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

Therapeutic Class

- **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 peptidase-4 (DPP-4) inhibitors and the glucagon-like peptide-1 receptor agonists, or incretin mimetics. The DPP-4 inhibitors include alogliptin, linagliptin, saxagliptin, and sitagliptin, which are all available as single-entity agents (alogliptin [Nesina®], linagliptin [Tradjenta®], saxagliptin [Onglyza®], and sitagliptin [Januvia®]) or in fixed-dose combination products (alogliptin/metformin [Kazano®], alogliptin/pioglitazone [Oseni®], 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 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.[2-12]

  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 and have also been shown to decrease fasting plasma glucose.[13,14] 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.[13-15]

  The DPP-4 inhibitors are available as a fixed-dose combination product with metformin. Metformin, a biguanide, improves glucose tolerance in type 2 diabetics by lowering both basal and postprandial plasma glucose. Specifically, the actions of metformin result in decreased hepatic glucose production, decreased intestinal absorption of glucose, and improvement in insulin sensitivity via increased peripheral glucose uptake and utilization.[3,5] Additionally, alogliptin is available in a fixed-dose combination with pioglitazone. Pioglitazone is a thiazolidinedione, an agonist for peroxisome proliferator-activated receptor-gamma (PPARγ). PPAR receptors are found in adipose, skeletal muscle and liver tissue and activation of these receptors modulates transcription of insulin response genes that control glucose and lipid metabolism, providing an overall effect of increasing insulin sensitivity in muscle and adipose tissue while inhibiting hepatic gluconeogenesis.[3] Sitagliptin is also available as a fixed-dose combination product with simvastatin. Simvastatin is a 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG CoA) inhibitor, and works to improve lipid profiles by inhibiting HMG CoA reductase, the enzyme that catalyzes the rate-limiting step in cholesterol biosynthesis.[12] It should be noted that in September 2013, Merck pharmaceuticals, the manufacturer the sitagliptin/simvastatin fixed-dose combination product issued a notice to voluntarily discontinue the manufacturing of this agent for business reasons. Patients currently receiving the agent were recommended to discuss alternative treatment options at their next physician appointment.[1] Overall, the DPP-4 inhibitors are significantly more effective compared to placebo in reducing glycosylated hemoglobin (HbA_{1c}), fasting plasma glucose, and post-prandial glucose, with no major

effect on body weight. Combination therapy with a DPP-4 inhibitor and metformin consistently demonstrates improved benefits in glycemic control over monotherapy with either a DPP-4 inhibitor or metformin, limited within class head-to-head trials have been conducted.[17-64]

Two meta-analyses revealed that DPP-4 inhibitors are not associated with an increased risk of cardiovascular events or cancer compared to placebo or other antidiabetic agents, respectively.[38,62] However, a recent clinical trial suggested an increased risk of heart-failure with saxagliptin compared to placebo.[39] The Food and Drug Administration announced the intention of further reviewing the risk of cardiovascular outcomes with this agent.[65]

With regards to the specific DPP-4 inhibitor agents, all single-entity agents are available for once-daily dosing. Three fixed-dose combination products contain metformin immediate-release (alogliptin/metformin [Kazano®], linagliptin/metformin [Jentadueto®] and sitagliptin/metformin [Janumet®]) which are available for twice-daily dosing. One other fixed-dose combination product (alogliptin/pioglitazone [Oseni®]) contains pioglitazone and is also dosed once daily. 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. The fixed-dose combination of alogliptin/pioglitazone [Oseni®] carries a boxed warning regarding the risk of use in patients with congestive heart failure as the TZD component may cause or exacerbate congestive heart failure in some patients. 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.[2-12] Currently, none of the DPP-4 inhibitors are available generically.

Table 1. Medications Included Within the Therapeutic Class Review[2-12]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Single-Entity Agents			
Alogliptin (Nesina®)	Monotherapy or combination therapy as adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes	Tablet: 6.25 mg 12.5 mg 25 mg	-
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			
Alogliptin/ metformin (Kazano®)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes	Tablet (alogliptin/ metformin): 12.5/500 mg	-

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
		12.5/1000 mg	
Alogliptin/ pioglitazone (Oseni®)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes	Tablet (alogliptin/ pioglitazone): 12.5/15 mg 12.5/30 mg 12.5/45 mg 25/15 mg 25/30 mg 25/45 mg	-
Linagliptin/ metformin (Jentadueto®)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes*	Tablet (linagliptin/ metformin): 2.5/500 mg 2.5/850 mg 2.5/1,000 mg	-
Saxagliptin/ metformin (Kombiglyze XR®)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes†	Tablet (saxagliptin/ metformin ER): 5/500 mg 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): 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 (sitagliptin/ simvastatin): 100/10 mg 100/20 mg 100/40 mg	-

*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

- 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.[17-68] Of note, there have been minimal clinical efficacy or safety trials conducted with any of the DPP-4 inhibitor fixed-dose combination products; bioequivalence of these products with co-administration of the individual drug components has been demonstrated for all tablet strengths.[6-12]Available trials evaluating the fixed-dose

combination of sitagliptin/metformin support its efficacy and safety in the management of type 2 diabetes. Specifically, combination therapy was associated with significantly improved glycemic control compared to metformin monotherapy.[58]

- In studies, alogliptin was associated with significant decreases in glycosylated hemoglobin (HbA_{1c}) from baseline as monotherapy compared to placebo. In addition, in studies with metformin or pioglitazone combination therapy with alogliptin, significant decreases in HbA_{1c} were observed and more patients' specific HbA_{1c} goals compared to the monotherapy comparator. As an add-on therapy in patients already being treated with metformin, pioglitazone, metformin/pioglitazone, glipizide or insulin therapy, the additions of alogliptin demonstrated significant improvements in HbA_{1c} from baseline compared to placebo.[17-24]
- Overall, linagliptin is more effective compared to placebo in decreasing glycosylated hemoglobin 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.[25-28] Combination therapy with linagliptin and pioglitazone has been shown to be more efficacious in terms of reducing HbA_{1c} compared to pioglitazone monotherapy.[54]
- Similar results were achieved with saxagliptin when compared to placebo.[30-37] In addition, combination therapy with saxagliptin and metformin was "superior" to monotherapy with either agent in observed reductions in HbA_{1c}, FPG, and post-prandial glucose (PPG), and a significantly greater proportion of patients achieved glycemic goals with combination therapy.[56,57]
- Similar to the results of clinical trials evaluating other DPP-4 inhibitors, sitagliptin is consistently more efficacious in improving glycemic control compared to placebo, and combination therapy with sitagliptin and metformin is more efficacious than monotherapy with either agent.[41-52]
- In a single head-to-head trial, saxagliptin demonstrated non-inferiority to sitagliptin in reducing HbA_{1c}. However, a significantly greater proportion of patients achieved an HbA_{1c} ≤6.5% and achieved significant reductions in FPG with sitagliptin compared to saxagliptin.[53] While the beneficial effects of the DPP-4 inhibitors in improving HbA_{1c}, FPG, and PPG compared to placebo are well established, observed improvements in body weight and β cell function with these agents are not consistent.[17-64,66]
- In general, meta-analyses and systematic reviews evaluating incretin-based therapies, including the DPP-4 inhibitors, support the results observed in randomized-controlled trials evaluating these agents.[38,54,63-68] Two meta-analyses revealed that DPP-4 inhibitors are not associated with an increased risk of cardiovascular events or cancer compared to placebo or other antidiabetic agents, respectively.[38,62]

Key Points within the Medication Class

- According to Current Clinical Guidelines:[70-75]
    - According to current clinical guidelines for the management of type 2 diabetes, metformin remains the cornerstone of most antidiabetic treatment regimens.
    - Additionally, patients with a high glycosylated hemoglobin (HbA_{1c}) will likely require combination or triple therapy in order to achieve glycemic goals.
    - At this time, uniform recommendations on the best agent to be combined with metformin cannot be made; therefore, advantages and disadvantages of specific antidiabetic agents for each patient should be considered.
    - The dipeptidyl peptidase-4 (DPP-4) inhibitors are recommended as a potential second-line treatment option to be added in combination with metformin in patients not achieving glycemic goals.
    - 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.
    - Patients who are not appropriate for initial therapy with metformin, may be initiated on another oral antidiabetic agent, such as a sulfonylurea/glinide, pioglitazone, or a DPP-4 inhibitor, and in occasional cases where weight loss is seen as an essential aspect of

therapy, initial therapy with an incretin mimetic may be useful. Among all current clinical guidelines, preference of one DPP-4 inhibitor over another is not stated.

- Other Key Facts:
  - All single-entity agents are available for once-daily dosing.
  - Single-entity linagliptin is the only agent within the class that does not require renal and hepatic dosing.
  - The metformin component in certain fixed-dose combination products requires caution in patients with renal and hepatic dysfunction.
  - 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.
  - The DPP-4 inhibitors are associated with low risk of hypoglycemia and is weight neutral when used as monotherapy.
  - DPP-4 inhibitors improve the function of β cells in the pancreas.

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6. Kazano® [package insert]. Deerfield (IL) Takeda Pharmaceuticals America, Inc.; 2013 Jun.
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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 alogliptin, linagliptin, saxagliptin, and sitagliptin, which are all available as single-entity agents (alogliptin [Nesina®], linagliptin [Tradjenta®], saxagliptin [Onglyza®], and sitagliptin [Januvia®]) or in fixed-dose combination products (alogliptin/metformin [Kazano®], alogliptin/pioglitazone [Oseni®], 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 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.[2-12]

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 and have also been shown to decrease fasting plasma glucose.[13,14] 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.[13-15]

The DPP-4 inhibitors are available as a fixed-dose combination product with metformin. Metformin, a biguanide, improves glucose tolerance in type 2 diabetics by lowering both basal and postprandial plasma glucose. Specifically, the actions of metformin result in decreased hepatic glucose production, decreased intestinal absorption of glucose, and improvement in insulin sensitivity via increased peripheral glucose uptake and utilization.[3,5] Additionally, alogliptin is available in a fixed-dose combination with pioglitazone. Pioglitazone is a thiazolidinedione, an agonist for peroxisome proliferator-activated receptor-gamma (PPARγ). PPAR receptors are found in adipose, skeletal muscle and liver tissue and activation of these receptors modulates transcription of insulin response genes that control glucose and lipid metabolism, providing an overall effect of increasing insulin sensitivity in muscle and adipose tissue while inhibiting hepatic gluconeogenesis.[3] Sitagliptin is also available as a fixed-dose combination product with simvastatin. Simvastatin is a 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG CoA) inhibitor, and works to improve lipid profiles by inhibiting HMG CoA reductase, the enzyme that catalyzes the rate-limiting step in cholesterol biosynthesis.[12] It should be noted that in September 2013, Merck pharmaceuticals, the manufacturer the sitagliptin/simvastatin fixed-dose combination product issued a notice to voluntarily discontinue the manufacturing of this agent for business reasons. Patients currently receiving the agent were recommended to discuss alternative treatment options at their next physician appointment.[16]

Overall, the DPP-4 inhibitors are significantly more effective compared to placebo in reducing glycosylated hemoglobin (HbA_{1c}), fasting plasma glucose, and post-prandial glucose, with no major effect on body weight. Combination therapy with a DPP-4 inhibitor and metformin consistently demonstrates improved benefits in glycemic control over monotherapy with either a DPP-4 inhibitor or metformin, limited within class head-to-head trials have been conducted.[17-64]

Two meta-analyses revealed that DPP-4 inhibitors are not associated with an increased risk of cardiovascular events or cancer compared to placebo or other antidiabetic agents, respectively.[38,62] However, a recent clinical trial suggested an increased risk of heart-failure with saxagliptin compared to placebo.[39] The Food and Drug Administration announced the intention of further reviewing the risk of cardiovascular outcomes with this agent.[65]

With regards to the specific DPP-4 inhibitor agents, all single-entity agents are available for once-daily dosing. Three fixed-dose combination products contain metformin immediate-release (alogliptin/metformin [Kazano®], linagliptin/metformin [Jentadueto®] and sitagliptin/metformin [Janumet®]) which are available for twice-daily dosing. One other fixed-dose combination product (alogliptin/pioglitazone [Oseni®]) contains pioglitazone and is also dosed once daily. 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. The fixed-dose combination of alogliptin/pioglitazone [Oseni®] carries a boxed warning regarding the risk of use in patients with congestive heart failure as the TZD component may cause or exacerbate congestive heart failure in some patients. 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.[2-12] 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 a high HbA_{1c} will likely require combination or triple therapy in order to achieve glycemic goals. At this time, uniform recommendations on the best agent to be combined with metformin cannot be made; therefore, advantages and disadvantages of specific antidiabetic agents for each patient should be considered. The DPP-4 inhibitors are recommended as a potential second-line treatment option to be added in combination with metformin in patients not achieving glycemic goals. 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. Patients who are not appropriate for initial therapy with metformin, may be initiated on another oral antidiabetic agent, such as a sulfonylurea/glinide, pioglitazone, or a DPP-4 inhibitor, and in occasional cases where weight loss is seen as an essential aspect of therapy, initial therapy with an incretin mimetic may be useful. Among all current clinical guidelines, preference of one DPP-4 inhibitor over another is not stated.[70-75]

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Single-Entity Agents		
Alogliptin (Nesina®)	Dipeptidyl peptidase-4 inhibitors	-
Linagliptin (Tradjenta®)	Dipeptidyl peptidase-4 inhibitors	-
Saxagliptin (Onglyza®)	Dipeptidyl peptidase-4 inhibitors	-

Generic Name (Trade name)	Medication Class	Generic Availability
Sitagliptin (Januvia®)	Dipeptidyl peptidase-4 inhibitors	-
Combination Products		
Alogliptin/metformin (Kazano®)	Dipeptidyl peptidase-4 inhibitors/biguanide	-
Alogliptin/pioglitazone (Oseni®)	Dipeptidyl peptidase-4 inhibitors/thiazolidinedione	-
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[2-12]

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			
Alogliptin		✔	
Linagliptin		✔	
Saxagliptin		✔	
Sitagliptin		✔	
Combination Products			
Alogliptin/metformin	✔		
Alogliptin/pioglitazone	✔		
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[74]

Generic Name	Bioavailability (%)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Single-Entity Agents				
Alogliptin	100	76	*N*-demethylated	21
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				
Alogliptin/metformin	100/50 to 60	76/90	*N*-demethylated/None	21/6.2
Alogliptin/pioglitazone	100/Not reported	76/15 to 30	*N*-demethylated, M-I/Pioglitazone keto derivative, Pioglitazone hydroxyl derivative	21/3 to 7 (16 to 24*)
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.[17-68] Of note, there have been minimal clinical efficacy or safety trials conducted with any of the DPP-4 inhibitor fixed-dose combination products; bioequivalence of these products with co-administration of the individual drug components has been demonstrated for all tablet strengths.[6-12]Available trials evaluating the fixed-dose combination of sitagliptin/metformin support its efficacy and safety in the management of type 2 diabetes. Specifically, combination therapy was associated with significantly improved glycemic control compared to metformin monotherapy.[58]

In studies, alogliptin was associated with significant decreases in glycosylated hemoglobin (HbA_{1c}) from baseline as monotherapy compared to placebo. In addition, in studies with metformin or pioglitazone combination therapy with alogliptin, significant decreases in HbA_{1c} were observed and more patients' specific HbA_{1c} goals compared to the monotherapy comparator. As an add-on therapy in patients already being treated with metformin, pioglitazone, metformin/pioglitazone, glipizide or insulin therapy, the additions of alogliptin demonstrated significant improvements in HbA_{1c} from baseline compared to placebo.[17-24]

Overall, linagliptin is more effective compared to placebo in decreasing glycosylated hemoglobin 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.[25-28] Combination therapy with linagliptin and pioglitazone has been shown to be more efficacious in terms of reducing HbA_{1c} compared to pioglitazone monotherapy.[54]

Similar results were achieved with saxagliptin when compared to placebo.[30-37] In addition, combination therapy with saxagliptin and metformin was "superior" to monotherapy with either agent in observed reductions in HbA_{1c}, FPG, and post-prandial glucose (PPG), and a significantly greater proportion of patients achieved glycemic goals with combination therapy.[56,57]

Similar to the results of clinical trials evaluating other DPP-4 inhibitors, sitagliptin is consistently more efficacious in improving glycemic control compared to placebo, and combination therapy with sitagliptin and metformin is more efficacious than monotherapy with either agent.[41-52]

In a single head-to-head trial, saxagliptin demonstrated non-inferiority to sitagliptin in reducing HbA_{1c}. However, a significantly greater proportion of patients achieved an HbA_{1c} ≤6.5% and achieved significant reductions in FPG with sitagliptin compared to saxagliptin.[53] While the beneficial effects of the DPP-4 inhibitors in improving HbA_{1c}, FPG, and PPG compared to placebo are well established, observed improvements in body weight and β cell function with these agents are not consistent.[17-64,66]

