/metformin 50/500 to 1,00 mg BID	DB, MC, PG, RCT Treatment-naïve type 2 diabetics 18 to 78 years of	N=1,250 18 weeks	Primary: Change in baseline HbA_{1c} Secondary:	Primary: Combination therapy significantly decreased HbA_{1c} compared to metformin (-2.4 vs -1.8%; *P*<0.001). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs metformin 500 to 1,000 mg BID	age, and an HbA_{1c} of ≥7.5%		Proportion of patients achieving an HbA_{1c} <7.0 and <6.5%, change in baseline FPG, proinsulin:insulin ratio, and β cell function	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).
Esposito et al[47] 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).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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 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
Frederich et al[48] Saxagliptin 2.5 to 10 mg QD vs glyburide, metformin, or placebo	SR (RCTs) 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
Fakhoury et al[49] Incretin-based therapies (exenatide, liraglutide, vildagliptin,* and sitagliptin) vs	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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo				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[50] 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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				(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.
Shyangdan et al[51] 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 DPP-4 inhibitors (60 vs 35%; *P*<0.0001) and 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, 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).

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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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 (-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.

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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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 dinner (*P*=0.004) and insulin glargine at 03000 hr (*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).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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.
Richter et al[52] DPP-4 inhibitors (sitagliptin or vildagliptin*) as monotherapy or in combination with other hypoglycemic agents vs other hypoglycemic agents as monotherapy combination or lifestyle	MA Type 2 diabetics ≥18 years of age	N=12,684 12 to 52 weeks	Primary: Change in baseline HbA_{1c}, adverse events Secondary: Weight gain or weight loss, β cell function	Primary: There was a significant HbA_{1c} difference between placebo and sitagliptin of -0.7% in favor of sitagliptin (95% CI, -0.8 to -0.6; *P*<0.00001). There was no difference between the treatments in the incidence of severe adverse events, discontinuation due to adverse events, and hypoglycemic episodes. All-cause infections were significantly increased with sitagliptin compared to placebo and other hypoglycemic agents (RR, 1.15, 95% CI, 1.02 to 1.31, *P*=0.03). Secondary: The mean difference in weight between sitagliptin compared to placebo and other hypoglycemic agents was 0.66 kg (95% CI, 0.37 to 0.94; *P*<0.00001), in

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
interventions				favor of the comparators. Pooling of data on the effects of DPP-4 inhibitors on β cell function was not performed due to lack of data and differing methods used in the trials to evaluate the outcome.
Pinelli et al[53] GLP-1 receptor agonist, long-acting formulations at maximum doses (liraglutide, exenatide ER, albiglutide*, and lixisenatide*) vs exenatide and sitagliptin	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; 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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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 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
Schwarz et al[54] Scenario 1: Rosiglitazone added to metformin	Cost-effectiveness (Analysis based on cost inputs from six countries	N=not reported Duration not reported	Primary: Costs of adding sitagliptin to metformin compared to	Primary: Adding sitagliptin to metformin was predicted to be either cost saving or cost-effective compared to adding rosiglitazone or glipizide to metformin. In the six countries included in the analysis, adding sitagliptin to metformin compared to rosiglitazone was associated with discounted ICER values ranged from

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs sitagliptin added to metformin Scenario 2: glipizide added to metformin vs sitagliptin added to metformin Scenario 3: glipizide added to metformin (change to rosiglitazone and metformin if glipizide failure) vs sitagliptin added to metformin (change to rosiglitazone and metformin if sitagliptin failure)	and clinical data from Scott et al[28] and Nauck et al[40]) Type 2 diabetics not at target HbA_{1c} (>6.5%)		glipizide or rosiglitazone Secondary: Not reported	sitagliptin being cost saving to €4,766/QALY (cost-effective). For scenario 2, the discounted ICER for adding sitagliptin compared to glipizide ranged from €5,949/QALY to €20,350/QALY. For Scenario 3, the discounted ICER for adding sitagliptin compared to glipizide ranged from €6,029/QALY to €13,655/QALY. 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, SC=subcutaneous
Study abbreviations: AC=active-comparator, CI=confidence interval, DB=double-blind, DD=double-dummy, ES=extension study, MA=meta-analysis, MC=multicenter, OL=open-label, OR=odds ratio, PC=placebo-controlled, PG=parallel-group, POR=pooled odds ratio, RCT=randomized-controlled trial, RR=relative risk, SR=systematic review, WMD=weighted mean difference, XO=cross-over
Miscellaneous: AUC=area under the curve, BMI=body mass index, BNP=brain natriuretic peptide, BP=blood pressure, 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,

ICER=incremental cost-effectiveness ratio, IWQOL=Impact of Weight on Quality of life Questionnaire, LDL-C=low density lipoprotein-cholesterol, MI=myocardial infarction, PGWB=Psychological General Well-being index, PPG=post-prandial glucose, QALY=quality-adjusted life year, QOL=quality of life, QUICKI=Quantitative insulin sensitivity check index, SBP=systolic blood pressure, TC=total cholesterol, TG=triglycerides, TNF-α=tumor necrosis factor-α, TZD=thiazolidinedione

Special Populations

Table 5. Special Populations[2-9,61]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Single-Entity Agents					
Linagliptin	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Safety and efficacy in children have not been established.	No dosage adjustment required.	No dosage adjustment required.	B	Unknown; use with caution.
Saxagliptin	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Safety and efficacy in children have not been established.	Renal dose adjustment is required; with moderate to severe renal dysfunction and end-stage renal disease, a dose of 2.5 mg once-daily is recommended.	No dosage adjustment required.	B	Unknown; use with caution.
Sitagliptin	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Safety and efficacy in children have not been established.	Renal dose adjustment is required; with moderate to severe renal dysfunction and end-stage renal disease, lower doses are recommended.	No dosage adjustment required with mild to moderate hepatic dysfunction. Not studied with severe hepatic dysfunction.	B	Unknown; use with caution.
Combination Products					
Linagliptin/ metformin	Use with caution as elderly patients are more likely to have decreased renal function.	Not studied with renal dysfunction; however, use is contraindicated.	Not studied in hepatic dysfunction; however, use is not recommended.	B	Unknown; use with caution.

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
	Safety and efficacy in children have not been established.				
Saxagliptin/ metformin	Use with caution as elderly patients are more likely to have decreased renal function. Safety and efficacy in children have not been established.	Contraindicated with renal dysfunction.	Not studied with hepatic dysfunction; however, use is not recommended.	B	Unknown; use with caution.
Sitagliptin/ metformin	Use with caution as elderly patients are more likely to have decreased renal function. Safety and efficacy in children have not been established.	Contraindicated with renal dysfunction.	Avoid with clinical or laboratory evidence of hepatic disease (sitagliptin/ metformin). No dosage adjustment required. Not studied with severe hepatic dysfunction (sitagliptin/ metformin extended-release).	B	Unknown; use with caution.
Sitagliptin/ simvastatin	Use with caution as elderly patients are more likely to have decreased renal function. Safety and efficacy in children have not been established.	Not recommended with moderate or severe renal dysfunction or end-stage renal disease.	Contraindicated with active liver disease.	X	Unknown; use with caution.

