



Department of Vermont Health Access

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

Overview/Summary

Dipeptidyl peptidase-4 (DPP-4) inhibitors reversibly block DPP-4, which is the enzyme responsible for the rapid degradation of incretin hormones. Incretin hormones are produced by the gastrointestinal tract in response to meals and are involved in the regulation of insulin. The antidiabetic actions of incretin hormones include the enhancement of meal stimulated insulin secretion, decreased glucagon secretion, improvements in β -cell function, and slowing of gastric emptying.¹⁻³ DPP-4 inhibitors primarily target postprandial glucose and have also been shown to decrease fasting plasma glucose levels.⁴⁻⁷

Saxagliptin (Onglyza[®]) and sitagliptin (Januvia[®]) are Food and Drug Administration (FDA)-approved as adjunct therapy to diet and exercise to improve glycemic control in adult patients with type 2 diabetes as both monotherapy and combination therapy with other antihyperglycemic agents.^{1,7} There is one combination product available, sitagliptin/metformin hydrochloride (Janumet[®]). This agent is FDA-approved as an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes when therapy with both metformin hydrochloride and sitagliptin is appropriate.⁸ Currently, all of the DPP-4 inhibitors are only available as branded products. However, metformin hydrochloride is available generically as a single entity product.

In general, DPP-4 inhibitors represent a novel approach in the management of type 2 diabetes and appear to have some advantages over other traditional oral antidiabetic agents. DPP-4 inhibitors are associated with a favorable side effect profile and also have a weight neutral effect. Unlike with sulfonylureas, the risk of hypoglycemia associated with the use of these agents is low due to the glucose-dependent nature of incretin hormone activity. Additionally, these agents have not been associated with the same increased risk of cardiovascular disease that has been observed with the thiazolidinediones. As mentioned earlier, DPP-4 inhibitors appear to improve the function of β -cells and although thiazolidinediones and metformin hydrochloride treat insulin resistance, they do not address the progressive decline in β -cell function that is observed in patients with type 2 diabetes.²

For the management of type 2 diabetes, current treatment algorithms, including the American Diabetes Association algorithm, advocate lifestyle interventions together with metformin hydrochloride as first-line therapy.^{9,10} The American Association of Clinical Endocrinologists medical guidelines for clinical practice for the management of diabetes do not designate a first-line therapy for the treatment of type 2 diabetes, but do include DPP-4 inhibitors among the recommended therapeutic choices either as monotherapy or in combination with metformin hydrochloride or a thiazolidinedione in both therapy naïve patients, as well as those on current treatment.⁹ The updated American Diabetes Association/European Association for the Study of Diabetes guideline states that α -glucosidase inhibitors, glinides, and DPP-4 inhibitors were not included in the treatment algorithm (neither tier-1 nor tier-2) due to their generally lower or equivalent overall glucose-lowering effectiveness and limited clinical data.¹⁰ However, these agents may be appropriate in selected patients.⁹ Additionally, patients with a high glycosylated hemoglobin will most likely require combination or triple therapy in order to achieve glycemic goals.

Medications**Table 1. Medications Included Within Class Review**

Generic Name (Trade name)	Medication Class	Generic Availability
Single Entity Products		
Saxagliptin (Onglyza [®])	Dipeptidyl peptidase-4 (DPP-4) inhibitors	-
Sitagliptin (Januvia [®])	Dipeptidyl peptidase-4 (DPP-4) inhibitors	-
Combination Product		
Sitagliptin/metformin hydrochloride (Janumet [®])	Dipeptidyl peptidase-4 (DPP-4) inhibitors	-

Indications**Table 2. Food and Drug Administration (FDA) Approved Indications^{1,7,8}**

Indication	Single Entity Agents		Combination Products
	Saxagliptin	Sitagliptin	Sitagliptin/Metformin Hydrochloride
Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes as either monotherapy or combination therapy	✓	✓	
Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes when therapy with both metformin hydrochloride and sitagliptin is appropriate			✓