In general, meta-analyses and systematic reviews evaluating incretin-based therapies, including the DPP-4 inhibitors, support the results observed in randomized-controlled trials evaluating these agents.[38,54,63-68] Two meta-analyses revealed that DPP-4 inhibitors are not associated with an increased risk of cardiovascular events or cancer compared to placebo or other antidiabetic agents, respectively.[38,62]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
DeFronzo et al[17] Alogliptin Study 010 Alogliptin 12.5 mg QD vs alogliptin 25 mg QD vs placebo All patients received counseling on diet and exercise.	DB, MC, PC, RCT Treatment naïve† patients 18 to 80 years of age with type 2 diabetes, an HbA_{1c} value 7.0 to 10.0%, a BMI 23 to 45 kg/m^2, exercise for ≥1 month and blood pressure ≤180/110 mm Hg	N=329 26 weeks	Primary: Mean change from baseline in HbA_{1c} at week 26 Secondary: Changes in FPG, hyperglycemic rescue, incidence of marked hyperglycemia‡, changes in body weight and safety endpoints.	Primary: Mean HbA_{1c} decreased significantly more with 12.5 mg (-0.56%; P<0.001) and 25 mg (-0.59%; P<0.001) alogliptin than with placebo (-0.02%) by week 26. Secondary: FPG reductions were significantly greater with alogliptin 12.5 and 25 mg than with placebo at week 26 (-10.3 and -16.4 vs 11.3 mg/dL, respectively; P<0.001 for both comparisons). The percentage of patients who required hyperglycemic rescue was significantly less with alogliptin 12.5 and 25 mg compared to placebo (9.8 and 7.6 vs 29.7%, respectively; P=0.001 and P<0.001, respectively). Differences between treatment and placebo of most other secondary endpoints, including weight loss, were not significant. Most common adverse events occurred with similar or lower frequency in those given alogliptin vs placebo. However, headache occurred more frequently with alogliptin (6.8 to 7.5%) than with placebo (4.7%).
Rosenstock et al[18] Alogliptin 25 mg QD vs alogliptin 12.5 mg QD and pioglitazone 30 mg QD vs alogliptin 25 mg QD and pioglitazone 30 mg QD vs	DB, PG, RCT Treatment naïve† patients 18 to 80 years of age with type 2 diabetes, an HbA_{1c} value 7.0 to 11.0%, a BMI 23 to 45 kg/m^2, who failed diet and exercise interventions for ≥2 months	N=655 26 weeks	Primary: Mean change from baseline in HbA_{1c} at week 26 Secondary: HbA_{1c} and FPG changes from baseline at each study visit, percentage of patients achieving specific HbA_{1c} goals, frequency of glycemic rescue and safety	Primary: Coadministration of the 25 mg dose with pioglitazone compared to 25 mg alone and to pioglitazone 30 mg alone resulted in statistically significant improvements from baseline in HbA_{1c} (-1.7 vs -1.0 and -1.2%, respectively; P<0.01 for both comparisons). Similar reductions were observed with the combination therapy arm involving the 12.5 mg strength. Secondary: Coadministration of the 25 mg dose with pioglitazone compared to 25 mg alone and to pioglitazone 30 mg alone resulted in statistically significant improvements from baseline in FPG (-50 vs -26 and -37 mg/dL, respectively; P<0.01 for both comparisons).In addition, each treatment resulted in prompt and progressive reductions in HbA_{1c} and FPG that were sustained throughout the 26 weeks. In addition, both combination therapy groups were associated with significantly greater percentage of patients meeting glycemic goals compared to monotherapy.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
pioglitazone 30 mg QD			evaluations	Fewer patients in the combination therapy groups required hyperglycemic rescue (3.7 and 2.4% with combination alogliptin 12.5 and 25 mg groups, respectively) than with either pioglitazone (6.1%) or alogliptin monotherapy (11.0%). The safety profile of combination therapy was consistent with that of the individual components. The most frequently reported adverse events included headache, back pain, urinary tract infection and peripheral edema.
Nauck et al[19] Alogliptin Study 008 Alogliptin 12.5 mg QD vs alogliptin 25 mg QD vs placebo All patients were stabilized on metformin and continued this agent throughout treatment at a dose ≥1,500 mg/day or the highest tolerated daily dose.	DB, PC, RCT Treatment naïve† patients 18 to 80 years of age with type 2 diabetes, an HbA_{1c} value 7.0 to 10% (despite a stable metformin regimen ≥3 months in duration), a BMI 23 to 45 kg/m^2, C-peptide concentration ≥0.26 nmol/L and SCR <1.5 mg/dL (men) or <1.4 mg⁄dL (women)	N=527 26 weeks	Primary: Mean change from baseline in HbA_{1c} at week 26 Secondary: HbA_{1c} and FPG changes from baseline at each study visit, incidence of marked hyperglycemia‡, hyperglycemic rescue, C-peptide, proinsulin, insulin and proinsulin⁄ insulin ratio, achievement of glycemic goals, changes in body weight and safety evaluations	Primary: The 25 mg combination arm compared to metformin monotherapy resulted in statistically significant improvements from baseline in HbA_{1c} (-0.6 vs -0.1%, respectively; P<0.001). Similar results were found with the 12.5 mg combination arm (P<0.001). Secondary: The 25 mg combination arm compared to metformin monotherapy resulted in statistically significant improvements from baseline in FPG (-17 vs 0 mg/dL, respectively; P<0.01). In addition, comparisons at all time points for measures of HbA_{1c} and FPG favored the combination arms. Fewer patients in the alogliptin treatment groups experienced marked hyperglycemia compared to the placebo group at each time point and the difference in overall incidence was statistically significant for both the 12.5 mg (P<0.001) and 25 mg (P=0.003). In addition, the incidence of hyperglycemic rescue was significantly lower (P≤0.004) for patients in the alogliptin treatment groups compared to the placebo group. There were no statistically significant differences between the alogliptin groups and placebo changes from baseline to week 26 in fasting plasma proinsulin and insulin levels. Relative to patients in the placebo group, a significantly greater percentage of patients in both the alogliptin 12.5 and 25 mg groups achieved HbA_{1c} levels of ≤7.0% (P<0.001) and ≤6.5% (P< 0.05).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Adverse events were similar across all treatment arms. In addition, the incidence of hypoglycemia was low in all treatment groups; there were no severe hypoglycemic events and no clinically significant hypoglycemic episodes reported.
DeFronzo et al[20] Alogliptin 12.5 mg QD vs alogliptin 25 mg QD vs pioglitazone 15 mg QD vs pioglitazone 30 mg QD vs pioglitazone 45 mg QD vs alogliptin 12.5 mg QD and pioglitazone 15 mg QD vs alogliptin 12.5 mg QD and pioglitazone 30 mg QD	DB, MC, PC, PG, RCT Patients 18 to 80 years of age with type 2 diabetes, an HbA_{1c} value 7.5% to 10.0%, FPG <16.7 mmol/L, BMI 23 to 45 kg/m^2, blood pressure ≤160/110 mm Hg, HGB ≥12 g/dL (men) or ≥10 g/dL (women), ALT ≤2.5 X ULN, TSH ≤ULN, SCR <133 µmol/L (men) or <124 µmol/L (women), and C-peptide concentration ≥0.26 nmol/L who were inadequately controlled on metformin at a dose of ≥1,500 mg/day for ≥2 months	N=1,554 26 weeks	Primary: Mean change from baseline in HbA_{1c} at week 26 Secondary: HbA_{1c} and FPG changes from baseline at each study visit, hyperglycemic rescue, C-peptide, proinsulin, insulin and proinsulin/ insulin ratio, HOMA-B, achievement of glycemic goals, changes in body weight and safety evaluations	Primary: Coadministration of alogliptin and pioglitazone provided significant improvements in HbA_{1c} and FPG compared to placebo, or either treatment as a single agent added to metformin therapy (P<0.01 for all comparisons). Secondary: More patients in the placebo group (41 of 129; 31.8%) required hyperglycemic rescue than in any active treatment group. The alogliptin and pioglitazone therapy groups had a higher percentage of patients requiring hyperglycemic rescue (8.5 to 14.7%) than any combination therapy (1.5 to 4.6%). Measures of β-cell function found a greater decrease in alogliptin 25 mg/pioglitazone compared to pioglitazone alone. However, the decrease in the alogliptin 12.5 mg/pioglitazone arms were similar to the pioglitazone arms alone. Body weight decreased slightly in patients receiving placebo (-0.7 kg) or alogliptin (-0.02 and -0.7 kg for the 12.5 and 25 mg groups, respectively), whereas there were modest but significant increases in body weight in all groups receiving pioglitazone (P values not reported). In general, the combination of alogliptin and pioglitazone was well tolerated. In addition, the incidence of adverse events was similar across treatment groups.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs alogliptin 12.5 mg QD and pioglitazone 45 mg QD vs alogliptin 25 mg QD and pioglitazone 15 mg QD vs alogliptin 25 mg QD and pioglitazone 30 mg QD vs alogliptin 25 mg QD and pioglitazone 45 mg QD vs placebo Patients received metformin at a dose of 1,500 mg/day.				
Pratley et al[21] Alogliptin Study 009 Alogliptin 12.5 mg QD vs alogliptin 25 mg QD	DB, MC, PC, PG, RCT Patients 18 to 80 years of age with type 2 diabetes, an HbA_{1c} value 7.5% to 10.0%	N=493 26 weeks	Primary: Mean change from baseline in HbA_{1c} at week 26 Secondary: HbA_{1c} and FPG changes from	Primary: The addition of alogliptin 25 mg daily to pioglitazone therapy resulted in significant improvements from baseline compared to placebo in HbA_{1c} (-0.8 vs -0.2%, respectively; P<0.01). Significant improvements from baseline compared to placebo were observed with the 12.5 mg arm. Secondary: The addition of alogliptin 25 mg daily to pioglitazone therapy resulted in

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo Concomitant therapy with metformin or sulfonylurea at pre-study doses was permitted.	inadequately controlled on a thiazolidinedione alone or in combination with metformin or a sulfonylurea		baseline at each study visit, hyperglycemic rescue, C-peptide, proinsulin, insulin and proinsulin/ insulin ratio, HOMA-B, achievement of glycemic goals, changes in body weight and safety evaluations	significant improvements from baseline compared to placebo FPG (-20 vs -6 mg/dL, respectively; P<0.01). Significant decreases from baseline were observed with the 12.5 mg arm compared to placebo. A significantly larger proportion of patients achieved HbA_{1c} ≤7.0% with alogliptin 12.5 or 25 mg than with placebo (44.2 and 49.2 vs 34.0%, respectively; P≤0.016). The percentage of patients with marked hyperglycemia was significantly lower for alogliptin than placebo (≤25% for both alogliptin groups vs 44.3%, respectively; P<0.001). The incidences of overall adverse events and hypoglycemia were similar across treatment groups, but cardiac events occurred more often with active treatment than placebo.
Bosi et al[22] Alogliptin 25 mg QD and pioglitazone 30 mg QD vs pioglitazone 45 mg QD All members received metformin at a dose ≥1,500 mg throughout the study.	AC, DB, MC, PG, RCT Patients 18 to 80 years of age with type 2 diabetes, an HbA_{1c} value 7.0 to 10%, FPG <15.3 mmol/L, BMI 23 to 45 kg/m^2, blood pressure ≤160/110 mm Hg, and C-peptide concentration ≥0.26 nmol/L who were inadequately controlled on metformin at a dose of ≥1,500 mg/day and	N=803 52 weeks	Primary: Mean change from baseline in HbA_{1c} at week 26 and 52 Secondary: Mean change from baseline in HbA_{1c} and FPG at all other visits, proportions of patients achieving glycemic goals, proinsulin: insulin ratio, C-peptide, HOMA-B, HOMA insulin resistance, body weight, serum triglycerides,	Primary: In combination with pioglitazone and metformin, alogliptin was associated with a significantly greater decrease compared to the titration of pioglitazone in HbA_{1c} (-0.7 vs -0.3%, respectively; P=0.025) and FPG (-15 vs -4 mg/L, respectively; P<0.001) at 52 weeks. Similar, the decrease was greater with the alogliptin group at 26 weeks (P<0.001). Secondary: In combination with pioglitazone and metformin, alogliptin was associated with a significantly greater decrease compared to the titration of pioglitazone in FPG (-15 vs -4 mg/L, respectively; P<0.001) at 52 weeks. Decreases favored alogliptin for HbA_{1c} and FPG at 26 weeks and other time points. At week 52, the proportions of patients achieving HbA_{1c} levels ≤7.0 (33.2 vs 21.3%, respectively) and ≤6.5% (8.7 vs 4.3%, respectively) were significantly higher in the alogliptin group than in the pioglitazone titration group (P<0.001 for all comparisons). Proinsulin: insulin ratio (-0.048 vs -0.007, respectively) and HOMA β-cell function (15.02 vs 2.06, respectively) were significantly improved in the alogliptin group compared to the pioglitazone titration group at 52 weeks (P<

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	pioglitazone 30 mg daily for ≥2 months		cholesterol and safety endpoints	0.001 for all comparisons). However, no statistically significant differences in mean change from baseline in C-peptide, HOMA insulin, in body weight, total cholesterol, HDL cholesterol, LDL-C, triglycerides or free fatty acids resistance were observed between the treatment groups at week 52 (P>0.05 for all comparisons). No meaningful differences in incidences of individual adverse events were observed between treatments.
Pratley et al[23] Alogliptin Study 007 Alogliptin 12.5 mg QD vs alogliptin 25 mg QD vs placebo All patients received glyburide at a dose ≥10 mg QD.	DB, MC, PC, RCT Patients 18 to 80 years of age with type 2 diabetes, an HbA_{1c} value 7.0 to 10.0%, FPG<15.3 mmol/L, BMI 23 to 45 kg/m^2 who were inadequately controlled on a sulfonylurea for ≥3 months	N=500 26 weeks	Primary: Mean change from baseline in HbA_{1c} at week 26 Secondary: Evaluation of the safety of alogliptin and the effects of alogliptin on additional measures of glycemic control, b-cell function, plasma lipids, weight and adverse events	Primary: The addition of alogliptin 25 mg to glyburide therapy resulted in statistically significant improvements from baseline in HbA_{1c} at week 26 when compared to placebo (-0.5 vs 0%, respectively; P<0.01). Significant decreases with the 12.5 mg strength compared to placebo were also noted. Secondary: Improvements observed in FPG with alogliptin 12.5 and 25 mg were not statistically significant compared to placebo (-5 and -8 vs 2 mg/dL, respectively; P>0.07). More patients in the alogliptin groups achieved HbA_{1c} levels ≤7.0% at week 26 compared to patients in the placebo group. However, only the comparison between alogliptin 25 mg (and not the 12.5 mg strength) and placebo reached statistical significance (34.8 and 29.6 vs 18.2%, respectively; P=0.002 and P=0.057). Fewer patients in the alogliptin (12.5 and 25 mg) groups required hyperglycemia rescue (14.9 and 15.7 vs 28.3%, respectively; P<0.05 for both comparisons). Modest improvements were observed in fasting insulin concentration, proinsulin: insulin ratio and HOMA-b with alogliptin treatment, however these differences were not considered significant. Minor nonsignificant increases in body weight were also observed with alogliptin. Adverse events were similar across all treatment groups. The incidences of hypoglycemia for placebo, alogliptin 12.5 mg and alogliptin 25 mg groups were

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				11.1, 15.8 and 9.6% respectively.
Rosenstock et al[24] Alogliptin 12.5 mg QD vs alogliptin 25 mg QD vs placebo All patients received insulin therapy with or without metformin.	DB, MC, PC, RCT Patients 18 to 80 years of age with type 2 diabetes, an HbA_{1c} value ≥8.0%, FPG<15.3 mmol/L, BMI 23 to 45 kg/m^2 who were inadequately controlled on insulin at a dose≥15 units and ≤100 units per day for at least 8 weeks	N=390 26 weeks	Primary: Mean change from baseline in HbA_{1c} at week 26 Secondary: Evaluation of the safety of alogliptin and the effects of alogliptin on additional measures of glycemic control, b-cell function, plasma lipids and weight.	Primary: The addition of alogliptin 25 mg once daily to insulin therapy compared to placebo resulted in statistically significant improvements from baseline at week 26 in HbA_{1c} (-0.7 vs -0.1, respectively; P<0.05). Similar decreases were observed with the 12.5 mg strength compared to placebo. Secondary: The addition of alogliptin 25 mg once daily to insulin therapy compared to placebo resulted in statistically significant improvements from baseline at week 26 in FPG (-12 vs 6 mg/dL, respectively; P<0.05). Decreases in FPG and HbA_{1c} compared to placebo with alogliptin were generally observed at all time points. The overall incidences of hyperglycemic rescue were significantly lower in the alogliptin 12.5 and 25 mg groups (21 and 20% respectively) than in the placebo group (40%; P<0.001 for both comparisons). Differences in other secondary endpoints including change in weight and lipid parameters from baseline did not differ significantly between treatment groups. Incidences of overall adverse events, and of gastrointestinal, dermatological and infection-related events, were similar among groups. There were no differences in the proportions of patients experiencing hypoglycemia among placebo (24%), alogliptin 12.5 mg (27%) and alogliptin 25 mg (27%).
Del Prato et al[25] Linagliptin 5 mg/day vs placebo	DB, MC, PC, PG, RCT Type 2 diabetics 18 to 80 years of age with BMI ≤40 kg/m^2, and either treatment-naïve or had previously received 1 oral antidiabetic agent	N=503 24 weeks	Primary: Change in baseline HbA_{1c} Secondary: Proportion of patients achieving an HbA_{1c} <7.0 or <6.5%, change in baseline HbA_{1c} by visit over time,	Primary: Adjusted mean differences of the change in HbA_{1c} significantly favored linagliptin compared to placebo (-0.69%; P<0.0001). Secondary: The proportion of patients with a baseline HbA_{1c} ≥7.0% who achieved an HbA_{1c} <7.0% receiving linagliptin and placebo were 25.2 vs 11.6% (OR, 2.9; P=0.0006). The difference between linagliptin and placebo in HbA_{1c} decreases from baseline increased over time and favored linagliptin (-0.46% at week six to -

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	(excluding TZDs)		proportion of patients with an HbA_{1c} decrease ≥0.5%, change in baseline FPG, and two-hour PPG, safety	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[26] Linagliptin 5 mg/day vs placebo All patients also received metformin ≥1,500 mg/day.	DB, MC, PC, PG, RCT Type 2 diabetics 18 to 80 years of age with BMI ≤40 kg/m^2, who had inadequate glycemic control on metformin ≥1,500 mg/day (HbA_{1c} 7.0 to 10.0%) or metformin in combination with ≤1 other oral	N=701 24 weeks	Primary: Change in baseline HbA_{1c} Secondary: Change in baseline FPG, two-hour PPG, body weight, and β cell function; change in baseline HbA_{1c} and FPG over time; proportion of patients achieving an HbA_{1c} <7.0	Primary: Linagliptin decreased HbA_{1c} by -0.49% compared to 0.15% with placebo (treatment difference, -0.64%; 95% CI, -0.78 to -0.50; P<0.0001). Secondary: Linagliptin significantly decreased FPG compared to placebo (-0.6 vs 0.6 mmol/L; treatment difference, -1.2 mmol/L; P<0.0001). Linagliptin significantly decreased PPG compared to placebo (-2.7 vs 1.0 mmol/L; treatment difference, -3.7 mmol/L; P<0.0001). Neither treatment was associated with a significant change in body weight (-0.4 vs -0.5 kg; P value not reported). HOMA-B demonstrated a clinically relevant difference between treatments in adjusted mean change from baseline at 24 weeks in favor of linagliptin of 11.9

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	antidiabetic agent (HbA_{1c} 6.5 to 9.0%) for ≥10 weeks prior to trial entry		and <6.5%; proportion of patients with an HbA_{1c} decrease ≥0.5%; proportion of patients who required rescue medication; safety	(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 signs.
Owens et al[27] Linagliptin 5 mg QD vs placebo	DB, MC, PC, PG, RCT Type 2 diabetics ≥18 to ≤80 years of age, BMI ≤40 kg/m^2, and HbA_{1c} ≥7.0 and ≤10.0%	N=1,058 24 weeks	Primary: Change in baseline HbA_{1c} Secondary: Proportion of patients achieving an HbA_{1c} <6.5 or	Primary: Linagliptin significantly decreased HbA_{1c} compared to placebo (treatment difference, -0.62%; 95% CI, -0.73 to 0.50; P<0.0001). Secondary: A significantly greater proportion of patients with baseline HbA_{1c} ≥7.0% achieved an HbA_{1c} <7.0% with linagliptin compared to placebo (29.2 vs 8.1%; P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Patients were also receiving metformin and a sulfonylurea.	despite receiving metformin ≥1,500 mg/day and the maximum tolerated dose of a sulfonylurea		<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	The proportion of patients achieving an HbA_{1c} decrease ≥0.5% was 58.2 and 30.2% with linagliptin and placebo (P value not reported). Linagliptin significantly decreased FPG (treatment difference, -7.0 mmol/L; 95% CI, -1.0 to -0.4; P<0.0001). Linagliptin significantly improved HOMA-B and HOMA-IR compared to placebo (P<0.001). No significant changes in body weight or waist circumference were observed with either treatment. Only placebo-treated patients experienced a meaningful decrease in TG (-12 mg/dL). Changes in TC, HDL-C, and LDL-C were similar between the two treatments. Of the patients receiving linagliptin, 5.4% required rescue medication compared to 13.0% of placebo-treated patients. The likelihood of requiring rescue medication was approximately three times lower with linagliptin (OR, 0.361; P<0.0001). Overall, 66.3 and 59.7% of patients receiving linagliptin and placebo experienced adverse events. The proportion of patients reporting severe adverse events was low with both treatments (2.4 vs 1.5%). Hypoglycemia was the most commonly reported adverse event (22.7 vs 14.8%). Symptomatic hypoglycemia was reported in 16.7 and 10.3% of patients. Hypoglycemia was generally mild or moderate, with severe hypoglycemia reported in 2.7 and 4.8% of patients.
Forst et al[28] Linagliptin 1, 5, or 10 mg/day vs	AC, DB, MC, PC, PG, RCT Type 2 diabetics 21 to 75 years of age with BMI 25 to 40 kg/m^2, who	N=333 12 weeks	Primary: Change in baseline HbA_{1c} Secondary: Change in baseline FPG and	Primary: Placebo corrected decreases in HbA_{1c} were -0.40±0.14 (P=0.006), -4.40±0.14 (P<0.001), and -8.00±1.50% (P<0.001) with linagliptin 1, 5, and 10 mg, respectively. Treatment with glimepiride significantly decreased HbA_{1c} compared to treatment with placebo -0.68% (P<0.0001). Secondary:

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placebo vs glimepiride (OL) 1 to 3 mg/day Patients were also receiving metformin.	had inadequate glycemic control on metformin alone (HbA_{1c} 7.5 to 10.0%)		body weight, proportion of patients achieving an HbA_{1c} ≤7.0%, proportion of patients with an HbA_{1c} decrease ≥0.5%, safety	Decreases in FPG were significantly greater with all doses of linagliptin compared to placebo. The placebo corrected FPG decrease were -1.1 (P=0.0020), -1.9 (P<0.0001), and -1.6 mmol/L (P<0.0001) with linagliptin 1, 5, and 10 mg, respectively. After 12 weeks a small decrease in body weight was observed with all doses of linagliptin (-0.15, -0.57, and -1.27 kg, respectively; P values not reported). Only one (1.4%) patient receiving placebo achieved an HbA_{1c} ≤7.0% compared to ten (approximately 15%), nine (approximately 15%), and 14 (21%) patients receiving linagliptin 1, 5, and 10 mg/day, respectively (P values not reported). A greater proportion of patients receiving linagliptin achieved an HbA_{1c} decrease ≥0.5% compared to patients receiving placebo (43.8 to 53.2 vs 12.9%; P value not reported). In addition, HbA_{1c} decreased by ≥1.0% in 14.1, 27.4, 22.7, and 7.7% with linagliptin 1 mg, linagliptin 5 mg, linagliptin 10 mg, and placebo (P values not reported). Linagliptin was well tolerated. The most commonly reported adverse events were considered to be of mild or moderate intensity; however, ten patients experienced severe adverse events. No episodes of hypoglycemia were reported. Three (4.6%) patients experienced hypoglycemia after dosing with glimepiride.
Haak et al[29] Linagliptin 5 mg QD vs metformin 500 mg BID vs metformin 1,000 mg BID	DB, MC, PC, RCT Patients 18 to 80 years of age with type 2 diabetes who were treatment-naïve (HbA_{1c} 7.5 to 11.0%) or who had received one other oral antidiabetic drug	N=791 24 weeks	Primary: Change from baseline in HbA_{1c} at week 24 Secondary: Change from baseline in FPG, change from baseline in HbA_{1c} and FPG over time, proportion of	Primary: After 24 weeks, the mean change in HbA_{1c} was 0.1% with placebo, -0.5% with linagliptin 5 mg QD, -0.6% with metformin 500 mg BID, -1.1% with metformin 1,000 mg BID, -1.2% with linagliptin plus metformin 500 mg, and -1.6% with linagliptin plus metformin 1,000 mg. The adjusted placebo-corrected mean changes in HbA_{1c} were -1.7% (95% CI, -2.0 to -1.4) for linagliptin plus metformin 1,000 mg; -1.3% (95% CI, -1.6 to -1.1) for linagliptin plus metformin 500 mg; -1.2% (95% CI, -1.5 to -0.9) for metformin 1,000 mg; -0.8% (95% CI, -1.0 to -0.5) for metformin 500 mg, and -0.6% (95% CI, -0.9 to -0.3) for linagliptin monotherapy (P<0.0001 for all).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs linagliptin 2.5 mg BID and metformin 500 mg BID vs linagliptin 2.5 mg BID and metformin 1,000 mg BID vs placebo	(HbA_{1c} 7.0 to 10.5%)		patients requiring rescue therapy after failing to achieve pre-specified glycemic targets or discontinuing because of lack of efficacy, safety	The mean treatment differences for linagliptin plus metformin 1,000 mg vs metformin and linagliptin monotherapy were -0.5% (95% CI, -0.7 to -0.3) and -1.1% (95% CI, -1.4 to -0.9), respectively. For linagliptin plus metformin 500 mg, the respective mean differences were -0.6% (95% CI, -0.8 to -0.4) and -0.8% (95% CI, -1.0 to -0.6; P<0.0001 for all). Secondary: The adjusted placebo-corrected mean changes in FPG from baseline were -3.3 mmol/L (95% CI, -4.0 to -2.6) and -2.4 mmol/L (95% CI, -3.1 to -1.7) in the linagliptin plus metformin 1,000 mg and linagliptin plus metformin 500 mg groups, respectively. This is compared to -2.3 mmol/L (95% CI, -3.0 to -1.7), -1.4 mmol/L (95% CI, -2.1 to -0.8) and -1.0 mmol/L (95% CI, -1.7 to -0.3) in the metformin 1,000 mg, metformin 500 mg, and linagliptin monotherapy groups, respectively (P<0.0001 for all). The proportion of patients requiring rescue therapy for inadequate glycemic control at week 24 was lower in the combination therapy groups (linagliptin plus metformin 1,000 mg, 4.3%; linagliptin plus metformin 500 mg, 7.3%) compared to either monotherapy alone (metformin 1,000 mg, 8.0%; metformin 500 mg, 13.5%; linagliptin, 11.1%). The proportion of patients reporting adverse events were comparable across the active treatment groups.
Hollander et al[30] 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	N=565 24 weeks	Primary: Change in baseline HbA_{1c} Secondary: Change in baseline FPG and PPG $AUC_{0\text{-}3hr}$, proportion of patients achieving an HbA_{1c} <7.0%	Primary: Saxagliptin significantly decreased HbA_{1c} compared to placebo (saxagliptin 2.5 mg, -0.66%; treatment difference, -0.36%; P<0.0007 vs placebo and saxagliptin 5 mg, -0.94%; treatment difference, -0.63%; P<0.0001 vs placebo). Secondary: Saxagliptin significantly decreased FPG compared to placebo (saxagliptin 2.5 mg treatment difference, -0.8 mmol/L; P<0.0053 vs placebo and saxagliptin 5 mg treatment difference, -1.0 mmol/L; P=0.0005 vs placebo). A significantly greater proportion of patients receiving saxagliptin achieved an HbA_{1c} <7.0% compared to patients receiving placebo (42.2 [P=0.0010] and 41.8 [P=0.0013] vs 25.6%).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	or 8 mg/day for ≥12 weeks), fasting C-peptide ≥0.3 nmol/L, and BMI ≤45 kg/m^2			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[31] Saxagliptin 2.5 and 5 mg QD vs placebo All patients also received glyburide 7.5 mg/day.	DB, MC, RCT Type 2 diabetics 18 to 77 years of age with inadequate glycemic control (HbA_{1c} ≥7.5 to ≤10.0%), on a submaximal sulfonylurea dose for ≥2 months before screening, fasting C-peptide ≥1 ng/mL, and BMI ≤40 kg/m^2	N=768 24 weeks	Primary: Change in baseline HbA_{1c} Secondary: Change in baseline FPG and PPG $AUC_{0\text{-}3hr}$, proportion of patients achieving an HbA_{1c} <7.0%, safety	Primary: Saxagliptin significantly decreased HbA_{1c} compared to placebo (-0.54 and -0.64 vs 0.08%; P<0.0001 for both). Secondary: Saxagliptin significantly decreased FPG compared to placebo (2.5 mg; P=0.0218 and 5 mg; P=0.002). Saxagliptin significantly decreased PPG $AUC_{0\text{-}3hr}$ compared to placebo (-4,296 and -5,000 vs 1,196 (mg/minute)/(dL); P<0.0001 for both). A significantly greater proportion of patients receiving saxagliptin achieved an HbA_{1c} <7.0% compared to patients receiving placebo (22.4 and 22.8 vs 9.1%; P<0.0001 for both). Overall saxagliptin was well tolerated. The proportion of patients reporting any adverse event was similar across all treatments; with no evidence of a dose-response relationship. The proportion of patients reporting at least one adverse event and at least one treatment-related adverse event was 75.0 and 19.8, 72.3 and 21.3, and 76.8 and 14.2% with saxagliptin 2.5 mg, saxagliptin 5 mg, and placebo. No events of Stevens-Johnson syndrome or angioedema were reported. Cardiac disorder events 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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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[32] 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, fasting C-peptide ≥1 ng/mL, and BMI ≤40 kg/m^2	N=768 52 weeks (76 weeks total)	Primary: Change in baseline HbA_{1c} Secondary: Change in baseline FPG and PPG AUC_{0-3hr}, proportion of patients achieving an HbA_{1c} <7.0%	Primary: 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_{0-3hr} decreases were maintained during the extension trial. A greater proportion of patients receiving saxagliptin achieved an HbA_{1c} <7.0% compared to patients receiving placebo (11.0 and 9.6 vs 5.3%; P value not reported). Similar results were observed with HbA_{1c} ≤6.5% (4.1 and 5.2 vs 1.5%; P value not reported).
Rosenstock et al (abstract)[33] 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}	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%).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
>10.0 to ≤12.0%]).				Decreases in HbA_{1c}, FPG, and PPG AUC were observed in the OL cohort.
DeFronzo et al[34] 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) ≥8 weeks, fasting C-peptide concentration ≥1 ng/mL, and BMI ≤40 kg/m^2	N=743 24 weeks	Primary: Change in baseline HbA_{1c} Secondary: Change in baseline FPG and PPG AUC_{0-3hr}, 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_{0-3hr} (-8,891, -9,586, and -8,137 vs -3,291 [mg/minute]/[dL]; P<0.0001 for all). A significantly greater proportion of patients achieved an HbA_{1c} <7.0% with saxagliptin compared to placebo (37.1, 43.5, and 44.4 vs 16.6%; P<0.0001 for all).
Stenlöf et al[35] Saxagliptin 5 mg QD vs placebo All patients also received metformin ER ≥1,500 mg/day.	DB, MC, PC, RCT Type 2 diabetics with inadequate glycemic control (HbA_{1c} 7.0 to 10.0%), and currently receiving stable doses of metformin IR or metformin ER (≥1,500 mg/day) as monotherapy for ≥8 weeks	N=93 4 weeks	Primary: Change in baseline 24-hour mean weighted glucose Secondary: Change in baseline four-hour mean weighted PPG, two-hour PPG (both assessed after the evening meal), three-day average mean daily	Primary: Saxagliptin significantly decreased 24-hour mean weighted glucose compared to placebo (-13.8 vs -3.0 mg/dL; P<0.0001). Secondary: Saxagliptin significantly decreased four-hour mean weighted PPG compared to placebo (-30.7 vs 0.4 mg/dL; P<0.0001). Similar results were observed with two-hour mean weighted PPG (-38.2 vs -2.8 mg/dL; P=0.0010). 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).

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			glucose, and two-day average FPG	
Barnett et al[36] Saxagliptin 5 mg QD vs placebo All patients also received insulin alone or in combination with metformin.	DB, MC, RCT Type 2 diabetics with inadequate glycemic control (HbA_{1c} 7.5 to 11.0% on stable insulin therapy (30 to 150 U/day alone or in combination with metformin) for at least 8 weeks	N=455 24 weeks	Primary: Change in HbA_{1c} from baseline to week 24 (or rescue), PPG, FPG, body weight, adverse events Secondary: Not reported	Primary: Patients treated with saxagliptin had significantly greater reductions in adjusted mean HbA_{1c} (difference, -0.41%; P<0.0001), PPG 180-minute AUC (-3829.8 mg/minute/dL; P=0.0011), and 120-minute PPG (-23.0 mg/dL; P=0.0016) at 24 weeks compared to placebo. Treatment with saxagliptin resulted in similar reductions in HbA_{1c} relative to placebo, irrespective of metformin treatment. At 24 weeks, difference in adjusted mean FPG for saxagliptin compared to placebo was -4.02 mg/dL (P=0.3958); 17.3 and 6.7% of patients in the saxagliptin and placebo groups, respectively, achieved HbA_{1c} <7.0%. Mean change from baseline in body weight at week 24 was 0.39 kg for saxagliptin and 0.18 kg for placebo. Hypoglycemia was reported in 18.4% and 19.9% of patients in the saxagliptin and placebo groups, respectively. Other adverse events reported in at least 5% of patients were urinary tract infection (5.9 vs 6.0%), influenza (3.0 vs 6.6%), and pain in extremity (1.6 vs6.0%). Secondary: Not reported
Rosenstock et al[37] 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).

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				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).
Frederich et al[38] 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
Scircia et al.[39] Saxagliptin 5 mg QD (2.5 mg daily in patients with an estimated glomerular filtration rate ≤50 ml per minute) vs. placebo	RCT Type 2 diabetics ≥40 years of age with an HbA_{1c} ≥6.5 to ≤12% and either a history of Established cardiovascular disease or multiple risk factors for vascular disease	N=16,492 2.1 years	Primary: A composite of cardiovascular death, myocardial infarction or ischemic stroke. Secondary: A composite endpoint (cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina,	Primary: A primary end-point event occurred in 613 patients in the saxagliptin group and in 609 patients in the placebo group (7.3 and 7.2%, respectively; HR, 1.00; 95% CI, 0.89 to 1.12; P=0.99 for superiority; P<0.001 for noninferiority); the results were similar in the “on-treatment” analysis (HR, 1.03; 95% CI, 0.91 to 1.17). Secondary: The major secondary end point of a composite of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, coronary revascularization, or heart failure occurred in 1,059 patients in the saxagliptin group and in 1,034 patients in the placebo group (12.8 and 12.4%, respectively; HR, 1/09; 95% CI, 0.94 to 1.11; P=0.66). More patients in the saxagliptin group than in the placebo group were

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			coronary revascularization, or heart failure), hospitalization rate for heart failure and cases of pancreatitis	hospitalized for heart failure (3.5 vs. 2.8%; HR, 1.27; 95% CI, 1.07 to 1.51; P=0.007). Rates of adjudicated cases of acute and chronic pancreatitis were similar in the two groups (acute pancreatitis, 0.3% in the saxagliptin group and 0.2% in the placebo group; chronic pancreatitis, <0.1 and 0.1% in the two groups, respectively).
Harashima et al[40] Sitagliptin 100 mg QD All patients received existing sulfonylurea therapy.	PRO, SA Type 2 diabetics ≥20 years of age inadequately controlled on sulfonylureas, with or without metformin and/or α-glucosidase inhibitors, HbA_{1c} ≥6.9%, no improvement in HbA_{1c} ≥0.5% within 3 months, and a wish to diet and exercise to improve health	N=82 52 weeks	Primary: Change in baseline HbA_{1c} Secondary: Changes in BMI, BP, urinary albumin excretion, unresponsive rate, hypoglycemia	Primary: Change in HbA_{1c} was -0.80% (95% CI, -0.90 to -0.68; P<0.001). Secondary: Change in BMI, SBP, DBP, and urinary albumin excretion were -0.38 kg/m^2 (95% CI, -0.72 to -0.04; P<0.05), -6.7/-3.6 mm Hg (95% CI, -10.0 to -3.4/-4.8 to -2.4; P<0.001), and -43.2 mg/gCr (95% CI, -65.7 to -20.8; P<0.001), respectively. The unresponsive rate was 6.1%. Mild hypoglycemia was observed in three cases.
Brazg et al[41] Sitagliptin 50 mg BID vs placebo All patients also received metformin ≥1,500 mg/day.	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	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,

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Patients received 1 drug regimen for 4 weeks then XO to the comparator group for 4 weeks.	9.6%			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[42] Sitagliptin 100 mg QD vs placebo	DB, MC, PC, RCT Japanese patients with type 2 diabetics, HbA_{1c} ≥6.5 to <10.0%, and FPG ≥126 to ≤240 mg/dL	N=151 12 weeks	Primary: Change in baseline HbA_{1c}, FPG, PPG, body weight; adverse effects Secondary: Not reported	Primary: Sitagliptin (-0.65%; 95% CI, -0.80 to -0.50) significantly decreased HbA_{1c} compared to placebo (0.41%; 95% CI, 0.26 to 0.56; treatment difference, -1.05%; 95% CI, -1.27 to -0.84; P <0.001). A significantly greater proportion of patients receiving sitagliptin achieved HbA_{1c} <7.0% compared to patients receiving placebo (P<0.001). Sitagliptin (-22.5 mg/dL; 95% CI, -28.0 to -17.0) significantly decreased FPG compared to placebo (9.4 mg/dL; 95% CI, 3.9 to 14.9; treatment difference, -31.9 mg/dL; 95% CI, -39.7 to -24.1; P<0.001). Sitagliptin (-69.3 mg/dL; 95% CI, -85.3 to -53.4) significantly decreased PPG compared to placebo (12.0 mg/dL; 95% CI, -6.5 to 30.5; treatment difference, -81.3 mg/dL; 95% CI, -105.8 to -56.9; P<0.001). 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[43] Sitagliptin 100 mg QD vs	DB, MC, PC, PG, RCT Type 2 diabetics 18 to 78 years of age, HbA_{1c} 7.0 to	N=190 30 weeks	Primary: Change in baseline HbA_{1c} at 18 weeks Secondary:	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

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placebo All patients also received metformin ≥1,500 mg/day	10.0% receiving metformin or other oral antihyperglycemic agents as monotherapy or being treated with metformin in combination with other oral antihyperglycemic agents		Change in baseline FPG at 18 weeks, two-hour PPG at 18 weeks, and HbA_{1c} at 30 weeks; safety and tolerability	and 3.3%; P values not reported). Secondary: Sitagliptin significantly decreased FPG compared to placebo (treatment difference, -1.4 mmol/L; 95% CI, -2.1 to -0.7; P<0.001). Sitagliptin significantly decreased two-hour PPG compared to placebo (treatment difference, -3.0 mmol/L; 95% CI, -4.2 to -1.9; P<0.001). Sitagliptin significantly decreased HbA_{1c} compared to placebo at week 30 (treatment difference, -1.0%; 95% CI, -1.4 to -0.6; P<0.001). The incidence of adverse events was similar with both treatments. No serious adverse events or discontinuations due to clinical adverse events 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[44] 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	DB, MC, PC, PG, RCT Type 2 diabetics 18 to 78 years of age with inadequate glycemic control (HbA_{1c} ≥7.0 to ≤10.0%) on metformin monotherapy	N=701 24 weeks	Primary: Change in baseline HbA_{1c} Secondary: Change in baseline FPG, PPG, insulin, C-peptide concentrations, β cell function, and lipid profile; safety	Primary: Sitagliptin significantly decreased HbA_{1c} compared to placebo (treatment difference, -0.65%; P<0.001). A significantly greater proportion of patients receiving sitagliptin achieved an HbA_{1c} <7.0% (47.0 vs 18.3%; P<0.001) and <6.5% (17.2 vs 4.9%; P<0.001) compared to patients receiving placebo. Secondary: Sitagliptin significantly decreased FPG compared to placebo (treatment difference, -25.4 mg/dL; P<0.001). Similar results were observed with PPG (treatment difference, -50.6 mg/dL; P≤0.001). Sitagliptin significantly increased fasting insulin (P<0.050) and fasting C-peptide (P<0.010) compared to placebo. There was observed improvement in fasting proinsulin:insulin ratio (P<0.010) and HOMA-B (P<0.001) consistent with improved β cell function with sitagliptin.

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met.				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[45] Sitagliptin 100 mg QD vs placebo All patients were also receiving pioglitazone 30 or 45 mg QD.	DB, MC, PC, PG, RCT Type 2 diabetics ≥18 years of age with inadequate glycemic control (HbA_{1c} ≥7.0 to ≤10.0%) on pioglitazone monotherapy	N=353 24 weeks	Primary: Change in baseline HbA_{1c} Secondary: Change in baseline FPG, fasting insulin, proinsulin, and lipid profiles; safety and tolerability	Primary: Combination therapy (-0.70%; 95% CI, -0.85 to -0.54) significantly decreased HbA_{1c} compared to placebo (P<0.001). A significantly greater proportion of patients receiving combination therapy achieved HbA_{1c} <7.0% compared to patients receiving placebo (45 vs 23%; P<0.001). Secondary: Combination therapy significantly decreased FPG compared to placebo (treatment difference, -17.7 mg/dL; 95% CI, -24.3 to -11.0; P<0.001). 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[46] Sitagliptin 100 mg QD vs	DB, DD, MC, PC, PG, RCT Type 2 diabetics 18 to 75 years of age, HbA_{1c} 6.7 to	N=441 24 weeks	Primary: Change in baseline HbA_{1c} Secondary: Change in	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).