Adverse Drug Events

Table 6. Adverse Drug Events[2-9]

Adverse Event	Single-Entity Agents*			Combination Products*			
	Linagliptin	Saxagliptin	Sitagliptin	Linagliptin/ Metformin†	Saxagliptin/ Metformin†	Sitagliptin/ Metformin†	Sitagliptin/ Simvastatin†
Abdominal pain	-	1.7 to 2.4	2.3	-	-	2.2 to 3.0	-
Arthralgia	5.7	-	-	-	-	-	-
Back pain	6.4	-	-	-	-	-	-
Cough	2.7	-	-	✔	-	-	-
Decreased appetite	-	-	-	✔	-	-	-
Diarrhea	-	-	3	6.3	5.8 to 9.9	2.4 to 7.5	-
Fracture	-	✔‡	-	-	-	-	-
Gastroenteritis	-	1.9 to 2.3	-	-	-	-	-
Headache	5.7	6.5 to 7.5	1.1 to 5.9	-	7.5	2.7 to 5.9	-
Hyperlipidemia	2.7	-	-	-	-	-	-
Hypersensitivity	✔	1.5	✔	✔	-	✔	-
Hypertriglyceridemia	2.4	-	-	-	-	-	-
Hypoglycemia	7.6 to 22.9	2.7 to 20.0	0.6 to 15.5	1.4 to 22.9	3.4 to 7.8	15.3 to 16.4	-
Infection	-	✔	-	-	-	-	-
Lymphopenia	-	0.5 to 1.5	-	-	-	-	-
Myalgia	✔	-	-	-	-	-	-
Nasopharyngitis	4.3	6.9	5.2 to 11.0	6.3	6.9	6.1 to 11.0	-
Nausea	-	-	1.4	✔	-	1.6 to 4.8	-
Pancreatitis	✔	✔	✔	✔	-	-	-
Peripheral edema	-	1.2 to 8.1	8.3	-	-	8.3	-
Pruritis	-	-	-	✔	-	-	-
Rash	-	0.2 to 0.3	-	-	-	-	-
Sinusitis	-	2.6 to 2.9	-	-	-	-	-
Thrombocytopenia	-	✔	-	-	-	-	-
Upper respiratory tract infection	-	7.7	4.5 to 15.5	-	-	5.5 to 6.2	-
Urinary tract infection	-	6.8	-	-	-	-	-
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 1.0 per 100 patient-years (pooled analysis of 2.5, 5, and 10 mg) compared to placebo (0.6 per 100 patient-years).

Contraindications/Precautions

The dipeptidyl peptidase-4 (DPP-4) inhibitors are contraindicated with hypersensitivity to the individual agents or any components of the formulations.[2-9] DPP-4 inhibitor fixed-dose combination products that contain metformin are also contraindicated with renal impairment and acute or chronic metabolic acidosis.[5-8] Sitagliptin/simvastatin is also contraindicated with concomitant administration of strong cytochrome P450 3A4 inhibitors, gemfibrozil, cyclosporine, or danazol; active liver disease; pregnancy; and nursing.[9]

The concurrent use of a DPP-4 inhibitor and an insulin secretagogue (e.g., sulfonylurea) may increase the risk of hypoglycemia; therefore, blood glucose should be monitored closely and a dosage reduction of the insulin secretagogue may be required.[2-9]

There have been post-marketing reports of acute pancreatitis in patients administering saxagliptin and sitagliptin; therefore, patients should be observed carefully for signs and symptoms of pancreatitis. If pancreatitis is suspected, treatment should be promptly discontinued and appropriate management should be initiated. It is unknown whether patients with a history of pancreatitis are at increased risk for the development of pancreatitis while administering saxagliptin and sitagliptin.[3,4,6-9]

There have also been post-marketing reports of serious hypersensitivity reactions in patients administering saxagliptin and sitagliptin. If a serious hypersensitivity reaction is suspected, treatment should be discontinued, assessment for other potential causes for the event should occur, and alternative treatment for diabetes should be initiated.[3,4,6-9] Furthermore, caution should be exercised in a patient with a history of angioedema to another DPP-4 inhibitor because it is unknown whether such patients will be predisposed to angioedema with saxagliptin.[3,6]

There have also been post-marketing reports of worsening renal function, including acute renal failure sometimes during dialysis, in patients receiving sitagliptin. Sitagliptin has not been found to be nephrotoxic in pre-clinical trials at clinically relevant doses, or in clinical trials.[3,7-9]

Lactic acidosis is a serious, metabolic complication that can occur due to metformin accumulation during treatment with all of the metformin-containing DPP-4 inhibitor fixed-dose combination products. Patients receiving such products should be educated to recognize and promptly report symptoms of lactic acidosis. If present, treatment should be discontinued until lactic acidosis is ruled out. Alcohol is known to potentiate the effect of metformin on lactate metabolism; therefore, patients should be warned against excessive alcohol intake while receiving metformin-containing products. In addition, cardiovascular collapse from whatever cause have been associated with lactic acidosis and may also cause pre-renal azotemia. When such events occur, treatment should be promptly discontinued. In addition, concomitant agents that may affect renal function or result in significant hemodynamic change or interfere with the disposition of metformin should be used with caution. Metformin-containing DPP-4 inhibitor fixed-dose combination products should be temporarily discontinued for any surgical procedure, except minor procedures not associated with restricted intake of food and fluids, and should not be restarted until the patient's oral intake has resumed and renal function has been evaluated as normal. In addition, these products should be temporarily discontinued in patients undergoing radiologic studies involving intravascular administration of iodinated contrast materials, because use of such products may result in acute alteration of renal function. Certain individuals appear to be pre-disposed to developing subnormal vitamin B12 levels, and in these patients, because of the metformin component, routine serum vitamin B12 measurement at two to three year intervals may be useful.[5-8]

The development of myopathy, manifested as muscle pain, tenderness, or weakness with creatine kinase above ten times the upper limit of normal, is associated with the use of simvastatin. Pre-disposing factors for myopathy included advanced age (≥65 years), female gender, uncontrolled hypothyroidism, and renal impairment. In addition, the risk of myopathy, including rhabdomyolysis, is dose related. All patients initiating therapy with sitagliptin/simvastatin, or whose dose of simvastatin is being increased, should be advised of the risk of myopathy, including rhabdomyolysis, and told to report promptly any unexplained

muscle pain, tenderness, or weakness. Treatment should be discontinued immediately if myopathy is diagnosed or suspected. Persistent increases in serum transaminases have occurred in approximately one percent of patients who received simvastatin in clinical trials; therefore, it is recommended that liver function tests be performed before the initiation of sitagliptin/simvastatin, and thereafter when clinically indicated. Increased in glycosylated hemoglobin and fasting serum glucose have also been reported with hydroxymethylglutaryl coenzyme A reductase inhibitors, including simavastatin.[9]

The DPP-4 inhibitors should not be used in type 1 diabetics or for the treatment of diabetic ketoacidosis due to a lack of efficacy in these specific patient populations.[2-9]

There have been no clinical trials establishing conclusive evidence of macrovascular risk reduction with the DPP-4 inhibitors or any other antidiabetic agent.[2-9]

These contraindications/precautions have resulted in the assignment by the Food and Drug Administration of the Black Box Warnings outlined below.