Pharmacokinetics**Table 3. Pharmacokinetics^{1,5,7}**

Generic Name	Bioavailability (%)	Metabolism	Excretion (%)	Active Metabolites	Half-Life (hours)
Single Entity Products					
Saxagliptin	High	Hepatic (CYP3A4/5)	Feces (22); urine (24, parent; 36, active metabolite)	Yes (5-hydroxy saxagliptin)	2.5 (parent); 3.1 (active metabolite)
Sitagliptin	87	Hepatic (minimal, CYP3A4 and CYP2C8)	Feces (13); urine (87)	None	12.4
Combination Product					
Saxagliptin/metformin hydrochloride	87 50-60 under fasting conditions	Hepatic (minimal, CYP3A4 and CYP2C8) Does not undergo hepatic metabolism	Feces (13); urine (87) ~90 of absorbed drug is renally eliminated unchanged in the urine	None None	12.4 17.6 hours (in blood) 6.2 hours (in plasma)

Clinical Trials

In placebo-controlled trials, saxagliptin achieved statistically significant reductions in glycosylated hemoglobin (HbA_{1c}), fasting plasma glucose (FPG), and postprandial glucose (PPG) levels.^{11,12} Specifically, in one dose-ranging study (2.5, 5, 10, 20, and 40 mg), after 12 weeks of treatment, placebo-subtracted adjusted mean changes from baseline in HbA_{1c} ranged from -0.45% to -0.63%; with no apparent significant dose-response relationship. Adjusted mean reductions from baseline in HbA_{1c} exceeded 0.7% for each of the saxagliptin doses administered.¹²

In a placebo-controlled trial, a greater proportion of patients in the sitagliptin group did achieve an HbA_{1c} level of <7% compared to placebo ($P<0.001$). In addition, reductions in two-hour PPG levels in patients receiving sitagliptin were significantly higher in the sitagliptin group ($P<0.001$).¹³

In three trials with sitagliptin doses ranging from 25 to 200 mg daily, all treatment groups achieved significant reductions in HbA_{1c} levels compared to placebo ($P<0.001$ to 0.05). There were also significant reductions in FPG levels in the sitagliptin group compared to placebo ($P<0.001$ to 0.05).¹⁴⁻¹⁶ Additionally, Aschner et al demonstrated a significant reduction in two-hour PPG levels from baseline in patients receiving sitagliptin compared to placebo ($P<0.001$).¹⁴ Overall treatment was well tolerated at all doses and the incidence of hypoglycemia between the treatment groups did not appear to be significant.

Frederich et al performed a systematic review of eight phase II or III trials to assess the relative risk (RR) of cardiovascular events. The investigator reported that cardiovascular events and cardiovascular death/myocardial infarction/stroke were less in the sitagliptin group compared to the comparator group (RR, 0.59; RR, 0.44, respectively; P values not reported). However, the authors note that these results should be tested in a prospective randomized controlled trial.¹⁷

A trial comparing sitagliptin doses of 5 to 50 mg to glipizide and placebo, resulted in all sitagliptin treatment groups achieving a significant reduction in HbA_{1c} levels compared to placebo (-0.38% to -0.77%; $P<0.001$). Patients in the glipizide group demonstrated a modest weight gain compared to placebo (P value not reported) while there were no significant differences in change of weight between sitagliptin and placebo. In this study, the incidence of hypoglycemia was highest with glipizide (17%); compared to sitagliptin (0% to 4%) and placebo (2%).¹⁸

In a double-blind, placebo-controlled, randomized trial evaluating the efficacy and safety of saxagliptin in combination with a thiazolidinedione (TZD) in patients with inadequate glycemic control on a TZD alone, saxagliptin provided significant improvements in HbA_{1c} (2.5 mg; $P<0.0007$ and 5 mg; $P<0.0001$), FPG (2.5 mg; $P<0.0007$ and 5 mg; $P<0.0001$), and PPG (2.5 mg and 5 mg; both $P<0.0001$) compared to placebo add-on therapy to a TZD.¹⁹