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placebo All patients also received glimepiride with or without metformin.	10.6%, and inadequately controlled on glimepiride with or without metformin		baseline FPG, plasma lipids, β cell function, and insulin resistance; safety and tolerability	A significantly greater proportion of patients receiving sitagliptin achieved an HbA_{1c} <7.0% compared to patients receiving placebo (17.1 vs 4.8%; P<0.001). A significantly greater proportion of patients receiving triple therapy achieved an HbA_{1c} <7.0% compared to patients receiving combination therapy with glimepiride plus metformin (22.6 vs 1.0%; P<0.001). No difference was observed between combination therapy with glimepiride plus sitagliptin compared to glimepiride (10.8 vs 8.7%; P<0.638). Secondary: Sitagliptin significantly decreased FPG compared to placebo (treatment difference, -20.1 mg/dL; 95% CI, -28.4 to -11.8; P<0.001). Sitagliptin demonstrated neutral effects on plasma lipids compared to placebo (specific figures not reported). A significant increase in HOMA-B was achieved with sitagliptin compared to placebo (11.3 [95% CI, 4.4 to 18.1] vs -0.7% [95% CI, -8.2 to 6.8]; P<0.001). There were no differences in fasting proinsulin, proinsulin:insulin ratio, HOMA-IR, and QUICKI between the treatments. 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).
Raz et al[47] Sitagliptin 100 and 200 mg QD	DB, MC, PC, PG, RCT Type 2 diabetics 18 to 75 years of	N=521 18 weeks	Primary: Change in baseline HbA_{1c} Secondary:	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).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo	age with an HbA_{1c} 7.0 to 10.0%		Change in baseline FPG, fasting insulin, proinsulin, and lipids; safety and tolerability	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[48] 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). 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).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary: There were fewer sitagliptin-treated patients compared to placebo-treated patients that required rescue therapy (8.8 and 4.8 vs 20.6%; P<0.001). No meaningful differences in clinical adverse effects were noted between the two treatments. The incidence of hypoglycemia was similar among the two treatments. Both doses of sitagliptin were well tolerated.
Hanefeld et al[49] Sitagliptin 25 and 50 mg QD vs sitagliptin 50 mg BID vs sitagliptin 100 mg QD vs placebo	DB, MC, PC, PG, RCT Type 2 diabetics 23 to 74 years of age and an HbA_{1c} 7.6 to 7.8%	N=555 12 weeks	Primary: Change in baseline HbA_{1c}, FPG, mean daily glucose, HOMA-B, QUICKI, and HOMA-IR Secondary: Adverse events, body weight	Primary: Sitagliptin significantly decreased HbA_{1c} by -0.39 to -0.56% compared to placebo (P<0.05). Sitagliptin significantly decreased FPG by -11.0 to -17.2 mg/dL compared to placebo (P<0.05), and the largest decrease was achieved with sitagliptin 100 mg QD. Sitagliptin significantly improved mean daily glucose (-14.0 to -22.6 mg/dL; P<0.05). HOMA-B was significantly increased (11.3 to 15.2; P<0.05) with sitagliptin, whereas there was no significant changes in QUICKI and HOMA-IR with sitagliptin compared to placebo. Secondary: Overall, there was a low frequency of hypoglycemia observed with sitagliptin. There was no change in body weight observed with any treatment.
Scott et al[50] Sitagliptin 5, 12.5, 25, and 50 mg BID vs placebo vs	AC, DB, PC, RCT Type 2 diabetics 21 to 75 years of age, inadequately controlled (HbA_{1c} 7.9%) with diet and exercise	N=743 12 weeks	Primary: Change in baseline HbA_{1c}, FPG, mean daily glucose, and body weight; adverse effects Secondary: Not reported	Primary: Sitagliptin (-0.38 to -0.77%) significantly decreased HbA_{1c} compared to placebo (P<0.001). Sitagliptin 50 mg achieved the greatest decrease. The placebo subtracted difference in HbA_{1c} of glipizide was -1.00%. Sitagliptin significantly decreased FPG and mean daily glucose compared to placebo (P values not reported). There was no difference between sitagliptin and placebo with changes in body weight. Glipizide resulted in a modest weight gain compared to placebo (no P

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
glipizide 5 to 20 mg/day				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
Goldstein et al[51] Sitagliptin 50 mg BID plus metformin 500 and 1,000 mg BID vs sitagliptin 100 mg QD vs metformin 500 and 1,000 mg BID vs placebo	DB, MC, PC, PG, RCT Type 2 diabetics 18 to 78 years of age and an HbA_{1c} of 7.5 to 11.0%	N=1,091 24 weeks	Primary: Change in baseline HbA_{1c} Secondary: Change in baseline FPG, fasting serum insulin, fasting serum proinsulin, lipid profiles, β cell function, insulin resistance; adverse events	Primary: Decreases in HbA_{1c} were significant with all active treatments as compared to placebo and for combination therapy compared to monotherapy (P<0.001). There was an additive effect seen in the combination treatment groups. The proportion of patients achieving an HbA_{1c} <7.0% was significantly greater with all active treatments compared to placebo (P<0.001). Secondary: Significant decreases in FPG were achieved between combination therapy and monotherapy, and between all active treatments compared to placebo (P<0.001). Data on fasting serum insulin and lipid profiles were not reported. Combination therapy demonstrated an additive effect, as compared to monotherapy, with regards to improvements in β cell function. HOMA-B increased with all active treatments compared to placebo (P<0.001). The combination therapy significantly increased HOMA-B compared to monotherapy (sitagliptin and low-dose metformin; P≤0.001). Significant improvements in the proinsulin:insulin ratio observed with all active treatments compared to placebo (P<0.05). Differences between combination therapy and monotherapy were also significant (P<0.05). The incidence of adverse events was similar between combination therapy and metformin. Gastrointestinal adverse events including diarrhea, nausea, abdominal pain, and vomiting were most frequently observed with metformin high-dose both as monotherapy and combination therapy. A low frequency of

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				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).
Scott et al[52] 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) and rosiglitazone (treatment difference, -30.6 mg/dL; 95% CI, -40.6 to -20.7; P value not reported) significantly decreased FPG compared to placebo. Rosiglitazone significantly decreased FPG compared to sitagliptin (treatment difference, -12.8 mg/dL; 95% CI, -22.6 to -3.0; P value not reported). Sitagliptin (treatment difference, 16.3; 95% CI, 2.3 to 30.3; P≤0.05) and rosiglitazone (treatment difference, 15.3; 95% CI, 1.0 to 29.6; P value not reported, respectively) had significant increases in HOMA-B compared to placebo. The increase in HOMA-B was not significantly different between sitagliptin and rosiglitazone (P value not reported). Rosiglitazone significantly decreased HOMA-IR compared to placebo (treatment difference, -2.4; 95% CI, -3.4 to -1.4; P value not reported) and sitagliptin (treatment difference, -1.6; 95% CI, -2.6 to -0.7; P value not reported). There decrease in HOMA-IR was similar between sitagliptin and placebo (treatment difference, -0.7; 95% CI, -1.7 to 0.2; P value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Rosiglitazone significantly decreased fasting serum insulin compared to placebo (treatment difference, -3.4 µIU/mL; 95% CI, -5.5 to -1.4; P value not reported) and sitagliptin (treatment difference, -3.53 µIU/mL; 95% CI, -5.50 to -1.40; P value not reported). The proinsulin:insulin ratio was similar across all treatments. Compared to placebo, LDL-C decreased with sitagliptin (treatment difference, -5.3 mg/dL; 95% CI, -14.5 to 3.9; P value not reported) and increased with rosiglitazone (treatment difference, 9.5 mg/dL; 95% CI, 0.2 to 18.7; P value not reported). Compared to placebo, TC significantly decreased with sitagliptin (treatment difference, -6.3 mg/dL; 95% CI, -11.8 to -0.9; P≤0.05) and increased with rosiglitazone (treatment difference, 5.1 mg/dL; 95% CI, -0.3 to 10.6; P value not reported). Compared to placebo, TG significantly decreased with sitagliptin (treatment difference, -16.7 mg/dL; 95% CI, -27.9 to 5.5; P≤0.05) and increased with rosiglitazone (treatment difference, 1.2 mg/dL; 95% CI, -10.1 to 12.6; P value not reported). Compared to sitagliptin, lipid profiles measurements significantly increased with rosiglitazone (P values not reported).
Scheen et al[53] 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,	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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			proinsulin, and β cell function	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.
Esposito et al[54] Alogliptin* 12.5 to 25 mg QD vs saxagliptin 5 mg QD vs sitagliptin 100 mg QD vs vildagliptin* 100 mg QD	MA (43 RCT) Type 2 diabetics were treatment-naïve or receiving background therapy with other agents	N=19,101 Duration not reported	Primary: Proportion of patients achieving an HbA_{1c} <7.0%, change in baseline body weight, incidence of hypoglycemia Secondary: Not reported	Primary: Proportion of patients achieving an $aHbA_{1c}$ <7.0% Treatment with saxagliptin demonstrated a greater chance to achieve n HbA_{1c} <7.0% compared to placebo (POR, 2.81; 95% CI, 2.31 to 3.72), but not compared to comparator drugs (POR, 0.95; 95% CI, 0.8 to 1.11). Saxagliptin was associated with a greater decrease in HbA_{1c} compared to placebo (WMD, -0.69%; 95% CI, -0.1 to -0.37), but not compared to comparator drugs (WMD, 0.15%; 95% CI, -0.14 to 1.7). Sitagliptin was associated with a greater chance to achieve an HbA_{1c} <7.0% compared to placebo (POR, 3.15; 95% CI, 2.47 to 3.72), but not compared to comparator drugs (POR, 0.70; 95%CI, 0.35 to 1.12). Sitagliptin was also associated with a greater decrease in HbA_{1c} compared to placebo (WMD, -0.78%; 95% CI, -0.93 to -0.63), but not compared to comparator drugs (WMD, 0.19%; 95% CI, -0.13 to 0.52). Change in baseline body weight Saxagliptin was associated with small and no significant changes in body weight compared to baseline or other comparator drugs (WMD, -0.56 kg; 95% CI, -2.8 to 1.7), but with a significant difference compared to placebo (0.63 kg; 95% CI, 0.03 to 1.17). The absolute change in weight was small and not significantly different from baseline with sitagliptin (0.08 kg); however, the difference compared to placebo was significant (WMD, 0.48 kg; 95% CI, 0.19 to 0.77). The 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).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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
Gomis et al[55] 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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				greater with combination therapy (2.3 vs 1.2 kg; treatment difference, 1.1 kg; 95% CI, 0.2 to 2.0; P=0.014). Overall, the proportion of patients who experienced at least one adverse event was similar with both treatments (52.5 vs 53.1%). Most adverse events were of mild to moderate intensity. Hypoglycemia occurred in 1.2 and 0.0% of patients receiving combination therapy and pioglitazone, respectively. Laboratory analyses did not reveal any clinically significant findings.
Jadzinsky et al[56] 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 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_{0-3hr}, 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_{0-3hr} (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[57]	AC, DB, ES, MC,	N=1,306	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Saxagliptin 5 and 10 mg QD plus metformin 500 mg/day vs saxagliptin 10 mg QD vs metformin 500 mg/day	RCT Type 2 diabetics 18 to 77 years of age, HbA_{1c} ≥8.0 to ≤12.0%, fasting C-peptide concentration ≥1 ng/mL, and BMI ≤40 kg/m^2	52 weeks (76 weeks total)	Change in baseline HbA_{1c} Secondary: Change in baseline body weight, proportion of patients achieving an HbA_{1c} <7.0 and ≤6.5%	Decreases in HbA_{1c} with saxagliptin 5 mg plus metformin were -2.31% (95% CI -2.44 to -2.18) and -2.33% (95% CI -2.46 to -2.20) with saxagliptin 10 mg plus metformin compared to -1.55 (95% CI, -1.70 to -1.40) and -1.79% (95% CI, -1.93 to -1.65) with saxagliptin and metformin monotherapies, respectively; P<0.0001 for combination therapy vs monotherapy). Secondary: Decreases in body weight were -1.2 kg with saxagliptin 5 mg plus metformin, -0.7 kg with saxagliptin 10 mg plus metformin, -0.3 kg with saxagliptin, and -1.0 kg with metformin (P values not reported). A greater proportion of patients achieved an HbA_{1c} <7.0% with saxagliptin 5 mg plus metformin and saxagliptin 10 mg plus metformin compared to sitagliptin and metformin (51.5 and 50.5 vs 25.0 and 34.7%, respectively; P values not reported). Similar results were observed with HbA_{1c} <6.5% (P values not reported).
Reasner et al[58] Sitagliptin/metformin 50/500 to 1,00 mg BID vs metformin 500 to 1,000 mg BID	DB, MC, PG, RCT Treatment-naïve type 2 diabetics 18 to 78 years of age, and an HbA_{1c} ≥7.5%	N=1,250 18 weeks	Primary: Change in baseline HbA_{1c} Secondary: Proportion of patients achieving an HbA_{1c} <7.0 and <6.5%, change in baseline FPG, proinsulin:insulin ratio, and β cell function	Primary: Combination therapy significantly decreased HbA_{1c} compared to metformin (-2.4 vs -1.8%; P<0.001). Secondary: A significantly greater proportion of patients receiving combination therapy achieved an HbA_{1c} <7.0% (49.2 vs 34.2%, respectively; P<0.001) and <6.5% (31.8 vs 16.0%, respectively; P<0.001) compared to patients receiving metformin. Combination therapy significantly decreased FPG compared to metformin (-3.8 vs -3.0 mg/dL; P<0.001). Combination therapy significantly decreased proinsulin:insulin ratio compared to metformin (-0.238 vs -0.186; P<0.05). Combination therapy significantly improved β cell function compared to metformin (P<0.05).
Bergenstal et al[59] DURATION-2	DB, DD, MC, PG, RCT	N=514	Primary: Change in	Primary: Exenatide ER (-1.5%; 95% CI, -1.7 to -1.4) significantly decreased HbA_{1c}

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Exenatide ER 2 mg SC once weekly vs sitagliptin 100 mg QD vs pioglitazone 45 mg QD All patients received existing metformin therapy.	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	26 weeks	baseline HbA_{1c} Secondary: Proportion of patients achieving an HbA_{1c} ≤6.5 or ≤7.0%, FPG, six-point self-monitored glucose concentrations, body weight, fasting lipid profile, fasting insulin profile, BP, cardiovascular risk markers, patient-reported quality of life, safety	compared to sitagliptin (-0.9% [95% CI, -1.1 to -0.7]; treatment difference, -0.6% [95% CI, -0.9 to -0.4]; P<0.0001) and pioglitazone (-1.2% [95% CI, -1.4 to -1.0]; treatment difference, -0.3% [95% CI, -0.6 to -0.1]; P=0.0165). Secondary: A significantly greater proportion of patients receiving exenatide achieved HbA_{1c} targets of ≤6.5 (P<0.0001 and P=0.0120) or ≤7.0% (P<0.0001 and P=0.0015) compared to patients receiving sitagliptin or pioglitazone. Exenatide ER (-1.8 mmol/L; 95% CI, -2.2 to -1.3) achieved significantly greater decreases in FPG compared to sitagliptin (-0.9 mmol/L [95% CI, -1.3 to -0.5]; treatment difference, -0.9 mmol/L [95% CI, -0.3 to -1.4]; P=0.0038), but not pioglitazone (-1.5 mmol/L [95% CI, -1.9 to -1.1]; treatment difference, -0.2 mmol/L [95% CI, -0.8 to 0.3]; P=0.3729). A significantly greater proportion of patients receiving exenatide ER (60%) achieved the FPG goal of ≤7 mmol/L compared to patients receiving sitagliptin (35%; P<0.0001), but no difference was observed between patients receiving pioglitazone (52%; P=0.1024). In all measurements of the six-point self-monitored glucose concentrations profile, decreases at week 26 were significantly greater with exenatide ER compared to sitagliptin, but not pioglitazone (P values not reported). Weight loss with exenatide ER (-2.3 kg; 95% CI, -2.9 to -1.7) was significantly greater compared to sitagliptin (difference, -1.5 kg; 95% CI, -2.4 to -0.7; P=0.0002) and pioglitazone (difference, -5.1 kg; 95% CI, -5.9 to -4.3; P<0.0001). Pioglitazone was the only treatment to achieve significant decreases in TG (-16%; 95% CI, -21 to -11) and increases in TC (0.16 mmol/L; 95% CI, 0.04 to 0.28), the former of which was significantly different compared to exenatide ER (-5%; 95% CI, -11 to 0). 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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				µIU/mL [95% CI, 4.9 to 10.1]; P<0.0001). Decreases in SBP with exenatide ER were significantly greater compared to sitagliptin (treatment difference, -4 mm Hg; 95% CI, -6 to -1), but not pioglitazone (data reported in graphical form only). All treatments achieved significant improvements in high-sensitivity CRP and adiponectin. Exenatide ER was the only treatment to achieve a significant improvement in BNP and albumin:creatinine ratio, with the changes in BNP being significantly greater compared to sitagliptin and pioglitazone (P values not reported). All five domains of weight-related quality of life and IWQOL total score were significantly improved with exenatide ER (IWQOL total score, 5.15; 95% CI, 3.11 to 7.19) and sitagliptin (4.56; 95% CI, 2.56 to 6.57), but not pioglitazone (1.20; 95% CI, -0.87 to 3.28), which improved only on self-esteem. Improvements in IWQOL with exenatide ER were significantly greater compared to sitagliptin (treatment difference, 3.94; 95% CI, 1.28 to 6.61; P=0.0038). All treatments achieved improvements in all domains of the PGWB and DTSQ total score, with greater improvement in overall satisfaction recorded with exenatide ER (3.96; 95% CI, 2.78 to 5.15) compared to sitagliptin (2.35 [95% CI, 1.19 to 3.51]; treatment difference, 1.61 [95% CI, 0.07 to 3.16]; P=0.0406). 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.
Alba et al.[60] sitagliptin 100 mg QD vs pioglitazone 30 mg QD	DB, MC, PG, RCT Type 2 diabetics 30 to 65 years of age, and either drug-naive with	N=211 21 weeks	Primary: Five-hour and three-hour glucose/insulin AUC and measures of dynamic β-cell	Primary: After 12 weeks, five-hour glucose total area under the curve decreased in all active treatments versus placebo; reduction with sitagliptin and pioglitazone was greater vs either monotherapy. The five-hour insulin total AUC increased with sitagliptin vs all other treatments and increased with sitagliptin and pioglitazone vs pioglitazone. The three-hour glucagon AUC decreased with sitagliptin vs placebo and decreased with sitagliptin and pioglitazone vs

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs. sitagliptin 100 mg QD and pioglitazone 30 mg, QD vs placebo	HbA_{1c} ≥7% and ≤10%, or on antihyperglycaemic agent monotherapy or low-dose combination therapy with HbA_{1c} ≥6.5 and ≤9.0%.		responsiveness to above-basal glucose Concentrations Secondary: Not reported	pioglitazone or placebo. Measures of dynamic β-cell responsiveness to above-basal glucose concentrations, increased with either monotherapy vs placebo and increased with sitagliptin and pioglitazone vs either monotherapy. The insulin sensitivity index, a composite index of insulin sensitivity, improved with pioglitazone and sitagliptin and pioglitazone vs placebo. The disposition index, a measure of the relationship between β-cell function and insulin sensitivity, improved with all active treatments vs placebo. Secondary: Not reported
Russell-Jones et al[61] DRUATION-4 Exenatide ER 2 mg SC once weekly vs metformin 2,000 mg/day vs pioglitazone 45 mg/day vs sitagliptin 100 mg/day	DB, DD, MC, PG, RCT Drug-naïve (patients excluded if treated with any antihyperglycemic drug for >7 days within 3 months of screening) adult type 2 diabetics with HbA_{1c} 7.1 to 11.0%, BMI 23 to 45 kg/m^2, and stable weight	N=820 26 weeks	Primary: Change in baseline HbA_{1c} Secondary: Proportion of patients achieving HbA_{1c} <7.0 and ≤6.5%, fasting serum glucose, seven-point self-monitored glucose concentrations, weight, lipid profile, insulin profile, safety and tolerability, patient-reported quality of life	Primary: Decreases in HbA_{1c} were -1.53±0.07, -1.48±0.07, -1.63±0.08, and -1.15±0.08% with exenatide ER, metformin (P=0.620 vs exenatide ER), pioglitazone (P=0.328 vs exenatide ER), and sitagliptin (P<0.001 vs exenatide ER). The HbA_{1c} at trial end was 6.94±0.07, 6.99±0.07, 6.84±0.08, and 7.32±0.08% with exenatide ER, metformin, pioglitazone, and sitagliptin, respectively. Secondary: Similar proportions of patients receiving exenatide ER and metformin achieved HbA_{1c} <7.0% (63 vs 55%; P value not reported). A significantly greater proportion of patients receiving exenatide ER achieved HbA_{1c} <7.0% compared to patients receiving sitagliptin (63 vs 43%; P<0.001), and ≤6.5% compared to patients receiving metformin (49 vs 36%; P=0.004) and sitagliptin, respectively (49 vs 26%; P<0.001). Decreases in fasting serum glucose at weeks 16 and 26 were significantly greater with exenatide ER compared to sitagliptin (P<0.001 for both). There were no differences observed with exenatide ER compared to metformin (P=0.155 at week 26) and pioglitazone (P=0.153 at week 26). Seven-point self-monitored glucose concentrations demonstrated similar decreases with exenatide ER, metformin, and pioglitazone. Exenatide ER demonstrated greater decreases at all time points compared to sitagliptin.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Mean decreases in post-meal excursions after 26 weeks were similar among all treatments. Decreases in weight were significantly greater with exenatide ER compared to pioglitazone and sitagliptin by weeks four and eight, and the effect was sustained through 26 weeks (P≤0.003 for all). There was no difference between exenatide ER and metformin after 26 weeks (-2.0 vs -2.0 kg; P=0.892). No clinically significant changes in serum lipids were observed with any treatment. Mean HOMA-B was significantly improved with exenatide ER compared to metformin, pioglitazone, and sitagliptin (P<0.001 for all). HOMA-S significantly improved with metformin and pioglitazone compared to exenatide ER (P<0.001 for both), and the change with exenatide ER was similar to sitagliptin (P=0.329). Serious adverse events were reported in 1.6, 5.3, 5.5, and 1.8% of patients receiving exenatide ER, metformin, pioglitazone, and sitagliptin, respectively. No serious adverse event was reported by more than one patient. Treatment-emergent adverse events reported by at least five percent of patients in any group included headache (highest with metformin), diarrhea (highest with metformin), injection site nodule (highest with exenatide ER), nasopharyngitis (highest with sitagliptin), nausea (highest with exenatide ER), dyspepsia (highest with exenatide ER), constipation (highest with exenatide ER), back pain (highest with metformin), arthralgia (highest with exenatide ER), hypertension (highest with pioglitazone), and peripheral edema (highest with pioglitazone). No major hypoglycemia was reported. One patient receiving sitagliptin with elevated lipase at screening experienced moderate chronic pancreatitis after eight days and discontinued from study treatment. All treatments resulted in improvements in perceived treatment satisfaction, weight-related quality of life, and binge eating behavior. All treatments, except pioglitazone, resulted in significant improvements in health status. Significant improvements in weight-related quality of life, binge eating behavior, and