Black Box Warning for Kombiglyze XR® (saxagliptin/metformin), Janumet®/Janumet XR® (sitagliptin/metformin), and Jentadueto® (linagliptin/metformin)[5-8,61]

WARNING
Lactic acidosis can occur due to metformin accumulation. The risk increases with conditions such as sepsis, dehydration, excess alcohol intake, hepatic impairment, renal impairment, and acute congestive heart failure. Symptoms include malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. Laboratory abnormalities include low pH, increased anion gap, and elevated blood lactate. If acidosis is suspected, discontinue treatment and hospitalize the patient immediately.

Drug Interactions

There are no documented clinically significant drug interactions associated with the dipeptidyl peptidase-4 (DPP-4) inhibitors (linagliptin, saxagliptin, and sitagliptin). The DPP-4 inhibitor fixed-dose combination products contain other drug components (i.e., metformin, simvastatin) that are associated with clinically significant drug interactions. These interactions are outlined in Table 7.[61]

Table 7. Drug Interactions[61]

Generic Name	Interacting Medication or Disease	Potential Result
Biguanides (metformin)	Iodinated contrast materials, parenteral	Increased risk of metformin-induced lactic acidosis.
HMG CoA reductase inhibitors (simvastatin)	Amiodarone	Plasma concentrations of HMG CoA reductase inhibitors may be elevated, increasing the risk of toxicity.
HMG CoA reductase inhibitors (simvastatin)	Azole antifungals	Increased plasma concentrations and adverse reactions of HMG CoA reductase inhibitors may occur.
HMG CoA reductase inhibitors (simvastatin)	Carbamazepine	Plasma concentrations of HMG CoA reductase inhibitors may be reduced, decreasing the therapeutic effect.
HMG CoA reductase inhibitors (simvastatin)	Cyclosporine	Increased plasma concentrations and adverse reactions of HMG CoA reductase inhibitors may occur.
HMG CoA reductase inhibitors (simvastatin)	Diltiazem	Plasma concentrations of HMG CoA reductase inhibitors may be elevated, increasing the risk of toxicity.
HMG CoA reductase	Fibric acid derivatives	Severe myopathy or rhabdomyolysis may occur.

Generic Name	Interacting Medication or Disease	Potential Result
inhibitors (simvastatin)		
HMG CoA reductase inhibitors (simvastatin)	Grapefruit juice	Increased plasma concentrations and adverse reactions of HMG CoA reductase inhibitors may occur.
HMG CoA reductase inhibitors (simvastatin)	Imatinib	Plasma concentrations of HMG CoA reductase inhibitors may be elevated, increasing the pharmacologic effects and risk of adverse reactions.
HMG CoA reductase inhibitors (simvastatin)	Macrolides and related antibiotics	Severe myopathy or rhabdomyolysis may occur because of increased HMG CoA reductase inhibitor plasma concentrations.
HMG CoA reductase inhibitors (simvastatin)	Nefazodone	The risk of rhabdomyolysis and myositis may be increased.
HMG CoA reductase inhibitors (simvastatin)	Nonnucleoside reverse transcriptase inhibitors	Severe myopathy or rhabdomyolysis may occur because of increased HMG CoA reductase inhibitor plasma concentrations. Efavirenz and nevirapine may reduce HMG CoA reductase inhibitor plasma concentrations.
HMG CoA reductase inhibitors (simvastatin)	Protease inhibitors	Increased plasma concentrations and adverse reactions of HMG CoA reductase inhibitors may occur.
HMG CoA reductase inhibitors (simvastatin)	Rifamycins	Plasma concentrations of HMG CoA reductase inhibitors may be decreased, decreasing the pharmacologic effect.
HMG CoA reductase inhibitors (simvastatin)	Verapamil	Plasma concentrations of HMG CoA reductase inhibitors and verapamil may be elevated, increasing the risk of toxicity.
HMG CoA reductase inhibitors (simvastatin)	Warfarin	The anticoagulant effect of warfarin may increase.

HMG CoA=hydroxymethylglutaryl coenzyme A

Dosage and Administration

Table 8. Dosing and Administration[2-9]

Generic Name	Adult Dose	Pediatric Dose	Availability
Single-Entity Agents			
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 glycemic control in adults with type 2 diabetes: Tablet: 100 mg QD	Safety and efficacy in children have not been established.	Tablet: 25 mg 50 mg 100 mg

Generic Name	Adult Dose	Pediatric Dose	Availability
Combination Products			
Linagliptin/ 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: 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.	Tablet (linagliptin/ Metformin): 2.5/500 mg 2.5/850 mg 2.5/1,000 mg
Saxagliptin/ 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: 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.	Tablet (saxagliptin/ metformin ER): 5/500 mg 2.5/1,000 mg 5/1,000 mg
Sitagliptin/ 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 ER is appropriate: Tablet (sitagliptin/metformin IR): initial, individualized based on the patient's current regimen and administered BID; maximum, 100/2,000 mg/day Tablet (sitagliptin/metformin ER): initial, individualized based on the patient's current regimen and administered QD; maximum, 100/2,000 mg/day	Safety and efficacy in children have not been established.	Tablet (sitagliptin/ metformin IR): 50/500 mg 50/1,000 mg Tablet (sitagliptin/ metformin ER): 50/500 mg 50/1,000 mg 100/1,000 mg
Sitagliptin/ simvastatin	Patients for whom treatment with both sitagliptin and simvastatin is appropriate: Tablet: initial, individualized based on the patient's current regimen and administered QD; usual starting dose is 100/40 mg QD	Safety and efficacy in children have not been established.	Tablet (sitagliptin/ Simvastatin): 100/10 mg 100/20 mg 100/40 mg

BID=twice daily, ER=extended-release, IR=immediate-release, QD=once daily

Clinical Guidelines

Current clinical guidelines are summarized in Table 9. Please note that guidelines addressing the treatment of type 2 diabetes are presented globally, addressing the role of various medication classes. Due to the dipeptidyl peptidase-4 inhibitor fixed-dose combination product sitagliptin/simvastatin (Juvisync®), clinical guidelines for the management of hyperlipidemia have also been included for completeness.

Table 9. Clinical Guidelines

Clinical Guideline	Recommendations
American Diabetes Association: **Standards of Medical Care in Diabetes (2011)**[55]	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 hyperglycemic crisis with a random plasma glucose

Clinical Guideline	Recommendations
	≥200 mg/dL. Prevention/delay of type 2 diabetes • An ongoing support program for weight loss of 7% of body weight and an increase in physical activity to ≥150 minutes/week of moderate activity, should be encouraged in patients with impaired glucose tolerance, impaired fasting glucose, or an HbA_{1c} 5.7 to 6.4%. • Metformin therapy for prevention of type 2 diabetes may be considered in patients at the highest risk for developing diabetes, such as those with multiple risk factors, especially if they demonstrate progression of hyperglycemia (e.g., HbA_{1c} ≥6.0%) despite lifestyle interventions. Glycemic goals in adults • A reasonable HbA_{1c} goal for many nonpregnant adults is <7.0%. • Based on data from randomized trials, it may be reasonable for providers to suggest more stringent HbA_{1c} goals for selected patients, if this can be achieved without significant hypoglycemia or other adverse effects of treatment. Such patients may include those with short duration of diabetes, long life expectancy, and no significant cardiovascular disease. • Conversely, less stringent HbA_{1c} goals may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions, and those with longstanding diabetes in whom the general goal is difficult to attain. Pharmacologic and overall approaches to treatment-type 2 diabetes • The treatment algorithm outlined below from the American Diabetes Association/European Association for the Study of Diabetes is recommended.[52] • Highlights of the algorithm include the following: o Intervention at the time of diagnosis with metformin in combination with lifestyle changes. o Continuing timely augmentation of therapy with additional agents (including early initiation of insulin therapy) as a means of achieving and maintaining recommended glycemic goals. o As glycemic goals are not achieved, treatment intensification is based on the addition of another agent from a different class. o The overall objective is to achieve and maintain glycemic control and to change interventions when therapeutic goals are not being met. o The precise drugs used and their exact sequence may not be as important as achieving and maintaining glycemic targets safely. o Medications not included in the algorithm still may be appropriate choices in individual patients to achieve glycemic goals. o Initiation of insulin at the time of diagnosis is recommended for patients presenting with weight loss or other severe