Additionally, saxagliptin has been evaluated as add-on therapy with metformin hydrochloride, a sulfonylurea, and a TZD. When used in combination with metformin hydrochloride, statistically significant reductions in HbA_{1c} levels were observed compared to monotherapy with either agent.^{20,21} The proportion of patients achieving an HbA_{1c} <7% was statistically significant for combination therapy (saxagliptin 5 mg plus metformin hydrochloride and saxagliptin 10 mg plus metformin hydrochloride) compared to monotherapy with either agent ($P<0.0001$ for both).²⁰ Similar results were seen in the second trial comparing the combination of saxagliptin and metformin hydrochloride.²¹

When used in combination with a sulfonylurea, combination therapy with saxagliptin achieved greater mean HbA_{1c} reductions from baseline compared to patients whose daily dose of the sulfonylurea was maximized. After 24 weeks, patients randomized to saxagliptin 2.5 or 5 mg plus a sulfonylurea had an adjusted mean change in HbA_{1c} from baseline of -0.54% and -0.64% compared to 0.08% in patients in the uptitrated sulfonylurea group (both $P<0.0001$).²²

Goldstein et al examined the efficacy and safety of initial combination therapy with sitagliptin and metformin hydrochloride in patients with type 2 diabetes, who were inadequately controlled on diet and exercise. This study examined sitagliptin and metformin hydrochloride in different dose combinations, both agents as monotherapy, and placebo. Changes in baseline HbA_{1c} were statistically significant in all active treatment groups compared to placebo and for combination therapy compared to monotherapy ($P<0.001$). The 100 mg sitagliptin and 2,000 mg metformin hydrochloride combination produced the greatest change from placebo of all treatment arms ($P<0.001$). The incidence of adverse events was similar among combination treatments and metformin hydrochloride monotherapy. A low frequency of hypoglycemia was reported and was similar among all groups. No change in weight was reported in the sitagliptin monotherapy group as compared to all other active treatment groups and placebo, where there was a significant reduction in body weight.²³

Brazg et al examined the effect of sitagliptin when added to metformin hydrochloride therapy in patients who were uncontrolled on metformin hydrochloride alone. The results of the study showed that the combination of sitagliptin and metformin hydrochloride was more efficacious in lowering the 24-hour mean glucose than the combination of placebo and metformin hydrochloride with the difference between them being statistically significant ($P<0.001$). No weight gain or hypoglycemic events were observed with sitagliptin relative to placebo during the study.²⁴

Charbonnel et al evaluated the efficacy and safety of sitagliptin when added to ongoing metformin hydrochloride therapy in patients who were inadequately controlled on metformin hydrochloride alone. The results indicated that at week 24 the combination of sitagliptin and metformin hydrochloride had a significant HbA_{1c} reduction when compared to placebo ($P<0.001$). The study also showed that more people in the sitagliptin and metformin hydrochloride group (47%) achieved an HbA_{1c} <7% compared to placebo (18.3%). Furthermore there was no increased risk of hypoglycemia or body weight increase when compared with placebo.²⁵

Raz et al evaluated the safety and efficacy of sitagliptin when added to ongoing metformin hydrochloride therapy in patients with type 2 diabetes. At week 18 the combination of sitagliptin and metformin hydrochloride significantly reduced HbA_{1c} from baseline ($P<0.001$). The between group difference in mean change from baseline was -1.0% ($P<0.001$). The incidence of adverse events was similar in both treatment groups and there were no statistically significant differences between the two treatment groups in the incidence of hypoglycemia or in the incidence of gastrointestinal adverse events. Over the 30 week period, a small decrease in mean weight of 0.5 kg was seen in both groups.²⁶