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				health status were reported with exenatide ER compared to pioglitazone (P values not reported).
Monami et al[62] DPP-4 inhibitors (linagliptin, alogliptin*, sitagliptin, saxagliptin, vildagliptin*) vs placebo or active comparator (oral hypoglycemic agents and/or insulin)	MA (53 trials) Patients with type 2 diabetes who were receiving a DPP-4 inhibitor	N=33,881 ≥24 weeks	Primary: Incidence of cancer Secondary: Incidence of pancreatitis, all-cause and cardiovascular mortality, incidence of major cardiovascular events	Primary: There were 176 cases of cancer (107 and 69 in patients receiving DPP-4 inhibitors and comparators, respectively); 12.5% were gastrointestinal, 5.7% were pancreatic, 6.2% were pulmonary, 14.7% were mammary gland/female genital tract, 11.3% were male urogenital tract, 3.4% were thyroid, and 26.1% were of another origin. There was no difference in the proportion of cases between patients receiving DPP-4 inhibitors or a comparator (P=0.90). Secondary: The risk of pancreatitis with DPP-4 inhibitors was 0.786 (P=0.55). The number of reported deaths was 28 and 31 with DPP-4 inhibitors and comparators, respectively. Cardiovascular deaths occurred in 10 patients receiving DPP-4 inhibitors and 20 patients receiving comparators. The risk for all-cause death and cardiovascular death in patients receiving DPP-4 inhibitors was 0.668 (P=0.149 and P=0.054, respectively). There were 137 and 120 major cardiovascular events reported with DPP-4 inhibitors and comparators, respectively. DPP-4 inhibitors were associated with a significantly lower risk of major cardiovascular events (OR, 0.689; P=0.006).
Fakhoury et al[63] Incretin-based therapies (exenatide, liraglutide, vildagliptin,* and sitagliptin) vs placebo	MA (38 RCTs: 8, exenatide; 7, liraglutide; 12, sitagliptin; 11, vildagliptin) Type 2 diabetics ≥18 years of age	N=Not reported Duration varied (4 to 52 weeks	Primary: Change in baseline HbA_{1c} and weight, hypoglycemia Secondary: Not reported	Primary: Sitagliptin (WMD, -0.79; 95% CI, -0.93 to -0.65; P<0.001) significantly decrease HbA_{1c} compared to placebo. Exenatide (WMD, -0.75; 95% CI, -0.83 to -0.67; P<0.001) and liraglutide (WMD, -1.03; 95% CI, -1.16 to -0.90; P<0.0010) significantly decreased baseline HbA_{1c}. In the adjusted analyses for exenatide, controlling for whether exenatide was given as monotherapy or in combination with another treatment provided the most variability, but even this estimate fell within the boundaries of the unadjusted model CI (WMD, -0.84; 95% CI, -0.95 to -0.73; P<0.001). In the adjusted analyses for liraglutide, no covariates were found to be significant. There was significant weight gain with sitagliptin (WMD, 0.60; 95% CI, 0.33 to 0.87; P<0.001) compared to placebo. Exenatide (WMD, -1.10; 95% CI, -1.32 to

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				-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
Richter et al[64] DPP-4 inhibitors (sitagliptin or vildagliptin*) as monotherapy or in combination with other hypoglycemic agents vs other hypoglycemic agents as monotherapy combination or lifestyle interventions	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 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[66]	MA, SR (5 RCTs)	N=not reported	Primary: Change in	Primary: Pooled analysis demonstrates modest decreases in HbA_{1c} favoring long-acting

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
GLP-1 receptor agonist, long-acting formulations at maximum doses (liraglutide, exenatide ER, albiglutide*, and lixisenatide*) vs exenatide and sitagliptin	Adult type 2 diabetics	Duration varied (not reported)	baseline HbA_{1c}, FPG, PPG, weight, BP, and lipid profile; safety Secondary: Not reported	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 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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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
Amori et al[67] Incretin-based therapies (exenatide, liraglutide, sitagliptin, and vildagliptin*) vs non-incretin-based therapy (placebo or hypoglycemic agent)	MA (29 RCTs) Type 2 diabetics	N=12,996 Duration varied (12 to 52 weeks)	Primary: Change in baseline HbA_{1c} Secondary: FPG, proportion of patients achieving an HbA_{1c} <7.0%	Primary: Pooled analysis of trials comparing GLP-1 analogues to placebo demonstrated a significant difference in the decrease in HbA_{1c} favoring GLP-1 analogues (WMD, -0.97; 95% CI, -1.13 to -0.81). Specifically, no difference in the HbA_{1c} was found in OL, non-inferiority trials between exenatide and insulin glargine or biphasic aspart (WMD, -0.06; 95% CI, -0.22 to 0.10). Liraglutide demonstrated similar HbA_{1c} efficacy compared to OL glimepiride titrated to glycemic goals or DB maximum dose metformin (data not reported). Secondary: Compared to placebo, FPG was significantly decreased with GLP-1 analogues (WMD, -27 mg/dL; 95% CI, -33 to -21).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Exenatide-treated patients were more likely to achieve an HbA_{1c} <7.0% compared to placebo treated patients (45 vs 10%, respectively; RR, 4.2; 95% CI, 3.2 to 5.5), while no difference in the proportions of patients achieving this goal was observed between exenatide and insulin therapy in NI trials (39 vs 35%, respectively; RR, 1.1; 95% CI, 0.8 to 1.5). Data with liraglutide were not reported.
Shyangdan et al[56] 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 quality of life, safety, mortality, morbidity, BP, FPG, PPG, lipid profile, β cell function	Primary: Change in baseline HbA_{1c} Exenatide ER significantly decreased HbA_{1c} compared to TZDs (-1.5 vs -1.2%; P=0.02), DPP-4 inhibitors (-1.5 vs -0.9%; P<0.0001), and insulin glargine (-1.5 vs -1.3%; treatment difference, -0.2%; 95% CI, -0.35 to -0.05; P=0.03). There was no difference in the proportion of patients achieving an HbA_{1c} <7.0% between exenatide ER and TZDs (60 vs 52%; P=0.15). A significantly greater proportion of patients receiving exenatide ER achieved an HbA_{1c} <7.0% compared to patients receiving DPP-4 inhibitors (60 vs 35%; P<0.0001) and patients receiving insulin glargine (60 vs 48%; P=0.03). Compared to placebo, treatment with liraglutide 1.2 mg significantly decreased HbA_{1c} (-1.15%; 95% CI, -1.33 to -0.96; P<0.00001). Patients receiving liraglutide 1.2 mg were more likely to achieve an HbA_{1c} <7.0% compared to patients receiving placebo (OR, 2.91; 95% CI, 1.74 to 4.87; P<0.05). Liraglutide 1.2 mg decreased HbA_{1c} to a greater extent compared to TZDs (-0.64%; 95% CI -0.83 to -0.45; P value not reported). The likelihood of achieving an HbA_{1c} <7.0% was greater with liraglutide 1.2 mg compared to TZDs (OR, 1.60; 95% CI, 1.18 to 2.15; P value not reported). Liraglutide 1.2 mg decreased HbA_{1c} to a greater extent compared to DPP-4 inhibitors (-0.34%; 95% CI, -0.53 to -0.15; P value not reported). The likelihood of achieving an HbA_{1c} <7.0% was greater with liraglutide 1.2 mg compared to DPP-4 inhibitors (OR, 2.56; 95% CI, 1.94 to 3.37; P value not reported). Liraglutide 1.2 mg was not associated with a decrease in HbA_{1c} compared to sulfonylureas (-0.01%; 95% CI -0.27 to 0.29; P value not reported). The likelihood of achieving an HbA_{1c} <7.0% was not greater with liraglutide 1.2 mg compared to sulfonylureas (OR, 0.98; 95% CI, 0.84 to 1.14; P=0.78). Compared to placebo, liraglutide 1.8 mg significantly decreased an HbA_{1c} (-

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				1.15%; 95% CI, -1.31 to -0.99; P<0.05). Patients receiving liraglutide 1.8 mg were more likely to achieve HbA_{1c} <7.0% compared to patients receiving placebo (OR, 3.25; 95% CI, 1.97 to 5.36; P<0.05). Liraglutide 1.8 mg decreased HbA_{1c} to a greater extent compared to TZDs (-0.69%; 95% CI -0.88 to -0.50%; P value not reported). The likelihood of achieving an HbA_{1c} <7.0% was greater with liraglutide 1.8 mg compared to TZDs (OR, 1.91; 95% CI, 1.43 to 2.53; P value not reported). Liraglutide 1.8 mg decreased HbA_{1c} to a greater extent compared to DPP-4 inhibitors (-0.60%; 95% CI -0.78 to -0.42; P value not reported). The likelihood of achieving HbA_{1c} <7.0% was greater with liraglutide 1.8 compared to DPP-4 inhibitors (OR, 1.99; 95% CI, 1.48 to 2.66; P value not reported). Liraglutide 1.8 mg was not associated with a reduction in HbA_{1c} compared to sulfonylureas (-0.02%; 95% CI -0.30 to 0.26; P value not reported). The likelihood of achieving an HbA_{1c} <7.0% was not greater with liraglutide 1.8 mg compared to sulfonylureas (OR, 1.09; 95% CI, 0.94 to 1.26; P=0.27). Liraglutide decreased HbA_{1c} to a greater extent compared to insulin glargine (-0.24%; 95% CI, -0.49 to 0.01; P value not reported). The likelihood of achieving an HbA_{1c} <7.0% was not different between insulin glargine and liraglutide (OR, 1.16; 95% CI, 0.96 to 1.40; P value not reported). Liraglutide 1.2 mg was associated with a non-significant increase in HbA_{1c} compared to 1.8 mg (0.10%; 95% CI, -0.03 to 0.23; P=0.13). Patients receiving liraglutide 1.2 mg were not more likely to achieve an HbA_{1c} <7.0% compared to the 1.8 mg dose (P=0.92). Incidence of hypoglycemia The incidence of minor hypoglycemia was similar between exenatide ER and TZDs. The incidence of minor hypoglycemia was higher with DPP-4 inhibitors (five vs two patients) and insulin glargine (26 vs 8%) compared to exenatide ER. The incidence of major hypoglycemia was higher with insulin glargine compared to exenatide ER (two vs one patients). Overall, there was no difference in the incidence of minor hypoglycemia between liraglutide 1.2 mg and placebo (P=0.42), and there was significantly more hypoglycemia with liraglutide 1.8 mg (OR, 1.66; 95% CI, 1.15 to 2.40;

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				P=0.007). The incidence of minor hypoglycemia was higher with insulin glargine compared to liraglutide (29 vs 27%). Liraglutide was associated with a significantly higher rate of minor hypoglycemia compared to TZDs (P=0.048), and similar rates compared to DPP-4 inhibitors (P values not reported). Liraglutide was associated with a significantly lower incidence of hypoglycemia compared to sulfonylureas (P<0.00001). Weight loss Exenatide ER significantly decreased weight compared to TZDs (-2.3 vs 2.8 kg; P<0.00001), DPP-4 inhibitors (-2.3 vs -0.8 kg; P=0.0009), and insulin glargine (-2.6 vs 1.4 kg; P<0.00001). Patients receiving liraglutide 1.2 mg experienced an average weight loss of -0.75 kg (95% CI, -1.95 to 0.45; P=0.22). Liraglutide 1.2 mg was associated with a greater decrease in weight compared to insulin glargine (-3.40 kg; 95% CI, -4.31 to -2.49; P value not reported), TZDs (-3.40 kg; 95% CI, -4.31 to -2.49; P value not reported), DPP-4 inhibitors (-1.90 kg; 95% CI, -2.65 to -1.15; P value not reported), and sulfonylureas (-3.60 kg; 95% CI, -4.15 to -3.05; P value not reported). Patients receiving liraglutide 1.8 mg experienced a significant weight loss compared to placebo (-1.33 kg; 95% CI, -2.38 to 0.27; P=0.0014). Liraglutide 1.8 mg was associated with a greater decrease in weight compared to TZDs (-2.30 kg; 95% CI, -2.85 to -1.75; P value not reported), DPP-4 inhibitors (-2.42 kg; 95% CI, -3.17 to -1.67; P value not reported), and sulfonylureas (-3.80 kg; 95% CI, -4.35 to -3.25; P value not reported). Patients were more likely to experience weight gain with liraglutide 1.2 compared to 1.8 mg (0.48 kg; 95% CI, 0.16 to 0.80; P value not reported). Secondary: Data on mortality and morbidity were not reported for any treatment. Quality of life Exenatide ER significantly improved weight-related quality of life and IWQOL total scores compared to TZDs (IWQOL treatment difference, 3.94; 95% CI,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				1.28 to 6.61; P=0.0038). Both exenatide ER (IWQOL total score, 5.15; 95% CI, 3.11 to 7.19) and DPP-4 inhibitors (4.56; 95% CI, 2.56 to 6.57) resulted in significant improvements in weight-related quality of life and IWQOL total scores. Treatment satisfaction was significantly greater with exenatide ER compared to DPP-4 inhibitors (treatment difference, 1.61; 95% CI, 0.07 to 3.16; P=0.0406). Exenatide ER significantly improved the self-esteem IWQOL domain and one EQ-5D dimensions compared to insulin glargine. Data for liraglutide were not reported. Safety Withdrawals due to adverse events were greater with exenatide ER compared to TZDs (6.9 vs 3.6%), DPP-4 inhibitors (6.9 vs 3.0%), and insulin glargine (4.7 vs 0.9%). More serious adverse events occurred with TZDs (6 vs 3%) compared to exenatide ER. The incidence of serious adverse events was similar between exenatide ER and DPP-4 inhibitors (3 vs 3%) and insulin glargine (5 vs 4%). Compared to placebo, withdrawals due to adverse events were between 5 and 10% with liraglutide 1.2 mg and between 4 and 15% with liraglutide 1.8 mg. Withdrawals were also higher with liraglutide compared to sulfonylureas (9.4 to 12.9 vs 1.3 to 3.0%). Liraglutide was associated with more gastrointestinal adverse events (nausea, vomiting, and diarrhea) compared to insulin glargine, TZDs, DPP-4 inhibitors, and sulfonylureas. BP There was no difference in the decreases in SBP and DBP between exenatide ER and TZDs. Exenatide ER significantly decreased SBP compared to DPP-4 inhibitors (treatment difference, -4 mm Hg; 95% CI, -6 to -1; P=0.0055). There was no difference in the decrease in DBP between treatments. Data comparing exenatide ER and insulin glargine were not reported. Liraglutide 1.2 mg did not significantly decrease SBP (P=0.15) compared to placebo (P=0.15) and DPP-4 inhibitors (P=0.76). Liraglutide 1.8 mg significantly decreased SBP (P=0.05) compared to placebo, but not DPP-4 inhibitors (P=0.86). Liraglutide also significantly decreased SBP compared to

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				insulin glargine (P=0.0001) and sulfonylureas (P value not reported). No difference in SBP was observed between liraglutide and DPP-4 inhibitors. There was no difference between liraglutide in the decrease in DBP compared to placebo, insulin glargine, or sulfonylureas. DPP-4 inhibitors significantly decreased DBP compared to liraglutide 1.8 mg (P value not reported). Data comparing liraglutide and TZDs were not reported. FPG There was no difference in the decrease in FPG between exenatide ER and TZDs (-1.8 vs -1.5 mmol/L; P=0.33). Exenatide ER significantly decreased FPG compared to DPP-4 inhibitors (-0.90 mmol/L; 95% CI, -1.50 to -0.30; P=0.0038), and insulin glargine significantly decreased FPG compared to exenatide ER (-0.70 mmol/L; 95% CI, 0.14 to 1.26; P=0.01). Liraglutide significantly decreased FPG compared to placebo (1.2 mg; P<0.0001 and 1.8 mg; P<0.00001), TZDs (P≤0.006), and DPP-4 inhibitors (P<0.00001). There was no difference between liraglutide and insulin glargine or sulfonylureas in decreases in FPG (P value not reported). PPG There was no difference in the decrease in PPG between exenatide ER and TZDs. Exenatide ER significantly decreased PPG at all measurements on a six-point self-monitored glucose concentrations profile compared to DPP-4 inhibitors (P<0.05). Both exenatide ER and insulin glargine decreased PPG at all eight time points, with significant difference in favor of exenatide ER after dinner (P=0.004) and insulin glargine at 03000 hour (P=0.022) and before breakfast (P<0.0001). Liraglutide significantly decreased PPG compared to placebo (P value not reported), TZDs (P<0.05), and sulfonylureas (liraglutide 1.8 mg; P<0.0001). There was no difference between liraglutide and insulin glargine in decreases in PPG (P value not reported). It was reported that PPG recorded in trials comparing liraglutide and DPP-4 inhibitors was highly variable. Lipid profile TZDs significantly decreased TG compared to exenatide ER. Exenatide ER

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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.
Schwarz et al[69] Scenario 1: Rosiglitazone added to metformin vs sitagliptin added to metformin Scenario 2: glipizide added to metformin vs sitagliptin added to metformin	Cost-effectiveness Type 2 diabetics not at target HbA_{1c} (>6.5%)	N=not reported Duration not reported	Primary: Costs of adding sitagliptin to metformin compared to glipizide or rosiglitazone Secondary: Not reported	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 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

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

*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, PRO=prospective, RCT=randomized-controlled trial, RR=relative risk, SA=single-arm, 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, QUICKI=Quantitative insulin sensitivity check index, SBP=systolic blood pressure, TC=total cholesterol, TG=triglycerides, TZD=thiazolidinedione

Special Populations

Table 5. Special Populations[2-12,76]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Single-Entity Agents					
Alogliptin	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients.	Renal dose adjustment is required; with moderate to severe renal dysfunction and end-stage renal disease, lower doses are recommended.	No dose adjustments are required in patients with mild to moderate hepatic impairment. Not studied with severe hepatic dysfunction.	B	Unknown; use with caution
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.	Renal dose adjustment is required; with moderate to severe renal dysfunction and end-stage renal disease, lower	No dosage adjustment required with mild to moderate hepatic dysfunction.	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.	doses are recommended.	Not studied with severe hepatic dysfunction.		
Combination Products					
Alogliptin/ metformin	Use with caution as elderly patients are more likely to have decreased renal function. 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.	Not studied with hepatic dysfunction; however, use is not recom-mended.	B	Unknown; use with caution.
Alogliptin/ pioglitazone	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients.	Renal dose adjustment is required; with moderate renal dysfunction, lower doses are recommended. Alogliptin/ pioglitazone is not recom-mended in patients with severe renal impairment or with end-stage renal disease.	No dose adjustments are required in patients with mild to moderate hepatic impairment. Not studied with severe hepatic dysfunction.	C	Unknown; use with caution.
Linagliptin/ metformin	Use with caution as elderly patients are more likely to have decreased renal function. Safety and efficacy in children have not been established.	Not studied with renal dysfunction; however, use is contraindicated.	Not studied in hepatic dysfunction; however, use is not recommended.	B	Unknown; use with caution.
Saxagliptin/ metformin	Use with caution as elderly patients are more likely to have decreased renal function.	Contraindicated with renal dysfunction.	Not studied with 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.				
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[2-12]