Clinical Guideline	Recommendations
	hyperglycemia symptoms or signs.
American Diabetes Association/European Association for the Study of Diabetes: **Management of Hyperglycemia in Type 2 Diabetes: A Consensus Algorithm for the Initiation and Adjustment of Therapy (2009)**[56]	• The goal of the recommended algorithm is to achieve and maintain HbA_{1c} levels <7.0% and to change interventions at as rapid a pace as titration of medications allows when target glycemic goals are not being achieved. • The α-glucosidase inhibitors, amylin agonists, dipeptidyl peptidase-4 (DPP-4) inhibitors, and glinides are not included in the two tiers of preferred agents in the algorithm due to their lower or equivalent overall glucose-lowering effectiveness compared to the first- and second-tier agents, and/or due to limited clinical data or relative expense. These agents may be appropriate choices in selected patients. <u>Tier 1: well-validated core therapies</u> • These interventions represent the best established and most effective and cost-effective therapeutic strategies for achieving target glycemic goals, and are the preferred route of therapy for most type 2 diabetic patients. • Step 1: Lifestyle interventions and metformin should be initiated concurrently at diagnosis of type 2 diabetes. • Step 2: If lifestyle interventions and the maximal tolerated dose of metformin fail to achieve or sustain glycemic goals after two to three months, insulin or a sulfonylurea should be added. The choice between insulin or a sulfonylurea will be based on the HbA_{1c} levels, with consideration given to insulin (the more effective glycemia-lowering agent) for patients with an HbA_{1c} >8.5%. However, many newly diagnosed type 2 diabetic patients will usually respond to oral medications. • Step 3: If lifestyle interventions, metformin and basal insulin or a sulfonylurea do not achieve glycemic goals, insulin therapy should be initiated or intensified. <u>Tier 2: less well-validated therapies</u> • In selected clinical settings, the tier 2 algorithm may be considered. • Specifically, when hypoglycemia is particularly undesirable, the addition of exenatide or pioglitazone may be considered. Rosiglitazone is not recommended. • Additionally, if a major consideration is weight loss and the HbA_{1c} level is close to target (<8.0%), then exenatide may be an option (at the time of publication only exenatide had Food and Drug Administration [FDA] approval). • If these interventions do not effectively achieve glycemic goals or if they are not tolerated, the addition of a sulfonylurea could be considered or the tier 2 interventions should be discontinued and basal insulin should be initiated. <u>Rationale for selecting specific combinations</u> • Over time the majority of patients will require more than one medication. • When selecting combination therapy, in general, antihyperglycemic drugs with different mechanisms of action will have the greatest synergy.

Clinical Guideline	Recommendations
	• Combination insulin and metformin therapy is a particularly effective means of lowering glycemia with limited weight gain. Special considerations/patients • In the setting of severely uncontrolled diabetes with catabolism, combination insulin and lifestyle intervention therapy is the treatment of choice.
American College of Physicians: **Oral Pharmacologic Treatment of Type 2 Diabetes Mellitus (2012)**[57]	• Oral pharmacologic therapy in patients with type 2 diabetes should be added when lifestyle modifications, including diet, exercise, and weight loss, have failed to adequately improve hyperglycemia. • Monotherapy with metformin for initial pharmacologic therapy is recommended to treat most patients with type 2 diabetes. • It is recommended that a second agent be added to metformin to patients with persistent hyperglycemia when lifestyle modifications and monotherapy with metformin fail to control hyperglycemia.
American Association of Clinical Endocrinologists/ American College of Endocrinology: **Statement by an American Association of Clinical Endocrinologists/ American College of Endocrinology Consensus Panel on Type 2 Diabetes Mellitus: An Algorithm for Glycemic Control (2009)**[58]	Principles underlying the algorithm • Lifestyle (dietary and exercise) modifications are essential for all patients with diabetes. • Achieving an HbA_{1c} 6.5% is recommended as the primary goal; however, the goal must be customized for individual patients. • If glycemic goals are not achieved, dosages of medications can be titrated, regimens can be changed (add or discontinue medications), or, in certain instances, glycemic goals can be reconsidered and revised. • When using combination therapy it is important to have medications that have complementary mechanisms of action. • Effectiveness of therapy must be re-evaluated frequently, typically every two to three months. Stratification by current HbA_{1c} • Patients with an HbA_{1c} ≤7.5% may be able to achieve a goal of 6.5% with monotherapy; however, if monotherapy fails to achieve this goal, the usual progression is to combination therapy, and then to triple therapy. Insulin therapy, with or without additional agents, should be initiated if goals still fail to be achieved. • Patients with an HbA_{1c} 7.6 to 9.0% should be initiated on combination therapy as monotherapy in these patients is likely not to achieve glycemic goals. If combination therapy fails, triple therapy and then insulin therapy, with or without additional oral agents, should be administered. • Patients with an HbA_{1c} >9.0% have a small possibility of achieving glycemic goals, even with combination therapy. In these patients, if they are asymptomatic triple therapy based on a combination of metformin and an incretin mimetic or a DPP-4 inhibitor combined with either a sulfonylurea or a thiazolidinedione (TZD) should be initiated. If patients are symptomatic or if they have failed therapy with similar agents, insulin therapy with or without additional oral agents should be initiated. Management of patients with a HbA_{1c} 6.5 to 7.5% • In these patients monotherapy with metformin, an α-glucosidase inhibitor, a DPP-4 inhibitor, or a TZD are recommended. Because of