When sitagliptin was used in combination with pioglitazone in a trial by Rosenstock et al, there was no increased risk of hypoglycemia compared to the combination of pioglitazone and placebo. This trial also showed a significant reduction in HbA_{1c} and FPG levels with the combination of sitagliptin and pioglitazone compared to the combination of pioglitazone and placebo ($P<0.001$ for both measures).²⁷

In a study conducted by Hermansen et al, the addition of sitagliptin to glimepiride with or without metformin hydrochloride, significantly decreased HbA_{1c} levels compared to placebo ($P<0.001$). A larger decrease was seen in patients on triple active therapy compared to dual active therapy. In addition, more patients in the triple active treatment group achieved an HbA_{1c} <7% compared to those in receiving glimepiride and metformin hydrochloride ($P<0.001$). In this trial, sitagliptin was well tolerated, both with glimepiride alone and in combination with metformin hydrochloride.²⁸

A study by Scott et al compared the addition of sitagliptin, rosiglitazone or placebo to metformin hydrochloride therapy. The reduction of HbA_{1c} was statistically significant in the sitagliptin group compared to placebo ($P\leq 0.001$). There were no significant differences between the sitagliptin group and rosiglitazone group in reduction of HbA_{1c} or proportion of patients achieving HbA_{1c} <7% (P values not reported).²⁹

In a study comparing the addition of metformin hydrochloride or sitagliptin to rosiglitazone, the metformin hydrochloride group had a significant decrease in body mass index at 12 months compared to the sitagliptin ($P>0.05$). There was no significant difference between the groups in reduction of HbA_{1c}, FBG, PPG and homeostasis model assessment- β -cell function. The fasting plasma insulin, fasting plasma proinsulin and proinsulin to fasting plasma insulin ratio were significantly decreased in the metformin hydrochloride group compared to sitagliptin group at 12 months ($P<0.05$ to $P<0.01$).³⁰

Exenatide and sitagliptin were compared in a randomized cross-over trial for two weeks on each treatment. Two-hour PPG was significantly lower in the exenatide group compared to sitagliptin ($P<0.0001$). In addition, after the switching from the sitagliptin to exenatide, there was a further reduction in 2-hour PPG. However, after switching from exenatide to sitagliptin there was an increase in 2-hour PPG. Except for fasting glucose reduction, which showed no difference between the groups, there was a significant improvement with exenatide compared to sitagliptin in all other outcomes.³¹

When compared to sitagliptin in combination with metformin hydrochloride, liraglutide resulted in a significant reduction in HbA_{1c} ($P<0.0001$). Treatment with liraglutide also resulted in significant reductions in FPG and weight loss (P values not reported), but both liraglutide and the sitagliptin achieved similar improvements in β -cell function and systolic and diastolic blood pressure (P values not reported). More treatment-emergent adverse events were reported with liraglutide.³²

In a trial conducted by Bergenstal et al, once weekly exenatide achieved significantly greater reductions in HbA_{1c} compared to both daily pioglitazone ($P<0.05$) and sitagliptin ($P<0.05$) after 26 weeks of treatment. All patients were receiving combination therapy with metformin hydrochloride. In addition, treatment with exenatide resulted in significantly greater reductions in FPG and six-point self-monitored blood glucose profiles compared to sitagliptin ($P=0.0038$ and P value not reported), but not pioglitazone ($P=0.3729$ and P value not reported). Exenatide significantly reduced weight compared to either treatment ($P=0.0002$ and $P<0.001$).³³ Please note that once weekly dosing of exenatide is not the Food and Drug Administration approved dosage.