Adverse Event	Single-Entity Agents*				Combination Products*					
	Alogliptin	Linagliptin	Saxagliptin	Sitagliptin	Alogliptin/ Metformin†	Alogliptin/ Pioglitazone†	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	-	-	4.2	4.2	-	-	-	-
Cough	-	2.7	-	-	-	-	✔	-	-	-
Decreased appetite	-	-	-	-	-	-	✔	-	-	-
Diarrhea	-	-	-	3	5.5	-	6.3	5.8 to 9.9	2.4 to 7.5	-
Fracture	-	-	✔‡	-	-	-	-	-	-	-
Gastroenteritis	-	-	1.9 to 2.3	-	-	-	-	-	-	-
Headache	4.2	5.7	6.5 to 7.5	1.1 to 5.9	5.3	-	-	7.5	2.7 to 5.9	-
Hyperlipidemia	-	2.7	-	-	-	-	-	-	-	-
Hypersensitivity	0.8	✔	1.5	✔	-	-	✔	-	✔	-
Hypertension	-	-	-	-	5.5	-	-	-	-	-
Hypertriglyceridemia	-	2.4	-	-	-	-	-	-	-	-
Hypoglycemia	1.5 to 27	7.6 to 22.9	2.7 to 20.0	0.6 to 15.5	-	0.8 to 4.5	1.4 to 22.9	3.4 to 7.8	15.3 to 16.4	-
Infection	-	-	✔	-	-	-	-	-	-	-
Lymphopenia	-	-	0.5 to 1.5	-	-	-	-	-	-	-
Myalgia	-	✔	-	-	-	-	-	-	-	-
Nasopharyngitis	4.4	4.3	6.9	5.2 to 11.0	6.8	4.9	6.3	6.9	6.1 to 11.0	-
Nausea		-	-	1.4	-	-	✔	-	1.6 to 4.8	-
Pancreatitis	0.2	✔	✔	✔	-	-	✔	-	-	-
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	4.2	-	7.7	4.5 to 15.5	8.0	4.1	-	-	5.5 to 6.2	-
Urinary tract infection	-	-	6.8	-	4.2	-	-	-	-	-
Vomiting	-	-	2.2 to 2.3	-	-	-	✔	-	1.1 to 2.2	-
Weight gain	-	2.3	-	-	-	-	-	-	-	-

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

Contraindications/Precautions

Table 7. Contraindications[2-12]

Contraindication(s)	Single-Entity Agents				Combination Products					
	Alogliptin	Linagliptin	Saxagliptin	Sitagliptin	Alogliptin/ Metformin	Alogliptin/ Pioglitazone	Linagliptin/ Metformin	Saxagliptin/ Metformin	Sitagliptin/ Metformin	Sitagliptin/ Simvastatin
Active liver disease	-	-	-	-	-	-	-	-	-	✔
Acute or chronic metabolic acidosis, including diabetic ketoacidosis	-	-	-	-	✔	-	✔	✔	✔	-
Concomitant administration of strong cytochrome P450 3A4 inhibitors, gemfibrozil, cyclosporine, or danazol	-	-	-	-	-	-	-	-	-	✔
Congestive heart failure, New York Heart Association Class III or IV	-	-	-	-	-	✔	-	-	-	-
Hypersensitivity	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Nursing mothers	-	-	-	-	-	-	-	-	-	✔
Renal impairment	-	-	-	-	✔	-	✔	✔	✔	-
Women who are pregnant or may become pregnant	-	-	-	-	-	-	-	-	-	✔

Table 8. Warnings and Precautions[2-12]

Warning(s)/Precaution(s)	Single-Entity Agents				Combination Products					
	Alogliptin	Linagliptin	Saxagliptin	Sitagliptin	Alogliptin/ Metformin	Alogliptin/ Pioglitazone	Linagliptin/ Metformin	Saxagliptin/ Metformin	Sitagliptin/ Metformin	Sitagliptin/ Simvastatin
Alcohol intake; alcohol is known to potentiate the effect of metformin on lactate metabolism	-	-	-	-	-	-	✔	✔	✔	-
Bladder cancer: Preclinical and clinical trial data, and results from an observational study suggest an increased risk of bladder cancer in pioglitazone users. The observational data further	-	-	-	-	-	✔	-	-	-	-

Warning(s)/Precaution(s)	Single-Entity Agents				Combination Products					
	Alogliptin	Linagliptin	Saxagliptin	Sitagliptin	Alogliptin/ Metformin	Alogliptin/ Pioglitazone	Linagliptin/ Metformin	Saxagliptin/ Metformin	Sitagliptin/ Metformin	Sitagliptin/ Simvastatin
suggest that the risk increases with duration of use. Do not use in patients with active bladder cancer. Use caution when using in patients with a prior history of bladder cancer.										
Change in clinical status of patients with previously controlled type 2 diabetes; a patient with type 2 diabetes previously well controlled on therapy who develops laboratory abnormalities or clinical illness should be evaluated promptly for evidence of ketoacidosis or lactic acidosis	-	-	-	-	-	-	-	✔	✔	-
Concomitant medications affecting renal function or metformin; concomitant medications that may affect renal function or result in significant hemodynamic change or may interfere with the disposition of metformin, such as cationic drugs that are eliminated by renal tubular secretion, should be used with caution	-	-	-	-	-	-	-	✔	✔	-
Congestive heart failure: Fluid retention may occur and can exacerbate or lead to congestive heart failure. Combination use with insulin and use in congestive heart failure New York Heart Association Class I and II may increase risk. Monitor patients for signs and symptoms.	-	-	-	-	-	✔	-	-	-	-
Edema; Dose-related	-	-	-	-	-	✔	-	-	-	-

Warning(s)/Precaution(s)	Single-Entity Agents				Combination Products					
	Alogliptin	Linagliptin	Saxagliptin	Sitagliptin	Alogliptin/ Metformin	Alogliptin/ Pioglitazone	Linagliptin/ Metformin	Saxagliptin/ Metformin	Sitagliptin/ Metformin	Sitagliptin/ Simvastatin
edema may occur										
Endocrine function; increases in glycosylated hemoglobin and fasting serum glucose levels have been reported with hydroxymethylglutaryl coenzyme A reductase inhibitors, including simvastatin	-	-	-	-	-	-	-	-	-	✔
Fractures; Increased incidence in female patients. Apply current standards of care for assessing and maintaining bone health.	-	-	-	-	-	✔	-	-	-	-
Hepatic effects; Postmarketing reports of hepatic failure, sometimes fatal. Causality cannot be excluded.	✔	-	-	-	✔	✔	-	-	-	-
Hypersensitivity reactions; there have been postmarketing reports of serious hypersensitivity reactions with therapy	✔	-	✔	✔	✔	✔	✔	✔	✔	✔
Hypoxic states; cardiovascular collapse from whatever cause have been associated with lactic acidosis and may also cause prerenal azotemia, and if such events occur, therapy should be promptly discontinued	-	-	-	-	-	-	✔	✔	✔	-
Lactic acidosis; lactic acidosis is a serious, metabolic complication that can occur due to metformin accumulation during therapy	-	-	-	-	✔	-	✔	✔	✔	-
Liver dysfunction; persistent increases in serum transaminases have occurred in	-	-	-	-	-	-	-	-	-	✔

Warning(s)/Precaution(s)	Single-Entity Agents				Combination Products					
	Alogliptin	Linagliptin	Saxagliptin	Sitagliptin	Alogliptin/ Metformin	Alogliptin/ Pioglitazone	Linagliptin/ Metformin	Saxagliptin/ Metformin	Sitagliptin/ Metformin	Sitagliptin/ Simvastatin
approximately one percent of patients who received simvastatin in clinical trials; therefore, liver function tests should be performed before the initiation of treatment, and thereafter when clinically indicated										
Loss of control of blood glucose; when a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a temporary loss of glycemic control may occur, and at such times it may be necessary to temporarily withhold therapy	-	-	-	-	-	-	-	-	✔	-
Macrovascular outcomes; there have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with therapy or any other antidiabetic drug	✔	✔	✔	✔	✔	✔	✔	✔	✔	-
Macular edema: Postmarketing reports. Recommend regular eye exams in all patients with diabetes according to current standards of care with prompt evaluation for acute visual changes.	-	-	-	-	-	✔	-	-	-	-
Monitoring of renal function; risk of metformin accumulation and lactic acidosis increases with the degree of renal impairment	-	-	-	-	-	-	✔	✔	✔	-
Myopathy/rhabdomyolysis; simvastatin occasionally causes myopathy manifested as muscle	-	-	-	-	-	-	-	-	-	✔

Warning(s)/Precaution(s)	Single-Entity Agents				Combination Products					
	Alogliptin	Linagliptin	Saxagliptin	Sitagliptin	Alogliptin/ Metformin	Alogliptin/ Pioglitazone	Linagliptin/ Metformin	Saxagliptin/ Metformin	Sitagliptin/ Metformin	Sitagliptin/ Simvastatin
pain, tenderness, or weakness with creatine kinase above ten times the upper limit of normal (the risk of myopathy, including rhabdomyolysis, is dose related)										
Pancreatitis; there have been postmarketing reports of acute pancreatitis in patients receiving therapy	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Radiologic studies with intravascular iodinated contrast materials; intravascular contrast studies with iodinated materials can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving metformin, and therapy should be temporarily discontinued in patients undergoing such studies	-	-	-	-	✔	-	✔	✔	✔	-
Renal impairment; there have been postmarketing reports of altered renal function with therapy	-	-	-	✔	-	-	-	-	✔	✔
Surgical procedures; use of therapy should be temporarily suspended 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	-	-	-	-	-	-	-	✔	✔	-
Use of medications known to cause hypoglycemia;	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔

Warning(s)/Precaution(s)	Single-Entity Agents				Combination Products					
	Alogliptin	Linagliptin	Saxagliptin	Sitagliptin	Alogliptin/ Metformin	Alogliptin/ Pioglitazone	Linagliptin/ Metformin	Saxagliptin/ Metformin	Sitagliptin/ Metformin	Sitagliptin/ Simvastatin
patients receiving therapy in combination with an insulin secretagogue or insulin may have an increased risk of hypoglycemia										
Vitamin B_{12} levels; the risk of a decrease to subnormal levels of previously normal serum vitamin B_{12} levels may be relevant in patients receiving long term metformin therapy, and adverse hematologic and neurologic reactions have been reported postmarketing		-	-	-	✔	-	✔	✔	✔	-

Black Box Warning for Kazano® (alogliptin/ metformin)[6]

WARNING
Lactic acidosis is a rare, but serious, complication that 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. The onset of lactic acidosis is often subtle, accompanied only by nonspecific symptoms such as 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 Kazano® (alogliptin/metformin) should be discontinued and the patient hospitalized immediately.

Black Box Warning for Kombiglyze XR® (saxagliptin/metformin)[8]

WARNING
Lactic acidosis is a rare, but serious, complication that 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. The onset of lactic acidosis is often subtle, accompanied only by nonspecific symptoms such as 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 Kombiglyze XR® (saxagliptin/metformin extended-release) should be discontinued and the patient hospitalized immediately.

Black Box Warning for Oseni® (alogliptin/ pioglitazone)[11]

WARNING
Thiazolidinediones, including pioglitazone, which is a component of Oseni® (alogliptin/ pioglitazone), cause or exacerbate congestive heart failure in

WARNING
some patients. After initiation of Oseni® (alogliptin/ pioglitazone), and after dose increases, monitor patients carefully for signs and symptoms of heart failure (e.g., excessive, rapid weight gain, dyspnea, and/or edema). If heart failure develops, it should be managed according to current standards of care and discontinuation or dose reduction of pioglitazone in Oseni® (alogliptin/ pioglitazone) must be considered. OSENI is not recommended in patients with symptomatic heart failure. Initiation of Oseni® (alogliptin/ pioglitazone) in patients with established New York Heart Association (NYHA) Class III or IV heart failure is contraindicated

Black Box Warning for Janumet®/Janumet XR® (sitagliptin/metformin [extended-release])[9,10]

WARNING
Lactic acidosis is a rare, but serious complication that can occur due to metformin accumulation. The risk increases with conditions such as sepsis, dehydration, excess alcohol intake, hepatic insufficiency, renal impairment, and acute congestive heart failure. The onset is often subtle, accompanied only by nonspecific symptoms such as 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, Janumet® or Janumet XR® should be discontinued and the patient hospitalized immediately.

Black Box Warning for Jentadueto® (linagliptin/metformin)[7]

WARNING
Lactic acidosis is a rare, but serious, complication that can occur due to metformin accumulation. The risk increases with conditions such as renal impairment, sepsis, dehydration, excess alcohol intake, hepatic impairment, and acute congestive heart failure. The onset is often subtle, accompanied only by nonspecific symptoms such as 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, Jentadueto® should be discontinued and the patient hospitalized 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, pioglitazone, simvastatin) that are associated with clinically significant drug interactions. These interactions are outlined in Table 9.[77]

Table 9. Drug Interactions[77]

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)	Azole antifungals	Increased plasma concentrations and adverse reactions of HMG CoA reductase inhibitors may occur.
HMG CoA reductase inhibitors (simvastatin)	Fibric acid derivatives	Severe myopathy or rhabdomyolysis may occur.
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)	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)	Amiodarone	Plasma concentrations of HMG CoA reductase inhibitors may be elevated, increasing the risk of toxicity.
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)	Cobicistat	Plasma concentrations of HMG CoA reductase inhibitors may be elevated, increasing the pharmacologic effects and risk of adverse reactions. This combination is contraindicated.
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 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	Mifepristone	Plasma concentrations of HMG CoA reductase

Generic Name	Interacting Medication or Disease	Potential Result
inhibitors (simvastatin)		inhibitors may be elevated, increasing the pharmacologic effects and risk of adverse reactions.This combination is contraindicated.
HMG CoA reductase inhibitors (simvastatin)	Nefazodone	The risk of rhabdomyolysis and myositis may be increased.
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.
Thiazolidinediones (pioglitazone)	Gemfibrozil	Plasma concentrations of thiazolidinediones may be elevated, increasing hypoglycemic and other adverse effects (e.g., peripheral and pulmonary edema) of these agents.
Thiazolidinediones (pioglitazone)	Rifamycins	Plasma concentrations and half life of TZD may be decreased, decreasing the pharmacologic effect.

HMG CoA=hydroxymethylglutaryl coenzyme A, TZD= thiazolidinediones

Dosage and Administration

Table 10. Dosing and Administration[2-12]

Generic Name	Adult Dose	Pediatric Dose	Availability
Single-Entity Agents			
Alogliptin	Monotherapy or combination therapy as adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes: Tablet: 25 mg QD	Safety and efficacy in children have not been established.	Tablet: 6.25 mg 12.5 mg 25 mg
Linagliptin	Monotherapy or combination therapy as adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes: Tablet: 5 mg QD	Safety and efficacy in children have not been established.	Tablet: 5 mg
Saxagliptin	Monotherapy or combination therapy as adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes: Tablet: 2.5 or 5 mg QD	Safety and efficacy in children have not been established.	Tablet: 2.5 mg 5 mg
Sitagliptin	Monotherapy or combination therapy as adjunct to diet and exercise to improve 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
Combination Products			
Alogliptin/ metformin	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes: Tablet: initial, individualized starting dose based on patient's current regimen, administered BID with food; maximum, 25/2,000 mg daily	Safety and efficacy in children have not been established.	Tablet (alogliptin/ metformin): 12.5/500 mg 12.5/1000 mg
Alogliptin/ pioglitazone	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes:	Safety and efficacy in	Tablet (alogliptin/

Generic Name	Adult Dose	Pediatric Dose	Availability
	Tablet: initial, individualized starting dose based on patient's current regimen, administered QD; maximum, 25/45 mg daily	children have not been established.	pioglitazone): 12.5/15 mg 12.5/30 mg 12.5/45 mg 25/15 mg 25/30 mg 25/45 mg
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): 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): 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, QD=once daily

Clinical Guidelines

Current clinical guidelines are summarized in Table 11. 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 11. Clinical Guidelines

Clinical Guideline	Recommendations
American Diabetes Association: **Standards of Medical Care in Diabetes (2014)**[70]	Current criteria for the diagnosis of diabetes • Glycosylated hemoglobin (HbA_{1c}) ≥6.5%. The test should be performed in a laboratory using a method that is National Glycohemoglobin Standardization Program certified and standardized to the Diabetes Control and Complications Trial assay; or • Fasting plasma glucose (FPG) ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least eight hours; or • Two hour plasma glucose ≥200 mg/dL (11.1 mmol/L) during an oral glucose tolerance test. The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water; or • In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L); • In the absence of unequivocal hyperglycemia, result should be confirmed by repeat testing. Prevention/delay of type 2 diabetes • Patients with impaired glucose tolerance, impaired fasting glucose, or an HbA_{1c} 5.7 to 6.4% should be referred to an effective ongoing support program targeting weight loss of 7% of body weight and increasing physical activity to at least 150 min/week of moderate activity such as walking. • Follow-up counseling appears to be important for success. • Based on the cost-effectiveness of diabetes prevention, such programs should be covered by third-party payers. • Metformin therapy for prevention of type 2 diabetes may be considered in those with impaired glucose tolerance, impaired fasting glucose, or an HbA_{1c} 5.7 to 6.4%, especially for those with BMI >35 kg/m^2, aged, 60 years, and women with prior gestational diabetes. • At least annual monitoring for the development of diabetes in those with prediabetes is suggested. • Screening for and treatment of modifiable risk factors for cardiovascular disease (CVD) is suggested. Glucose monitoring • Patients on multiple-dose insulin or insulin pump therapy should do self-monitoring of blood glucose at least prior to meals and snacks, occasionally postprandially, at bedtime, prior to exercise, when they suspect low blood glucose, after treating low blood glucose until they are normoglycemic, and prior to critical tasks such as driving. • When prescribed as part of a broader educational context, self-monitoring of blood glucose results may be helpful to guide treatment decisions and/or patient self-management for patients using less frequent insulin injections or noninsulin therapies. • When prescribing self-monitoring of blood glucose, ensure that patients receive ongoing instruction and regular evaluation of self-monitoring of blood glucose technique and self-monitoring of blood glucose results, as well as their ability to use self-monitoring of blood glucose data to adjust therapy. • Continuous glucose monitoring in conjunction with intensive insulin regimens can be a useful tool to lower HbA_{1c} in selected adults (aged ≥25 years) with type 1 diabetes.

Clinical Guideline	Recommendations
	• Although the evidence for HbA_{1c} lowering is less strong in children, teens, and younger adults, continuous glucose monitoring may be helpful in these groups. Success correlates with adherence to ongoing use of the device. • Continuous glucose monitoring may be a supplemental tool to self-monitoring of blood glucose in those with hypoglycemia unawareness and/or frequent hypoglycemic episodes. HbA_{1c} • Perform the HbA_{1c} test at least two times a year in patients who are meeting treatment goals (and who have stable glycemic control). • Perform the HbA_{1c} test quarterly in patients whose therapy has changed or who are not meeting glycemic goals. • Use of point-of-care testing for HbA_{1c} provides the opportunity for more timely treatment changes. Glycemic goals in adults • Lowering HbA_{1c} to below or around 7.0% has been shown to reduce microvascular complications of diabetes, and if implemented soon after the diagnosis of diabetes is associated with long-term reduction in macrovascular disease. Therefore, a reasonable HbA_{1c} goal for many nonpregnant adults is <7.0%. • Providers might reasonably suggest more stringent HbA_{1c} goals (such as <6.5%) for selected individual patients, if this can be achieved without significant hypoglycemia or other adverse effects of treatment. Appropriate patients might include those with short duration of diabetes, long life expectancy, and no significant CVD. • Less stringent HbA_{1c} goals (such as <8.0%) 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 long-standing diabetes in whom the general goal is difficult to attain despite diabetes self-management education, appropriate glucose monitoring, and effective doses of multiple glucose-lowering agents including insulin. Pharmacologic and overall approaches to treatment-type 1 diabetes • Recommended therapy consists of the following components: o Use of multiple dose insulin injections (three to four injections per day of basal and pre-prandial insulin) or continuous subcutaneous insulin infusion therapy. o Matching prandial insulin to carbohydrate intake, pre-meal blood glucose, and anticipated activity. o For most patients (especially with hypoglycemia), use insulin analogs. o For patients with frequent nocturnal hypoglycemia and/or hypoglycemia unawareness, use of sensor-augmented low glucose suspend threshold pump may be considered. Pharmacologic and overall approaches to treatment-type 2 diabetes • Metformin, if not contraindicated and if tolerated, is the preferred initial pharmacological agent for type 2 diabetes. • In newly diagnosed type 2 diabetic patients with markedly symptomatic and/or elevated blood glucose levels or HbA_{1c}, consider insulin therapy,

Clinical Guideline	Recommendations
	with or without additional agents, from the outset. • If noninsulin monotherapy at maximal tolerated dose does not achieve or maintain the HbA_{1c} target over three to six months, add a second oral agent, a glucagon-like peptide-1 (GLP-1) receptor agonist, or insulin. • A patient-centered approach should be used to guide choice of pharmacological agents. Considerations include efficacy, cost, potential side effects, effects on weight, comorbidities, hypoglycemia risk, and patient preferences. • Due to the progressive nature of type 2 diabetes, insulin therapy is eventually indicated for many patients with type 2 diabetes.
American Diabetes Association/ European Association for the Study of Diabetes: **Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach (2012)**[71]	Key points • Glycemic targets and glucose-lowering therapies must be individualized. • Diet, exercise, and education remain the foundation of any type 2 diabetes treatment program. • Unless there are prevalent contraindications, metformin is the optimal first line drug. • After metformin, there are limited data to guide treatment decisions. Combination therapy with an additional one to two oral or injectable agents is reasonable, aiming to minimize side effects where possible. • Ultimately, many patients will require insulin therapy alone or in combination with other agents to maintain glucose control. • All treatment decisions, where possible, should be made in conjunction with the patient, focusing on his/her preferences, needs, and values. • Comprehensive cardiovascular risk reduction must be a major focus of therapy. Initial drug therapy • It is generally agreed that metformin, if not contraindicated and if tolerated, is the preferred and most cost-effective first agent. • Metformin should be initiated at, or soon after, diagnosis, especially in patients in whom lifestyle intervention alone has not achieved, or is unlikely to achieve, HbA_{1c} goals. • Patients with high baseline HbA_{1c} (e.g., ≥9.0%) have a low probability of achieving a near-normal target with monotherapy; therefore, it may be justified to start directly with a combination of two non-insulin agents or with insulin itself in this circumstance. • If a patient presents with significant hyperglycemic symptoms and/or has dramatically elevated plasma glucose concentrations or HbA_{1c} (e.g., ≥10.0 to 12.0%), insulin therapy should be strongly considered from the outset. Such therapy is mandatory when catabolic features are exhibited or, of course, if ketonuria is demonstrated, the latter reflecting profound insulin deficiency. • If metformin cannot be used, another oral agent could be chosen, such as a sulfonylurea/glinide, pioglitazone, or a dipeptidyl peptidase 4 (DPP-4) inhibitor; in occasional cases where weight loss is seen as an essential aspect of therapy, initial treatment with a GLP-1 receptor agonist might be useful. • Where available, less commonly used drugs (alpha-glucosidase inhibitors, colesevelam, bromocriptine) might also be considered in selected patients, but their modest glycemic effects and side effect profiles make them less attractive candidates. • Specific patient preferences, characteristics, susceptibilities to side

Clinical Guideline	Recommendations

effects, potential for weight gain, and hypoglycemia should play a major role in drug selection.