Clinical Guideline	Recommendations
	the established safety and efficacy of metformin, it is the cornerstone of monotherapy and is usually the most appropriate initial choice for monotherapy. • If monotherapy, even after appropriate dosage titration, is unsuccessful in achieving glycemic goals combination therapy should be initiated. • Because of the established safety and efficacy of metformin, it is considered the cornerstone of combination therapy for most patients. When contraindicated, a TZD may be used as the foundation for combination therapy options. • Due to the mechanism of action (insulin sensitizer) of metformin and TZDs, it is recommended that the second agent in combination therapy be an incretin mimetic, DPP-4 inhibitor, or a secretagogue (glinide or sulfonylurea). • The glucagon-like-peptide-1 (GLP-1) receptor agonists (incretin mimetics) and DPP-4 inhibitors are associated with less hypoglycemia compared to the secretagogues. • Despite the gastrointestinal side effects, dosing frequency and injection-based therapy, the GLP-1 agonists are preferred due to its greater effectiveness in reducing post-prandial glucose excursions (relative to the DPP-4 inhibitors) and the potential for weight loss. • Combination metformin and TZD therapy is efficacious but carries risks of adverse events associated with both agents. The combination is recommended with a higher priority than a secretagogue because of a lower risk of hypoglycemia and greater flexibility in timing of administration. • The combination therapies of metformin and an α-glucosidase inhibitor and metformin and colesevelam are also included in the algorithm because of their safety and the ability of colesevelam to lower lipid profiles. • If combination therapy fails after each medication has been titrated to its maximally effective dose then triple therapy should be initiated. • The following triple therapy regimens are considered: o Metformin + GLP-1 agonist + TZD. o Metformin + GLP-1 agonist + glinide. o Metformin + GLP-1 agonist + sulfonylurea. o Metformin + DPP-4 inhibitor + TZD. o Metformin + DPP-4 inhibitor + glinide. o Metformin + DPP-4 inhibitor + sulfonylurea. • Because of the established safety and efficacy of metformin, it is considered the cornerstone for triple therapy. • The GLP-1 agonist, exenatide, is the second preferred component of triple therapy because of its safety (low risk of hypoglycemia) and its potential for inducing weight loss. It also inhibits glucagon secretion in a glucose-dependent manner after consumption of means resulting in increased satiety and delayed gastric emptying. • The third component of triple therapy is recommended in order to minimize the risk of hypoglycemia. • The combination with metformin, especially when combined with an incretin mimetic, may counteract the weight gain often associated with glinides, sulfonylureas, and TZDs. • When triple therapy fails to achieve glycemic goals, insulin therapy is

Clinical Guideline	Recommendations
	needed. Management of patients with a HbA_{1c} 7.6 to 9.0% • The management of these patients is similar to that just described except patients can proceed directly to combination therapy because monotherapy is unlikely to be successful in these patients. • The following combination therapy regimens are considered: o Metformin + GLP-1 agonist. o Metformin + DPP-4 inhibitor. o Metformin + TZD. o Metformin + sulfonylurea. o Metformin + glinide. • Metformin is again considered the cornerstone of combination therapy. • A GLP-1 agonist or DPP-4 inhibitor is the preferred second component in view of the safety and efficacy of these agents in combination with metformin. Additionally, a GLP-1 agonist is given higher priority in view of its somewhat greater effect on reducing post-prandial glucose (PPG) excursions and its potential for inducing substantial weight loss. • TZDs are positioned lower due to the risks of weight gain, fluid retention, congestive heart failure, and fractures associated with their use. • Glinides and sulfonylureas are relegated to the lowest position because the greater risk of inducing hypoglycemia. • When combination therapy fails to achieve glycemic goals, triple therapy should be started. • The following triple therapy regimens are considered: o Metformin + GLP-1 agonist + TZD. o Metformin + DPP-4 inhibitor + TZD. o Metformin + GLP-1 agonist + sulfonylurea. o Metformin + DPP-4 inhibitor + sulfonylurea. o Metformin + TZD + sulfonylurea. • Metformin is the foundation to which either a TZD or sulfonylurea is added, followed by incretin-based therapy with either a GLP-1 agonist or a DPP-4 inhibitor. • The preference for metformin and the GLP-1 agonist or DPP-4 inhibitor is based on the safety of these agents and minimal associated risks of hypoglycemia. • TZDs are assigned a higher priority than a sulfonylurea because of their lower risk of hypoglycemia. • A GLP-1 agonist is assigned a higher priority than a DPP-4 inhibitor because of its somewhat greater effect on reducing PPG excursions and the possibility that it might induce considerable weight loss. • Metformin + TZD + sulfonylurea is relegated to the lowest priority due to an increased risk of weight gain and hypoglycemia. • α-glucosidase inhibitors, colesevelam, and glinides are not considered as options in these patients due to their limited HbA_{1c}-lowering potential. • The considerations for insulin therapy in these patients are similar to those used in patients with an HbA_{1c} 6.5 to 7.5%.

Clinical Guideline	Recommendations
	Management of patients with a HbA_{1c} >9.0% • Patients who are drug-naïve with an HbA_{1c} >9.0% are unlikely to achieve glycemic goals with the use of one, two, or even three agents (other than insulin). • For patients who are asymptomatic, particularly with a relatively recent onset of diabetes, there is a good chance that some endogenous β-cell function exists; implying that combination or triple therapy may be sufficient. • The following combination and triple therapy regimens are considered: o Metformin + GLP-1 agonist. o Metformin + GLP-1 agonist + sulfonylurea. o Metformin + DPP-4 inhibitor. o Metformin + DPP-4 inhibitor + sulfonylurea. o Metformin + TZD. o Metformin + TZD + sulfonylurea. o Metformin + GLP-1 agonist + TZD. o Metformin + DPP-4 inhibitor + TZD. • Metformin again provides the foundation of treatment in these patients. • An incretin-based therapy can be added with a GLP-1 agonist being preferred due to its greater effectiveness at controlling post-prandial glycemia and its potential for inducing weight loss. However the DPP-4 inhibitors in combination with metformin have also demonstrated a robust benefit for drug-naïve patients in this HbA_{1c} range. • A sulfonylurea or a TZD can also be added, with a sulfonylurea being preferred because of its somewhat greater efficacy and more rapid onset of action. • If patients are symptomatic (polydipsia, polyuria, weight loss) or if they have already failed the aforementioned treatment regimens, insulin therapy should be initiated without delay. • Insulin therapy for these patients follows the same principals as outlined previously for patients with different HbA_{1c} levels. • This algorithm favors the use of GLP-1 agonists (at the time of publication only exenatide had FDA approval) and DPP-4 inhibitors with higher priority due to their effectiveness and overall safety profiles. Additionally, due to the increasing amount of literature indicating the serious risks of hypoglycemia, these agents are becoming preferred in most patients in place of secretagogues. • The algorithm moves sulfonylureas to a lower priority due to the risks of hypoglycemia and weight gain associated with their use, as well as the failure of these agents to provide improved glycemic control after use for a relatively short period. • A TZD is considered a “well-validated” effective agent due to demonstrated extended durability of action, but these agents have a lower priority for many patients in light of their potential side effects. • The three classes of medications; α-glucosidase inhibitors, colesevelam, and glinides, are considered in relatively narrow, well-defined clinical situations, due to their limited efficacy.
American Association of Clinical Endocrinologists: **Medical Guidelines for**	Glycemic management-all patients with diabetes • Encourage patients to achieve glycemic levels as near normal as possible without inducing clinically significant hypoglycemia.