Advancing to dual combination therapy

- If monotherapy alone does not achieve/maintain HbA_{1c} target over approximately three months, the next step would be to add a second oral agent, a GLP-1 receptor agonist or basal insulin. Notably the higher the HbA_{1c}, the more likely insulin will be required.
- On average, any second agent is typically associated with an approximate further reduction in HbA_{1c} of approximately 1.0%.
- If no clinically meaningful glycemic reduction is demonstrated, then adherence having been investigated, that agent should be discontinued, and another with a different mechanism of action substituted.
- Uniform recommendations on the best agent to be combined with metformin cannot be made, thus advantages and disadvantages of specific drugs for each patient should be considered.
- It remains important to avoid unnecessary weight gain by optimal medication selection and dose titration.
- For all medications, consideration should also be given to overall tolerability.

Advancing to triple combination therapy

- Some trials have shown advantages of adding a third non-insulin agent to a two drug combination that is not yet or no longer achieving the glycemic target. However, the most robust response will usually be with insulin.
- Many patients, especially those with long standing disease, will eventually need to be transitioned to insulin, which should be favored in circumstances where the degree of hyperglycemia (e.g., HbA_{1c} ≥8.5%) makes it unlikely that another drug will be of sufficient benefit.
- In using triple combinations the essential consideration is to use agents with complementary mechanisms of action.
- Increasing the number of drugs heightens the potential for side effects and drug-drug interactions which can negatively impact patient adherence.

Anti-hyperglycemia Therapy in Type 2 Diabetes: General Recommendations

Initial Drug Monotherapy	Metformin				
Efficacy (↓HbA_{1c})	High				
Hypoglycemia	Low risk				
Weight	Neutral/loss				
Side Effects	Gastrointestinal/lactic acidosis				
If needed to reach individualized HbA_{1c} target after approximately three months, proceed to two drug combination therapy (order not meant to denote any specific preference)					
Two Drug Combin-ations	Metformin + sulfonylurea	Metformin + thia-zolidinedione (TZD)	Metformin + DPP-4 inhibitor	Metformin + GLP-1 receptor agonist	Metformin + insulin (usually basal)
Efficacy (↓HbA_{1c})	High	High	Inter-mediate	High	Highest
Hypoglycemia	Moderate risk	Low risk	Low risk	Low risk	High risk
Weight	Gain	Gain	Neutral	Loss	Gain

<table>
<tr><th>Clinical Guideline</th><th>Recommendations</th></tr>
<tr><td></td><td>
<table>
<tr><td>Major Side Effects</td><td>Hypo-glycemia</td><td>Edema, heart failure, bone fracture</td><td>Rare</td><td>Gastro-intestinal</td><td>Hypo-glycemia</td></tr>
<tr><td colspan="6">If needed to reach individualized HbA_{1c} target after approximately three months, proceed to three drug combination therapy (order not meant to denote any specific preference)</td></tr>
<tr><td>Three Drug Combin-ations</td><td>Metformin + sulfonylurea +</td><td>Metformin + TZD +</td><td>Metformin + DPP-4 inhibitor +</td><td>Metformin + GLP-1 receptor agonist +</td><td>Metformin + insulin therapy +</td></tr>
<tr><td></td><td>TZD, DPP-4 inhibitor, GLP-1 receptor agonist, or insulin</td><td>Sulfonylurea, or DPP-4 inhibitor, GLP-1 receptor agonist, or insulin</td><td>Sulfonyl-urea, TZD, or insulin</td><td>Sulfonyl-urea, TZD, or insulin</td><td>TZD, DPP-4 inhibitor, or GLP-1 receptor agonist</td></tr>
<tr><td colspan="6">If combination therapy that includes basal insulin has failed to achieve HbA_{1c} target after three to six months, proceed to a more complex insulin strategy, usually in combination with one or two non-insulin agents</td></tr>
<tr><td>More Complex Insulin Strategies</td><td colspan="5">Insulin (multiple daily doses)</td></tr>
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<tr><td>American College of Physicians: Oral Pharmacologic Treatment of Type 2 Diabetes Mellitus (2012)[72]</td><td>
• 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.
</td></tr>
<tr><td>American Association of Clinical Endocrinologists: Medical Guidelines for Clinical Practice for Developing a Diabetes Mellitus Comprehensive Care Plan (2011)[73]</td><td>
<u>Antihyperglycemic pharmacotherapy</u>
• The choice of therapeutic agents should be based on their differing metabolic actions and adverse effect profiles as described in the 2009 American Association of Clinical Endocrinologists/ American College of Endocrinology Diabetes Algorithm for Glycemic Control.[59]
• Insulin should be considered for patients with type 2 diabetes mellitus when noninsulin antihyperglycemic therapy fails to achieve target glycemic control or when a patient, whether drug naïve or not, has symptomatic hyperglycemia.
• Antihyperglycemic agents may be broadly categorized by whether they predominantly target FPG or postprandial glucose (PPG) levels. These effects are not exclusive; drugs acting on FPG passively reduce PPG, and drugs acting on PPG passively reduce FPG, but these broad categories can aid in therapeutic decision-making.
• TZDs and sulfonylureas are examples of oral agents primarily affecting FPG. Metformin and incretin enhancers (DPP-4 inhibitors) also favorably affect FPG.
• When insulin therapy is indicated in patients with type 2 diabetes to target FPG, therapy with long-acting basal insulin should be the initial choice in most cases; insulin analogues glargine and detemir are preferred over intermediate-acting neutral protamine Hagedorn (NPH) because they are associated with less hypoglycemia.
• The initial choice of an agent targeting FPG or PPG involves comprehensive patient assessment with emphasis given to the glycemic profile obtained by self-monitoring of blood glucose.
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Clinical Guideline	Recommendations
	• When postprandial hyperglycemia is present, glinides and/or α-glucosidase inhibitors, short- or rapid-acting insulin, and metformin should be considered. Incretin-based therapy (DPP-4 inhibitors and GLP-1 receptor agonists) also target postprandial hyperglycemia in a glucose-dependent fashion, which reduces the risks of hypoglycemia. • When control of postprandial hyperglycemia is needed and insulin is indicated, rapid-acting insulin analogues are preferred over regular human insulin because they have a more rapid onset and offset of action and are associated with less hypoglycemia. • Pramlintide can be used as an adjunct to prandial insulin therapy to reduce postprandial hyperglycemia, HbA_{1c}, and weight. • Premixed insulin analogue therapy may be considered for patients in whom adherence to a drug regimen is an issue; however, these preparations lack component dosage flexibility and may increase the risk for hypoglycemia compared to basal insulin or basal-bolus insulin. Basal-bolus insulin therapy is flexible and is recommended for intensive insulin therapy. • Intensification of pharmacotherapy requires glucose monitoring and medication adjustment at appropriate intervals when treatment goals are not achieved or maintained. • Most patients with an initial HbA_{1c} level >7.5% will require combination therapy using agents with complementary mechanisms of action.
American Association of Clinical Endocrinologists: American Association of Clinical Endocrinologists: **Comprehensive Diabetes Management Algorithm 2013 Consensus Statement (2013)**[74]	Principles underlying the algorithm • Lifestyle optimization is essential for all patients with diabetes; however, should not delay needed pharmacotherapy, which can be initiated simultaneously and adjusted based on patient response to lifestyle efforts. The need for medical therapy should not be interpreted as a failure of lifestyle management, but as an adjunct to it. • Achieving an HbA_{1c} ≤6.5% is recommended as the primary goal if it can be achieved in a safe and affordable manner; however, higher targets may be appropriate for certain individuals and may change for a given individual over time. • Minimizing risk of hypoglycemia and weight gain is a priority. It is a matter of safety, adherence, and cost. • For optimal glycemic control, therapies with complementary mechanisms of action must typically be used in combination. • Therapeutic effectiveness must be evaluated frequently until stable (e.g., every three months). • Safety and efficacy should be given higher priority than the initial acquisition cost of medications, as medication cost is only a small part of the total cost of diabetes care. In assessing the cost of a medication, consideration should be given to monitoring requirements and risks of hypoglycemia and weight gain. • Rapid-acting insulin analogs are superior to regular insulin because they are more predictable. • Long-acting insulin analogs are superior to neutral protamine Hagedorn (NPH) insulin because they provide a fairly flat response for approximately 24 hours and provide better reproducibility and consistency, both between and within patients, with a corresponding reduction in hypoglycemia risk. Monotherapy • Patients with recent-onset diabetes and those with mild hyperglycemia

Clinical Guideline	Recommendations
	(HbA_{1c} ≤7.5%), initial monotherapy with metformin (at doses of 1,500 to 2,000 mg/day) and life-style modifications will achieve their glycemic goals in a majority of patients. • In patients with intolerance or contraindications to metformin, acceptable therapeutic alternatives that reduce glucose without weight gain or hypoglycemia (in order based on suggested hierarchy of usage) include: o GLP-1 receptor agonists. o DPP-4 inhibitors. o Alpha-glucosidase inhibitors. o Sodium glucose cotransporter 2 (SGLT-2) inhibitors. • TZD, sulfonylurea, and glinides (in order based on suggested hierarchy of usage) may be used but with caution due to possible weight gain and hypoglycemia. <u>Combination therapy</u> • Patients who present with an initial HbA_{1c} ≥7.5% or who do not reach their target HbA_{1c} with metformin in three months should be started on a second agent to be used in combination with metformin. • Patients who present with an initial HbA_{1c} >9.0% with no symptoms should be started on combination therapy or three-drug combination therapy. • In metformin-intolerant patients, two drugs from other classes with complimentary mechanisms of action should be used. • Combination (in order based on suggested hierarchy of usage) include metformin (or other first-line agent) plus: o GLP-1 receptor agonists. o DPP-4 inhibitors. o TZD. o SGLT-2 inhibitors. o Basal insulin. o Colesevelam. o Bromocriptine quick release. o Alpha-glucosidase inhibitors. o Sulfoureas and glinides. <u>Three-drug combination therapy</u> • Generally, the efficacy of a third antidiabetic agent added to dual therapy is reduced compared to the efficacy of the same drug used as monotherapy or combination therapy with one other agent. • Patients who present with an initial HbA_{1c} >9.0% with no symptoms should be started on combination therapy or three-drug combination therapy. • Patients who present with an HbA_{1c} <8.0% or who do not reach their target HbA_{1c} with two antidiabetic drugs after 3 months has a high likelihood of reaching target with a third agent. • Patients who present with an HbA_{1c} >9.0% or who do not reach their target HbA_{1c} with two antidiabetic drugs has are less likely of reaching target with a third agent or fourth agent and insulin should be considered. • Continuation with noninsulin therapies while starting basal insulin is common and does not increase cardiovascular risk, but may increase risk of hypoglycemia when sulfourea are used in conjunction with insulin. • Three-drug combination (in order based on suggested hierarchy of usage) include metformin (or other first-line agent), a second-line agent

Clinical Guideline	Recommendations
	plus: o GLP-1 receptor agonists. o TZD. o SGLT-2 inhibitors. o Basal insulin. o DPP-4 inhibitors. o Colesevelam. o Bromocriptine quick release. o Alpha-glucosidase inhibitors. o Sulfoureas and glinides Insulin therapy algorithm • Patients who present with an initial HbA_{1c} >9.0% and are symptomatic, should initiate therapy with insulin with or without other antidiabetic agents. • Start insulin if a patient has marked hyperglycemia despite treatment with several oral antidiabetic agents and is symptomatic with polyuria and weight loss. • Patients who are not at target HbA_{1c} despite the use of oral antidiabetic agents or GLP-1 therapy should be considered for insulin therapy. • Patients with an HbA_{1c} level >8.0% while receiving ≥2 antidiabetic agents, particularly individuals with long duration of diabetes, have significant impairment of beta cell insulin secretory capacity and are unlikely to reach the recommended target by the addition of further oral antidiabetic drugs. Basal insulin • Patients with an HbA_{1c} level >8.0% while receiving ≥2 oral antidiabetic agents or GLP-1 therapy can be started on single daily dose of basal insulin as an add-on to the patient's existing regimen. • Titrate insulin dose every two to three days to reach glycemic goals. • Basal insulin analogues (glargine and detemir) are preferred over NPH insulin because they have been shown to provide a relatively flat serum insulin concentration for up to 24 hours from a single daily injection. • Patients who fail to achieve glucose control with basal insulin or premixed insulin formulations can also be considered for basal intensification with a DPP-4 inhibitor or GLP-1 receptor agonist if the glucose level is not markedly elevated, because this approach tends to not cause weight gain or additional hypoglycemia. Basal-bolus insulin regimens • Patients who fail to achieve glucose control with basal insulin or premixed insulin formulations and those with symptomatic hyperglycemia and HbA_{1c} >10% often respond better to combined basal and mealtime bolus insulin. • A full basal-bolus program with an insulin basal analogue once or twice daily and a rapid-acting analogue at each meal is most effective and provides flexibility for patients with variable mealtimes and meal carbohydrate content. • Doses of insulin may be titrated every two to three days to reach glycemic goals. Basal insulin and incretin therapy regimens

Clinical Guideline	Recommendations
	• Use of the amylin analog pramlintide in conjunction with bolus insulin improves both glycemia and weight in patients with type 2 diabetes. • The incretin therapies (GLP-1 receptor agonists and DPP-4 inhibitors) have similar properties, and also increase endogenous insulin secretion. Therefore, the combination of basal insulin and incretin therapy decreases basal and postprandial glucose and may minimize the weight gain and hypoglycemia risk observed with basal-bolus insulin replacement.
American Association of Clinical Endocrinologists: **Medical Guidelines for Clinical Practice for the Management of Diabetes Mellitus (2007)**[75]	Glycemic management-all patients with diabetes • Encourage patients to achieve glycemic levels as near normal as possible without inducing clinically significant hypoglycemia. 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. Glycemic management-patients with type 2 diabetes • 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 has 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 SC 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

Clinical Guideline	Recommendations
	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. • 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. <u>Clinical support-clinical considerations in patients with type 1 diabetes</u> • Instruct patients to administer pre-prandial rapid-acting analog insulin 20 to 30 minutes before the meal when the pre-meal blood glucose levels is high and after the meal has begun when the pre-meal blood glucose level is below the reference range. • Measure 2:00 to 3:00 AM blood glucose periodically in all patients with diabetes to asses for nocturnal hypoglycemia, especially when the morning blood glucose level is elevated. • Consider using regular insulin instead of rapid-acting insulin analogs to obtain better control of post-prandial and pre-meal glucose levels in patients with gastroparesis. Insulin pump therapy may also be advantageous in these patients. • Some type 1 diabetics treated with basal insulin may require two daily injections of basal insulin for greater stability. • Carefully assess PPG levels when the HbA_{1c} level is elevated and pre-meal 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. • Arrange for continuous glucose monitoring for patients with unstable glucose control and for patients unable to achieve an acceptable HbA_{1c} level. Continuous glucose monitoring is particularly valuable in detecting both unrecognized nocturnal hypoglycemia and post-prandial hyperglycemia. • Some patients using pramlintide may achieve better post-prandial and pre-meal glucose control by combining it with regular insulin rather than rapid-acting analogs.

Clinical Guideline	Recommendations
	• Individualize insulin regimens to accommodate patient exercise patterns. • Treat hypoglycemic reactions with simple carbohydrates. 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 NPH insulin.
American College of Cardiology/American Heart Association Task Force on Practice Guidelines: **Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults (2013)**[78]	Statin treatment • The panel makes no recommendations for or against specific low density lipoprotein cholesterol (LDL-C) or non-high density lipoprotein cholesterol (HDL-C) targets for the primary or secondary prevention of arteriosclerotic cardiovascular disease (ASCVD). • High-intensity statin therapy should be initiated or continued as first-line therapy in women and men ≤75 years of age that have clinical ASCVD, unless contraindicated. • In individuals with clinical ASCVD in whom high-intensity statin therapy would otherwise be used, when high-intensity statin therapy is contraindicated or when characteristics predisposing to statin-associated adverse effects are present, moderate-intensity statin should be used as the second option if tolerated. • In individuals with clinical ASCVD >75 years of age, it is reasonable to evaluate the potential for ASCVD risk-reduction benefits and for adverse effects, drug-drug interactions and to consider patient preferences, when initiating a moderate- or high-intensity statin. It is reasonable to continue statin therapy in those who are tolerating it. • Adults ≥21 years of age with primary LDL-C ≥190 mg/dL should be treated with statin therapy (10-year ASCVD risk estimation is not required): use high-intensity statin therapy unless contraindicated. For individuals unable to tolerate high-intensity statin therapy, use the maximum tolerated statin intensity. • For individual's ≥21 years of age with an untreated primary LDL-C ≥190 mg/dL, it is reasonable to intensify statin therapy to achieve at least a 50% LDL-C reduction.

Clinical Guideline	Recommendations
	• For individuals ≥21 years of age with an untreated primary LDL-C ≥190 mg/dL, after the maximum intensity of statin therapy has been achieved, addition of a nonstatin drug may be considered to further lower LDL-C. Evaluate the potential for ASCVD risk reduction benefits, adverse effects, drug-drug interactions, and consider patient preferences. • Moderate-intensity statin therapy should be initiated or continued for adults 40 to 75 years of age with diabetes mellitus. • High-intensity statin therapy is reasonable for adults 40 to 75 years of age with diabetes mellitus with a ≥7.5% estimated 10-year ASCVD risk unless contraindicated. • In adults with diabetes mellitus, who are <40 or >75 years of age, it is reasonable to evaluate the potential for ASCVD benefits and for adverse effects, for drug-drug interactions, and to consider patient preferences when deciding to initiate, continue, or intensify statin therapy. • Adults 40 to 75 years of age with LDL-C 70 to 189 mg/dL, without clinical ASCVD or diabetes and an estimated 10-year ASCVD risk ≥7.5% should be treated with moderate- to high-intensity statin therapy. • It is reasonable to offer treatment with a moderate intensity statin to adults 40 to 75 years of age, with LDL-C 70 to 189 mg/dL, without clinica ASCVD or diabetes and an estimated 10-year ASCVD risk of 5.0 to <7.5%. • Before initiating statin therapy for the primary prevention of ASCVD in adults with LDL-C 70 to 189 mg/dL without clinical ASCVD or diabetes it is reasonable for clinicians and patients to engage in a discussion which considers the potential for ASCVD risk reduction benefits and for adverse effects, for drug-drug interactions, and patient preferences for treatment. • In adults with LDL-C <190 mg/dL who are not otherwise identified in a statin benefit group, or for whom after quantitative risk assessment a risk based treatment decision is uncertain, additional factors may be considered to inform treatment decision making. In these individuals, statin therapy for primary prevention may be considered after evaluating the potential for ASCVD risk reduction benefits, adverse effects, drug-drug interactions, and discussion of patient preference. <u>Statin safety</u> • To maximize the safety of statins, selection of the appropriate statin and dose in men and nonpregnant/nonnursing women should be based on patient characteristics, level of ASCVD risk, and potential for adverse effects. • Moderate-intensity statin therapy should be used in individuals in whom high-intensity statin therapy would otherwise be recommended when characteristics predisposing them to statin associated adverse effects are present. • Characteristics predisposing individuals to statin adverse effects include, but are not limited to: o Multiple or serious comorbidities, including impaired renal or hepatic function. o History of previous statin intolerance or muscle disorders. o Unexplained alanine transaminase elevations >3 times upper limit of normal. o Patient characteristics or concomitant use of drugs affecting statin metabolism. o >75 years of age.

Clinical Guideline	Recommendations
	• Additional characteristics that may modify the decision to use higher statin intensities may include, but are not limited to: o History of hemorrhagic stroke. o Asian ancestry. • Creatine kinase should not be routinely measured in individuals receiving statin therapy. • Baseline measurement of creatinine kinase is reasonable for individuals believed to be at increased risk for adverse muscle events based on a personal or family history of statin intolerance or muscle disease, clinical presentation, or concomitant drug therapy that might increase the risk for myopathy. • During statin therapy, it is reasonable to measure creatinine kinase in individuals with muscle symptoms, including pain, tenderness, stiffness, cramping, weakness, or generalized fatigue. • Baseline measurement of hepatic transaminase levels should be performed before initiating statin therapy. • During statin therapy, it is reasonable to measure hepatic function if symptoms suggesting hepatotoxicity arise (e.g., unusual fatigue or weakness, loss of appetite, abdominal pain, dark colored urine or yellowing of the skin or sclera). • Decreasing the statin dose may be considered when two consecutive values of LDL-C levels are <40 mg/dL. • It may be harmful to initiate simvastatin at 80 mg daily or increase the dose of simvastatin to 80 mg daily. • Individuals receiving statin therapy should be evaluated for new-onset diabetes mellitus according to the current diabetes screening guidelines. Those who develop diabetes mellitus during statin therapy should be encouraged to adhere to a heart healthy dietary pattern, engage in physical activity, achieve and maintain a healthy body weight, cease tobacco use, and continue statin therapy to reduce their risk of ASCVD events. • For individuals taking any dose of statins, it is reasonable to use caution in individuals >75 years of age, as well as in individuals that are taking concomitant medications that alter drug metabolism, taking multiple drugs, or taking drugs for conditions that require complex medication regimens (e.g., those who have undergone solid organ transplantation or are receiving treatment for human immunodeficiency virus (HIV). A review of the manufacturer's prescribing information may be useful before initiating any cholesterol-lowering drug. • It is reasonable to evaluate and treat muscle symptoms, including pain, tenderness, stiffness, cramping, weakness, or fatigue, in statin-treated patients according to the following management algorithm: o To avoid unnecessary discontinuation of statins, obtain a history of prior or current muscle symptoms to establish a baseline before initiating statin therapy. o If unexplained severe muscle symptoms or fatigue develop during statin therapy, promptly discontinue the statin and address the possibility of rhabdomyolysis by evaluating creatinine kinase, creatinine, and a urinalysis for myoglobinuria. • If mild to moderate muscle symptoms develop during statin therapy: o Discontinue the statin until the symptoms can be evaluated. o Evaluate the patient for other conditions that might increase the risk for muscle symptoms (e.g., hypothyroidism, reduced renal or

Clinical Guideline	Recommendations
	hepatic function, rheumatologic disorders such as polymyalgia rheumatica, steroid myopathy, vitamin D deficiency, or primary muscle diseases). o If muscle symptoms resolve, and if no contraindication exists, give the patient the original or a lower dose of the same statin to establish a causal relationship between the muscle symptoms and statin therapy. o If a causal relationship exists, discontinue the original statin. Once muscle symptoms resolve, use a low dose of a different statin. o Once a low dose of a statin is tolerated, gradually increase the dose as tolerated. o If, after two months without statin treatment, muscle symptoms or elevated creatinine kinase levels do not resolve completely, consider other causes of muscle symptoms listed above. o If persistent muscle symptoms are determined to arise from a condition unrelated to statin therapy, or if the predisposing condition has been treated, resume statin therapy at the original dose. • For individuals presenting with a confusional state or memory impairment while on statin therapy, it may be reasonable to evaluate the patient for nonstatin causes, such as exposure to other drugs, as well as for systemic and neuropsychiatric causes, in addition to the possibility of adverse effects associated with statin drug therapy. <u>Monitoring and optimizing statin therapy</u> • Adherence to medication and lifestyle, therapeutic response to statin therapy, and safety should be regularly assessed. This should also include a fasting lipid panel performed within four to 12 weeks after initiation or dose adjustment, and every three to 12 months thereafter. Other safety measurements should be measured as clinically indicated. • The maximum tolerated intensity of statin should be used in individuals for whom a high- or moderate-intensity statin is recommended, but not tolerated. • Individuals who have a less-than anticipated therapeutic response or are intolerant of the recommended intensity of statin therapy, the following should be performed: o Reinforce medication adherence. o Reinforce adherence to intensive lifestyle changes. o Exclude secondary causes of hyperlipidemia. • It is reasonable to use the following as indicators of anticipated therapeutic response to the recommended intensity of statin therapy. Focus is on the intensity of the statin therapy. As an aid to monitoring: o High-intensity statin therapy generally results in an average LDL-C reduction of ≥50% from the untreated baseline; o Moderate-intensity statin therapy generally results in an average LDL-C reduction of 30 to <50% from the untreated baseline; o LDL-C levels and percent reduction are to be used only to assess response to therapy and adherence. They are not to be used as performance standards. • Individuals at higher ASCVD risk receiving the maximum tolerated intensity of statin therapy who continue to have a less than-anticipated therapeutic response, addition of a nonstatin cholesterol-lowering drug(s)

Clinical Guideline	Recommendations
	may be considered if the ASCVD risk-reduction benefits outweigh the potential for adverse effects. • Higher-risk individuals include: o Individuals with clinical ASCVD <75 years of age. o Individuals with baseline LDL-C ≥190 mg/dL. o Individuals 40 to 75 years of age with diabetes mellitus. o Preference should be given to nonstatin cholesterol-lowering drugs shown to reduce ASCVD events in controlled trials. • In individuals who are candidates for statin treatment but are completely statin intolerant, it is reasonable to use nonstatin cholesterol lowering drugs that have been shown to reduce ASCVD events in controlled trials if the ASCVD risk-reduction benefits outweigh the potential for adverse effects. Non statin safety • Baseline hepatic transaminases, fasting blood glucose or hemoglobin A1c, and uric acid should be obtained before initiating niacin, and again during up-titration to a maintenance dose and every six months thereafter. • Niacin should not be used if: o Hepatic transaminase elevations are higher than two to three times upper limit of normal. o Persistent severe cutaneous symptoms, persistent hyperglycemia, acute gout or unexplained abdominal pain or gastrointestinal symptoms occur. o New-onset atrial fibrillation or weight loss occurs. • In individuals with adverse effects from niacin, the potential for ASCVD benefits and the potential for adverse effects should be reconsidered before reinitiating niacin therapy. • To reduce the frequency and severity of adverse cutaneous symptoms, it is reasonable to: o Start niacin at a low dose and titrate to a higher dose over a period of weeks as tolerated. o Take niacin with food or premedicating with aspirin 325 mg 30 minutes before niacin dosing to alleviate flushing symptoms. o If an extended-release preparation is used, increase the dose of extended-release niacin from 500 mg to a maximum of 2,000 mg/day over four to eight weeks, with the dose of extended release niacin increasing not more than weekly. o If immediate-release niacin is chosen, start at a dose of 100 mg three times daily and up-titrate to 3 g/day, divided into two or three doses. • Bile acid sequestrants should not be used in individuals with baseline fasting triglyceride levels ≥300 mg/dL or type III hyperlipoproteinemia, because severe triglyceride elevations might occur. • A fasting lipid panel should be obtained before bile acid sequestrants are initiated, three months after initiation, and every six to 12 months thereafter. • It is reasonable to use bile acid sequestrants with caution if baseline triglyceride levels are 250 to 299 mg/dL, and evaluate a fasting lipid panel in four to six weeks after initiation. Discontinue the bile acid sequestrants if triglycerides exceed 400 mg/dL. • It is reasonable to obtain baseline hepatic transaminases before initiating

Clinical Guideline	Recommendations
	ezetimibe. When ezetimibe is coadministered with a statin, monitor transaminase levels as clinically indicated, and discontinue ezetimibe if persistent alanine transaminase elevations >3 times upper limit of normal occur. • Gemfibrozil should not be initiated in patients on statin therapy because of an increased risk for muscle symptoms and rhabdomyolysis. • Fenofibrate may be considered concomitantly with a low- or moderate-intensity statin only if the benefits from ASCVD risk reduction or triglyceride lowering when triglycerides are >500 mg/dL, are judged to outweigh the potential risk for adverse effect. • Renal status should be evaluated before fenofibrate initiation, within three months after initiation, and every six months thereafter. Assess renal safety with both a serum creatinine level and an estimated glomerular filtration rate based on creatinine. • Fenofibrate should not be used if moderate or severe renal impairment, defined as estimated glomerular filtration rate <30 mL/min per 1.73 m^2, is present. • If estimated glomerular filtration rate is between 30 and 59 mL/min per 1.73 m^2, the dose of fenofibrate should not exceed 54 mg/day. • If, during follow-up, the estimated glomerular filtration rate decreases persistently to ≤30 mL/min per 1.73 m^2, fenofibrate should be discontinued. • If eicosapentaenoic acid and/or docosahexanoic acid are used for the management of severe hypertriglyceridemia, defined as triglycerides ≥500 mg/dL, it is reasonable to evaluate the patient for gastrointestinal disturbances, skin changes, and bleeding.
National Cholesterol Education Program: **Implications of Recent Clinical Trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines (2004)**[79]	• Therapeutic lifestyle changes remain an essential modality in clinical management. • When 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 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 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 and low HDL-C, especially in combination with statins. • In high risk patients with high triglycerides 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 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

Clinical Guideline	Recommendations
	HDL-C. Treatment of heterozygous familial hypercholesterolemia • Begin LDL-C lowering drugs in young adulthood. • Therapeutic lifestyle changes 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). Treatment of homozygous familial hypercholesterolemia • Statins may be moderately effective in some persons. • LDL-pheresis currently employed therapy (in some persons, statin therapy may slow down rebound hypercholesterolemia). Treatment of familial defective apolipoprotein B-100 • Therapeutic lifestyle changes indicated. • All LDL-C lowering drugs are effective. • Combined drug therapy required less often than in heterozygous familial hypercholesterolemia. Treatment of polygenic hypercholesterolemia • Therapeutic lifestyle changes 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 Adults (Adult Treatment Panel III) Final Report (2002)**[80]	General recommendations • With regards to therapeutic lifestyle changes, higher dietary intakes of omega-3 fatty acids in the form of fatty fish or vegetable oils are an option for reducing risk for coronary heart disease. 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 coronary heart disease 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 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. Statins • Statins should be considered as first-line drugs when LDL-lowering drugs are indicated to achieve LDL treatment goals. Bile acid sequestrants • 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

Clinical Guideline	Recommendations
	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. Nicotinic acid • 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. Fibric acid derivatives (fibrates) • 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 coronary heart disease 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. Omega-3 fatty acids • Omega-3 fatty acids (e.g., linolenic acid, docosahexaenoic acid, eicosapentaenoic acid) have two potential uses. • In higher doses, docosahexaenoic acid and eicosapentaenoic acid lower serum triglycerides by reducing hepatic secretion of triglyceride-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 coronary heart disease. 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	Lipid management • Goal: treatment with statin therapy; use statin therapy to achieve LDL-C of <100 mg/dL; for very high risk patients an LDL-C <70 mg/dL is reasonable; if triglycerides are ≥200 mg/dL, non-HDL-C should be <130 mg/dL, whereas non-HDL-C <100 mg/dL for very high risk patients is

Clinical Guideline	Recommendations
Blood Institute: **American Heart Association/ American College of Cardiology Guidelines for Secondary Prevention for Patients With Coronary and Other Atherosclerotic Vascular Disease: 2011 Update (2011)**[81]	reasonable. • Lifestyle modifications (daily physical activity and weight management) are strongly recommended for all patients. • In addition to lifestyle modifications, statin therapy should be prescribed in the absence of contraindications or documented adverse events. • An adequate dose of statin should be used that reduces LDL-C to <100 mg/dL and achieves ≥30% lowering of LDL-C. • Patients who have triglyceride ≥200 mg/dL should be treated with statins to lower non-HDL-C to <130 mg/dL. • Patients who have triglyceride >500 mg/dL should be started on fibrate therapy in addition to statin therapy to prevent acute pancreatitis. • If treatment with a statin does not achieve the goal selected for an individual patient, intensification of LDL-C-lowering drug therapy with a bile acid sequestrant or niacin is reasonable. • For patients who do not tolerate statins, LDL-C-lowering therapy with bile acid sequestrants and/or niacin is reasonable. • It is reasonable to treat very high risk patients with statin therapy to lower LDL-C to <70 mg/dL. • In patients who are at very high risk and who have triglyceride ≥200 mg/dL, a non-HDL-C goal of <100 mg/dL is reasonable. • The use of ezetimibe may be considered for patients who do not tolerate or achieve target LDL-C with statins, bile acid sequestrants, and/or niacin. • For patients who continue to have an elevated non-HDL-C while on adequate statin therapy, niacin or fibrate therapy or fish oil may be reasonable. • For all patients, it may be reasonable to recommend omega-3 fatty acids from fist or fish oil capsules (1 g/day) for cardiovascular disease risk reduction.
Institute for Clinical Systems Improvement: **Lipid Management in Adults (2013)**[82]	• Clinicians should use a quantitative estimate of cardiovascular risk to guide lipid management decision-making for the adult population. • Clinicians should initiate statin therapy regardless of LDL in patients with established ASCVD. • Clinicians should initiate statin therapy in patients whose LDL is greater than 100 and have a 10-year coronary heart disease risk > 10% or diabetes. • Combination therapy should be initiated only on an individual basis as no studies have shown a benefit of use at this time, and some studies have shown an increased risk of harm over statin monotherapy. • If patients are intolerant to a statin, clinicians are encouraged to have the patient try the other statins in reduced doses before ruling out all statins. If patients are unable to take a statin, then bile-acid sequestrants, niacin, fibric acid derivatives or fibrates, and ezetimibe are available.
American Heart Association: **Drug Therapy of High Risk Lipid Abnormalities in Children and Adolescents: A Scientific Statement From the American Heart Association**	• 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

Clinical Guideline	Recommendations
(2007)[83]	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 (2012)**[84]	<u>Drugs</u> • Currently available lipid-lowering drugs include statins, fibrates, bile acid sequestrants, niacin, and selective cholesterol absorption inhibitors (e.g., ezetimibe). • Statins, by reducing LDL-C, reduce cardiovascular morbidity and mortality as well as the need for coronary artery interventions. • Statins should be used as the drugs of first choice in patients with hypercholesterolemia or combined hyperlipidemia. • Selective cholesterol absorption inhibitors are not used as monotherapy to decrease LDL-C. • Bile acid sequestrants also decrease total cholesterol and LDL-C, but tend to increase triglyceride. • Fibrates and niacin are used primarily for triglyceride lowering and increasing HDL-C, while fish oils (omega-3 fatty acids) in doses of 2 to 4 g/day are used for triglyceride lowering. • Fibrates are the drugs of choice for patients with severely elevated triglyceride, and prescription omega-3 fatty acids might be added if elevated triglyceride is not decreased adequately. <u>Drug combinations</u> • Patients with dyslipidemia, particularly those with established cardiovascular disease, diabetes, or asymptomatic high risk patients, may not always reach treatment targets; therefore, combination treatment may be needed. • Combinations of a statin and a bile acid sequestrants or a combination of a statin and ezetimibe can be used for greater reduction in LDL-C than can be achieved with either agent used as monotherapy. • Another advantage of combination therapy is that lower doses of statins can be utilized, thus reducing the risk of adverse events associated with high dose statin therapy. However, statins should be used in the highest tolerable dose to reach LDL-C target level before combination therapy is initiated. • Combinations of niacin and a statin increase HDL-C and decrease triglyceride better than either drug used as monotherapy, but flushing is the main adverse event with niacin, which may affect compliance. • Fibrates, particularly fenofibrate, may be useful, not only for decreasing triglyceride and increasing HDL-C, but can further lower LDL-C when administered in combination with a statin. • If target levels cannot be reached with maximal doses of lipid-lowering therapy or combination therapy, patients will still benefit from treatment to the extent to which dyslipidemia has been improved. In these patients, increased attention to other risk factors may help to reduce total risk.
National Institute for Health and Clinical	• Statin therapy is recommended as part of the management strategy for the primary prevention of cardiovascular disease for adults who have a

Clinical Guideline	Recommendations
Excellence: **Lipid Modification (2010)**[85]	≥20% 10 year risk of developing cardiovascular disease. • Treatment for the primary prevention of cardiovascular disease should be initiated with simvastatin 40 mg. If there are potential drug interactions, or simvastatin 40 mg is contraindicated, a lower dose or alternative preparation such as pravastatin may be chosen. Higher intensity statins should not routinely be offered to people for the primary prevention of cardiovascular disease. • Fibrates, nicotinic acid or anion exchange resins should not routinely be offered for the primary prevention of cardiovascular disease. If statins are not tolerated, these treatments may be considered. • The combination of an anion exchange resin, fibrate, nicotinic acid or a fish oil supplement with a statin should not be offered for the primary prevention of cardiovascular disease. • Statin therapy is recommended for adults with clinical evidence of cardiovascular disease. People with acute coronary syndrome should be treated with a higher intensity statin. • Treatment for the secondary prevention of cardiovascular disease should be initiated with simvastatin 40 mg. If there are potential drug interactions, or simvastatin 40 mg is contraindicated, a lower dose or alternative preparation such as pravastatin may be chosen. In people taking statins for secondary prevention, consider increasing to simvastatin 80 mg or a drug of similar efficacy if a total cholesterol of <4 mmol/L (<155 mg/dL) or LDL-C <2 mmol/L (<77 mg/dL) is not attained. • Fibrates, nicotinic acid and anion exchange resins may be considered for secondary prevention in people with cardiovascular disease who are not able to tolerate statins. • People with primary hypercholesterolemia should be considered for ezetimibe treatment.

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 agents (alogliptin [Nesina®], linagliptin [Tradjenta®], saxagliptin [Onglyza®], and sitagliptin [Januvia®]) or in fixed-dose combination products in combination with metformin (alogliptin/metformin [Kazano®], linagliptin [Jentadueto®], saxagliptin/metformin extended-release [Kombiglyze XR®], sitagliptin/metformin [Janumet®] and /metformin ER [Janumet XR®]), pioglitazone (alogliptin/pioglitazone [Oseni®]) and simvastatin (sitagliptin/simvastatin [Juvisync®]). Specifically, the single-entity agents 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.[2-12] 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.[13-15] 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. It appears this medication class 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. Due to a limited number of within class head-to-head clinical trials, there is insufficient evidence to suggest that one DPP-4 inhibitor is more efficacious than another.[17-65]

According to current clinical guidelines, metformin remains the cornerstone of most antidiabetic treatment regimens. Patients with a high HbA_{1c} will likely require combination or triple therapy in order to achieve glycemic goals, and at this time, there are no uniform recommendations regarding the best agent to be combined with metformin. 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. 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. The DPP-4 inhibitors may also be useful as initial therapy in patients who cannot receive metformin. Among all current clinical guidelines, no one DPP-4 inhibitor is recommended or preferred over another.[70-75]

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