Clinical Guideline	Recommendations
Clinical Practice for the Management of Diabetes Mellitus (2007)[59]	Glycemic targets include the following: o HbA_{1c} ≤6.5%. o FPG <100 mg/dL. o Two-hour PPG <140 mg/dL. • Refer patients for comprehensive, ongoing education in diabetes self-management skills and nutrition therapy. • Initiate self-monitoring blood glucose levels. <u>Glycemic management-patients with type 2 diabetes</u> • Aggressively implement all appropriate components of care at the time of diagnosis. • Persistently monitor and titrate pharmacologic therapy until all glycemic goals are achieved. o First assess current HbA_{1c} level, fasting/pre-prandial glycemic profile, and two-hour PPG profile to evaluate the level of control and identify patterns. o After initiating pharmacologic therapy based on the patterns identified in the profile, persistently monitor and titrate therapy over the next two to three months until all glycemic goals are achieved. o If glycemic goals are not achieved at the end of two to three months, initiate a more intensive regimen and persistently monitor and titrate therapy over the next two to three months until all glycemic goals are achieved. o Recognize that patients currently treated with monotherapy or combination therapy who have not achieved glycemic goals will require either increased dosages of current medications or the addition of a second or third medication. o Consider insulin therapy in patients with HbA_{1c} >8.0% and symptomatic hyperglycemic, and in patients with elevated fasting blood glucose levels or exaggerated PPG excursions regardless of HbA_{1c} levels. o Initiate insulin therapy to control hyperglycemia and to reverse glucose toxicity when HbA_{1c} >10.0%. Insulin therapy can then be modified or discontinued once glucose toxicity is reversed. o Consider a continuous subcutaneous insulin infusion in insulin-treated patients. • Instruct patients whose glycemic levels are at or above target while receiving multiple daily injections or using an insulin pump to monitor glucose levels at least three times daily. Although monitoring glucose levels at least three times daily is recommended, there is no supporting evidence regarding optimal frequency of glucose monitoring with or without insulin pump therapy. • Instruct insulin-treated patients to always check glucose levels before administering a dose of insulin by injection or changing the rate of insulin infusion delivered by an insulin pump. • Instruct patients whose glycemic levels are above target while being treated with oral agents alone, oral agents plus once-daily insulin, or once-daily insulin alone to monitor glucose levels at least two times daily. There is no supporting evidence regarding optimal frequency of glucose monitoring in these patients.

Clinical Guideline	Recommendations
	• Instruct patients who are meeting target glycemic levels, including those treated non-pharmacologically, to monitor glucose levels at least once daily. • Instruct patients whose glycemic levels are above target or who experience frequent hypoglycemia to monitor glucose levels more frequently. Monitoring should include both pre-prandial and two-hour PPG levels and occasional 2:00 to 3:00 AM glucose levels. • Instruct patients to obtain comprehensive pre-prandial and two-hour PPG measurements to create a weekly profile periodically and before clinician visits to guide nutrition and physical activity, to detect post-prandial hyperglycemia, and to prevent hypoglycemia. • Instruct patients to monitor glucose levels anytime there is a suspected (or risk of) low glucose level and/or before driving. • Instruct patients to monitor glucose levels more frequently during illness and to perform a ketone test each time a measured glucose concentration is >250 mg/dL. Clinical support-clinical considerations in patients with type 2 diabetes • Combining therapeutic agents with different modes of action may be advantageous. • Use insulin sensitizers, such as metformin or TZDs, as part of the therapeutic regimen in most patients unless contraindicated or intolerance has been demonstrated. • Insulin is the therapy of choice in patients with advanced chronic kidney disease. • Metformin, TZDs, and incretin mimetics do not cause hypoglycemia. However, when used in combination with secretagogues or insulin, these medications may need to be adjusted as blood glucose levels decline. • The weight gain associated with TZDs in some patients may be partly offset by combination therapy with metformin. • Carefully assess PPG levels if the HbA_{1c} level is elevated and pre-prandial glucose measurements are at target levels. • Instruct patients to assess PPG levels periodically to detect unrecognized exaggerated PPG excursions even when the HbA_{1c} level is at or near target. • Individualize treatment regimens to accommodate patient exercise patterns. • Administer basal insulin in the evening if fasting glucose is elevated. • Long-acting insulin analogs are associated with less hypoglycemia than neutral protamine Hagedorn insulin.
National Cholesterol Education Program: **Implications of Recent Clinical Trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines (2004)**[62]	• Therapeutic lifestyle changes (TLC) remain an essential modality in clinical management. • When low density lipoprotein cholesterol (LDL-C) lowering drug therapy is employed in high risk or moderately high risk patients, it is advised that intensity of therapy be sufficient to achieve ≥30 to 40% reduction in LDL-C levels. If drug therapy is a component of cholesterol management for a given patient, it is prudent to employ doses that will achieve at least a moderate risk reduction. • Standard hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statin) doses are defined as those that lower LDL-C levels by 30 to 40%. The same effect may be achieved by combining lower

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	doses of statins with other drugs or products (e.g., bile acid sequestrants, ezetimibe, nicotinic acid, plant stanols/sterols). • When LDL-C level is well above 130 mg/dL (e.g., ≥160 mg/dL), the dose of statin may have to be increased or a second agent (e.g., a bile acid sequestrant, ezetimibe, nicotinic acid) may be required. Alternatively, maximizing dietary therapy (including use of plant stanols/sterols) combined with standard statin doses may be sufficient to attain goals. • Fibrates may have an adjunctive role in the treatment of patients with high triglycerides (TG) and low high-density lipoprotein cholesterol (HDL-C), especially in combination with statins. • In high risk patients with high TG or low HDL-C levels, consideration can be given to combination therapy with fibrates or nicotinic acid and a LDL lowering agent. • Several clinical trials support the efficacy of nicotinic acid, which raises HDL-C, for reduction of coronary heart disease (CHD) risk, both when used alone and in combination with statins. The combination of a statin with nicotinic acid produces a marked reduction of LDL-C and a striking rise in HDL-C. <u>Treatment of heterozygous familial hypercholesterolemia</u> • Begin LDL-C lowering drugs in young adulthood. • TLC indicated for all persons. • Statins, first line of therapy (start dietary therapy simultaneously). • Bile acid sequestrants (if necessary in combination with statins). • If needed, consider triple drug therapy (statins and bile acid sequestrants and nicotinic acid). <u>Treatment of homozygous familial hypercholesterolemia</u> • Statins may be moderately effective in some persons. • LDL-pheresis currently employed therapy (in some persons, statin therapy may slow down rebound hypercholesterolemia). <u>Treatment of familial defective apolipoprotein B-100</u> • TLC indicated. • All LDL-C lowering drugs are effective. • Combined drug therapy required less often than in heterozygous familial hypercholesterolemia. <u>Treatment of polygenic hypercholesterolemia</u> • TLC indicated for all persons. • All LDL-C lowering drugs are effective. • If necessary to reach LDL-C goals, consider combined drug therapy.
National Cholesterol Education Program: **Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in**	<u>General recommendations</u> • With regards to TLC, higher dietary intakes of omega-3 fatty acids in the form of fatty fish or vegetable oils are an option for reducing risk for CHD. This recommendation is optional because the strength of evidence is only moderate at present. National Cholesterol Education Program supports the American Heart Association's recommendation that fish be included as part of a CHD risk reduction diet. Fish in general is low in saturated fat and may contain some cardioprotective omega-3 fatty acids. However, a dietary recommendation for a

Clinical Guideline	Recommendations
Adults (Adult Treatment Panel III) Final Report (2002)[63]	specific amount of omega-3 fatty acids is not made. • Initiate LDL lowering drug therapy with a statin, bile acid sequestrant or nicotinic acid. • Statins should be considered as first line drugs when LDL lowering drugs are indicated to achieve LDL-C treatment goals. • After six weeks if LDL-C goal is not achieved, intensify LDL lowering therapy. Consider a higher dose of a statin or add a bile acid sequestrant or nicotinic acid. <u>Statins</u> • Statins should be considered as first-line drugs when LDL-lowering drugs are indicated to achieve LDL treatment goals. <u>Bile acid sequestrants</u> • Bile acid sequestrants should be considered as LDL lowering therapy for patients with moderate elevations in LDL-C, for younger patients with elevated LDL-C, for women with elevated LDL-C who are considering pregnancy and for patients needing only modest reductions in LDL-C to achieve target goals. • Bile acid sequestrants should be considered in combination therapy with statins in patients with very high LDL-C levels. <u>Nicotinic acid</u> • Nicotinic acid should be considered as a therapeutic option for higher risk patients with atherogenic dyslipidemia. • Nicotinic acid should be considered as a single agent in higher risk patients with atherogenic dyslipidemia who do not have a substantial increase in LDL-C levels, and in combination therapy with other cholesterol lowering drugs in higher risk patients with atherogenic dyslipidemia combined with elevated LDL-C levels. • Nicotinic acid should be used with caution in patients with active liver disease, recent peptic ulcer, hyperuricemia, gout and type 2 diabetes. • High doses of nicotinic acid (>3 g/day) generally should be avoided in patients with type 2 diabetes, although lower doses may effectively treat diabetic dyslipidemia without significantly worsening hyperglycemia. <u>Fibric acid derivatives (fibrates)</u> • Fibrates can be recommended for patients with very high TG to reduce risk for acute pancreatitis. • They also can be recommended for patients with dysbetalipoproteinemia (elevated beta-very LDL). • Fibrate therapy should be considered an option for treatment of patients with established CHD who have low levels of LDL-C and atherogenic dyslipidemia. • They also should be considered in combination with statin therapy in patients who have elevated LDL-C and atherogenic dyslipidemia. <u>Omega-3 fatty acids</u> • Omega-3 fatty acids (e.g., linolenic acid, docosahexaenoic acid [DHA], eicosapentaenoic acid [EPA]) have two potential uses. • In higher doses, DHA and EPA lower serum TGs by reducing hepatic

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	secretion of TG-rich lipoproteins. They represent alternatives to fibrates or nicotinic acid for treatment of hypertriglyceridemia, particularly chylomicronemia. Doses of 3 to 12 g/day have been used depending on tolerance and severity of hypertriglyceridemia. • Recent trials also suggest that relatively high intakes of omega-3 fatty acids (1 to 2 g/day) in the form of fish, fish oils or high-linolenic acid oils will reduce the risk for major coronary events in persons with established CHD. Omega-3 fatty acids can be a therapeutic option in secondary prevention (based on moderate evidence). The omega-3 fatty acids can be derived from either foods (omega-3 rich vegetable oils or fatty fish) or from fish-oil supplements. More definitive trials are required before strongly recommending relatively high intakes of omega-3 fatty acids (1 to 2 g/day) for either primary or secondary prevention.
American Heart Association /American College of Cardiology/National Heart, Lung, and Blood Institute: **American Heart Association/American College of Cardiology Guidelines for Secondary Prevention for Patients With Coronary and Other Atherosclerotic Vascular Disease: 2006 Update (2006)**[64]	Lipid management • For patients without atherosclerotic disease, including those with other risk factors, recommendations of the National Cholesterol Education Program guidelines and their 2004 update should still be considered current. • Therapeutic options to reduce non-HDL-C include the following: more intense LDL-C lowering therapy, or niacin (after LDL-C lowering therapy) or fibrate therapy (after LDL-C lowering therapy). • If TGs are ≥500 mg/dL, therapeutic options to prevent pancreatitis are fibrate or niacin before LDL lowering therapy. Treat LDL-C to goal after TG lowering therapy. • Dietary supplement niacin must not be used as a substitute for prescription niacin. All patients with coronary and other atherosclerotic vascular disease • In addition to other lifestyle modifications, increased consumption of omega-3 fatty acids in the form of fish or in capsule form (1 g/day) for risk reduction is encouraged. For treatment of elevated TGs, higher doses are usually necessary for risk reduction.
Institute for Clinical Systems Improvement: **Lipid Management in Adults (2011)**[65]	Clinical highlights • Initiate a statin with patients who have a history of CHD or CHD risk equivalents. • Establish lipid goals based on risk level. • Instruct patients on healthy lifestyle and adjunctive measures. • Patient adherence with recommended therapy should be reinforced during scheduled follow-up. • An LDL goal <70 mg/dL can be considered for patients with established coronary artery disease, non-cardiac atherosclerosis, or coronary artery disease equivalent. Ongoing drug therapy • The use of statin therapy is recommended in patients with established CHD or CHD risk equivalents (includes occlusive carotid disease, peripheral vascular disease, abdominal aortic aneurysm, and diabetes). • Combination therapy can be considered on an individual basis. • No primary prevention trials have addressed pharmacologic lipid treatment in patients at low risk for CHD, and there is no evidence to

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	support drug treatment in this population. • Primary prevention trials of pharmacologic lipid-lowering have not shown a decrease in mortality, although most have shown about a 30% reduction in CHD events. Monotherapy • Patients with risk factors for CHD but no history of disease who receive lipid-lowering therapy are likely to experience a decreased risk of CHD. • Patients with a history of CHD often benefit from statin therapy, and trials have consistently shown a decrease in risk of death from CHD. • The use of statin therapy is recommended in patients with established CHD or CHD risk equivalents (includes occlusive carotid disease, peripheral vascular disease, abdominal aortic aneurysm, and diabetes). • Statins are the drugs of choice for lowering LDL-C, and aggressive treatment with statins should be pursued. Statins also have a modest effect on reducing TG and increasing HDL-C. • Several trials with clinical endpoints support the use of statins in primary and secondary prevention. • If a patient is intolerant to a statin, patients should try another statin before ruling all of them out. • Incidence of muscle symptoms or signs is the most prevalent and important adverse effect of statin therapy. • Specific statin and dose should be selected based on cost and amount of lipid-lowering required. • If patients are unable to take a statin, then bile acid sequestrants, niacin, fibric acid derivatives or fibrates, and ezetimibe are available. • Many crystalline (immediate-release) and sustained-release preparations of niacin are available over-the-counter. The extended-release preparation of niacin is a prescription drug. Niacin exerts favorable effects on all lipids and lipoproteins, and is good for mixed hyperlipidemia. • Long-term use of niacin is usually limited for many patients due to side effects (e.g., flushing and pruritus, liver toxicity, gastrointestinal complaints, etc). • Combination therapy with niacin and a statin may increase the risk of myopathy based on early experience with lovastatin. • Prior to initiating a fibric acid (gemfibrozil, fenofibrate, and fenofibrate micronized), lifestyle therapies should be intensified for moderately elevated TG. With fibric acids, TG are reduced 30 to 50%, HDL-C is increased 10 to 20%, TC is reduced 5 to 20% in patients without elevated TG, and the effect on LDL-C is variable. Fibric acids are good for severe hypertriglyceridemia (>500 mg/dL) in patients at risk for pancreatitis and for prevention of CHD (not proven for fenofibrate). • Myositis, cholelithiasis, and cholecystitis can occur with fibric acid, and caution should be exercised with a history of liver disease. • The long-term effects of ezetimibe on cardiovascular morbidity and mortality are unknown. Ezetimibe is associated with a LDL-C lowering of about 18%, and additive LDL-C lowering occurs when used in combination with a statin. • The short-term tolerability of ezetimibe is similar to placebo, and the

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	long-term safety is unknown. • Bile acid sequestrants reduce LDL-C by 15 to 30% and TG may increase 15%; therefore, are these agents are useful for patients with moderately elevated LDL-C. The effects of the bile acid sequestrants are apparent within one week and maximum at two to three weeks. Bile acid sequestrants are good for combination therapy and are most potent with a statin. • Bile acid sequestrants are not systemically absorbed; therefore, side effects are limited to the gastrointestinal tract. In addition, drug interactions are minimized by taking other medications one hour before the sequestrant or four hours after. <u>Combination therapy</u> • It has become common practice to adjust medication therapy, including using combinations of medications, to achieve LDL-C goals. Common combinations include statin/fibrate, statin/niacin, and statin/ezetimibe. o A fibrate is commonly added to a statin, which results in enhanced lowering of LDL-C, as well as a higher incidence of myopathy. o No published clinical trial to date has evaluated the clinical benefit of combination therapy with a statin and niacin on vascular events. o The addition of ezetimibe to a statin significantly improves LDL-C over either agent alone. To date no large clinical trials have been completed evaluating this combination therapy compared to statin monotherapy on clinical vascular endpoints. • Combinations of lipid-lowering agents do not improve clinical outcomes more than statin monotherapy. • Combination therapy can be considered on an individual basis, but the additional cost, complexity, and risk for side effects argue against routine use until further trials indicate what groups of patients might benefit. • There are negative trials of cholesterylester transfer protein inhibitors when used in combination with statins. • No randomized-controlled trials looking at clinical vascular endpoints are available for other agents such as fish oils or bile-acid sequestrants used in combination therapy. <u>Lifestyle modifications</u> • Patients who are overweight should be advised to reduce their caloric intake to achieve weight loss. • Patients should follow a diet and exercise program for a reasonable amount of time to determine whether their LDL-C level is lowered to the target range. • A diet low saturated and trans fats, and high in soluble fiber, with consideration given to adding two grams of plant sterol/stanol is recommended. • Vitamin E supplementation should not be used. • Light to moderate consumption of alcohol may lower CHD rates. • Omega-3 fatty acids should be recommended in patients with

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	dyslipidemia (one gram of EPA/DHA by capsule supplement, or by eating at least two servings per week of fatty fish).
American Heart Association: **Drug Therapy of High Risk Lipid Abnormalities in Children and Adolescents: A Scientific Statement From the American Heart Association (2007)**[66]	• For children meeting criteria for lipid-lowering drug therapy, a statin is recommended as first line treatment. The choice of statin is dependent upon preference but should be initiated at the lowest dose once daily, usually at bedtime. • For patients with high risk lipid abnormalities, the presence of additional risk factors or high risk conditions may reduce the recommended LDL level for initiation of drug therapy and the desired target LDL levels. Therapy may also be considered for initiation in patients <10 years of age. • Additional research regarding drug therapy of high risk lipid abnormalities in children is needed to evaluate the long term efficacy and safety and impact on the atherosclerotic disease process. • Niacin is rarely used to treat the pediatric population. • Given the reported poor tolerance, the potential for very serious adverse effects, and the limited available data, niacin cannot be routinely recommended but may be considered for selected patients. • This guideline does not contain recommendations regarding the use of omega-3 acid ethyl esters.
European Society of Cardiology and Other Societies: **Guidelines on Cardiovascular Disease Prevention in Clinical Practice (2007)**[67]	• Statins are first line drugs for lowering LDL-C. • Bile acid sequestrants can serve as effective lipid-lowering alternatives. • Bile acid sequestrants tend to increase TG; therefore, should only be used when TG are <180 mg/dL or given in conjunction with TG lowering agents. • Niacin is considered an effective lipid lowering agent but flushing may limit use. • Niacin is more effective in increasing HDL-C than fibrates. • When TGs are 450 to 900 mg/dL, either fibrates or statins may be used as first line drugs, and niacin is considered a good drug for selected patients. • Fish oils are also TG lowering agents and might be useful as a third line therapy for patients with hypertriglyceridemia resistant to or intolerant of fibrates or niacin or in combination with other TG lowering drugs. • Combination therapy may be used in patients needing additional therapy to reach goals and the selection of appropriate drugs should vary based upon lipid levels.

Conclusions

The dipeptidyl peptidase-4 (DPP-4) inhibitors are Food and Drug Administration-approved as adjunct treatment to diet and exercise to improve glycemic control in adult patients with type 2 diabetes. Currently, there are single-entity products (linagliptin [Tradjenta®], saxagliptin [Onglyza®], and sitagliptin [Januvia®], as well as fixed-dose combination products containing metformin (linagliptin [Jentadueto®], saxagliptin/metformin extended-release [Kombiglyze XR®], and sitagliptin/metformin [Janumet®] and /metformin ER [Janumet XR®]) and simvastatin (sitagliptin/simvastatin [Juvisync®]). Specifically, the single-entity products are available for use either as monotherapy or in combination with other antidiabetic agents, and the fixed-dose combination products are available for use when treatment with both drug components is appropriate. Most of the products within the medication class are available for once-daily dosing; however, the fixed-dose combination products containing metformin immediate-release require twice-daily dosing. In addition, due to the specific drug components in the various fixed-

dose combination products, additional warnings, precautions, and dosing requirements may be required in addition to those associated with single-entity DPP-4 inhibitors.[2-9] All DPP-4 inhibitor products are only available as branded products.

The DPP-4 inhibitors represent a novel treatment approach in the management of type 2 diabetes and work by inhibiting the degradation of endogenous incretin hormones. These hormones are involved in the regulation of insulin and have multiple antidiabetic actions, including the enhancement of meal stimulated insulin secretion, decreased glucagon secretion, improvements in β cell function, and slowing of gastric emptying. In general, the DPP-4 inhibitors are associated with a favorable side effect profile and also have a weight neutral effect compared to other antidiabetic agents commonly used in the management of type 2 diabetes.[10-12] Overall, this medication class is significantly more effective compared to placebo in decreasing glycosylated hemoglobin (HbA_{1c}), fasting plasma glucose, and post-prandial glucose, and in achieving glycemic goals. Head-to-head trials with other antidiabetic agents are limited and not consistent in terms of "superiority". It appears this class of medication is most appropriately used as add-on therapy to other established antidiabetic agents, as combination therapy with a DPP-4 inhibitor and metformin consistently demonstrates "superiority" over monotherapy with either a DPP-4 inhibitor or metformin.[13-54]

According to current clinical guidelines for the management of type 2 diabetes, metformin remains the cornerstone of most antidiabetic treatment regimens. Additionally, patients with high HbA_{1c} will likely require combination or triple therapy in order to achieve glycemic goals.[55-59] The DPP-4 inhibitors are recommended as a potential second-line treatment option to be added to or used in combination with metformin in patients not achieving glycemic goals. In some clinical situations, the DPP-4 inhibitors may be used as monotherapy in patients with a lower HbA_{1c}; however, again metformin is usually the most appropriate initial choice for monotherapy.[57,58] While the American Diabetes Association does not endorse the use of DPP-4 inhibitors in their treatment algorithm of well-validated antidiabetic agents, they state these agents may be appropriate choices in selected patients.[55,56] Clinical guidelines note a lower rate of hypoglycemia and an established efficacy and safety profile when used in combination with metformin as advantages associated with the DPP-4 inhibitors compared to other classes of antidiabetic agents.[58] No one DPP-4 inhibitor is recommended or preferred over another.[55-59]

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