When the combination of sitagliptin and metformin hydrochloride was compared to the combination of glipizide and metformin hydrochloride, reductions in HbA_{1c} and FPG glucose levels were found to be similar. In addition, a similar proportion of patients reached an HbA_{1c} level $<7\%$ in both treatment groups. The combination of glipizide and metformin hydrochloride did demonstrate a higher rate of hypoglycemia compared to the combination of sitagliptin and metformin hydrochloride ($P<0.001$). However, there were no significant differences in overall serious clinical adverse events between the groups. Differences in weight changes were significant between the two therapies. Patients receiving glipizide and metformin hydrochloride had a least squares mean difference of -2.5 kg favoring the sitagliptin and metformin hydrochloride group ($P<0.001$).³⁴

A trial by Rigby et al examined the effect of colesevelam, rosiglitazone or sitagliptin on glycemic parameters and lipid profile. All groups demonstrated a significant reduction in HbA_{1c} (colesevelam [$P<0.031$], rosiglitazone [$P<0.001$] and sitagliptin [$P<0.009$]). Colesevelam had a significant reduction of low density lipoprotein, while rosiglitazone and sitagliptin had significant increases (P values not reported).³⁵

Schwarz et al performed a cost-effectiveness analysis based on cost data from six European countries and clinical data from Nauck et al³⁴ and Scott et al²⁹, which compared the addition of rosiglitazone, sitagliptin or glipizide to metformin hydrochloride. The addition of sitagliptin was either cost saving or cost-effective.³⁶

Meta-analyses evaluating incretin-based therapies (dipeptidyl peptidase-4 inhibitors or dipeptidyl peptidase-4 inhibitors and incretin mimetics) have been conducted.³⁷⁻³⁹ Of note, the analyses compare the incretin-based therapies to either placebo or other non-incretin based therapies and demonstrate similar results to what has been described previously.

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>Rosenstock et al (abstract)¹¹</p> <p>Saxagliptin 2.5 mg Daily</p> <p>vs</p> <p>saxagliptin 5 mg Daily</p> <p>vs</p> <p>saxagliptin 10 mg Daily</p> <p>vs</p> <p>placebo</p> <p>Trial was conducted with a separate OL cohort with patients receiving saxagliptin 10 mg Daily.</p>	<p>OL, PC, RCT</p> <p>Treatment naïve patients with type 2 diabetes and inadequate glycemic control with an HbA_{1C} ≥7% and ≤10%; OL trial was with treatment naïve patients with type 2 diabetes and inadequate glycemic control with an HbA_{1C} >10% to ≤12%</p>	<p>N=401 (N=66 in the OL cohort)</p> <p>24 weeks</p>	<p>Primary: HbA_{1C} change from baseline</p> <p>Secondary: FPG change from baseline, proportion of patients achieving HbA_{1C} <7%, and changes in PPG area under the curve</p>	<p>Primary: In the main treatment cohort, saxagliptin demonstrated statistically significant decreases in adjusted mean HbA_{1C} changes from baseline (-0.43%, -0.46%, and -0.54% vs 0.19% for placebo; all <i>P</i><0.0001).</p> <p>Secondary: Adjusted mean FPG was significantly reduced from baseline for all doses of saxagliptin compared to placebo (-15, -9, and -17 mg/dL vs 6 mg/dL; <i>P</i>=0.0002, <i>P</i>=0.0074, <i>P</i><0.0001).</p> <p>A greater number of patients treated with saxagliptin achieved HbA_{1C} <7% at week 24 for saxagliptin 2.5, 5, and 10 mg vs placebo (35% [<i>P</i>=NS], 38% [<i>P</i>=0.0443], 41% [<i>P</i>=0.0133] vs 24%).</p> <p>The reduction in PPG area under the curve for saxagliptin 2.5 mg (-6,868 mg-minute/dL), 5 mg (-6,896 mg-minute/dL), and 10 mg (-8,804 mg-minute/dL) vs placebo (-647 mg-minute/dL) was statistically significant for saxagliptin 5 mg (<i>P</i>=0.0002) and 10 mg (<i>P</i><0.0001).</p> <p>Reductions in HbA_{1C}, FPG, and PPG area under the curve were also observed in the OL cohort at 24 weeks.</p>
<p>Rosenstock et al¹²</p> <p>Saxagliptin 2.5 mg Daily (low-dose cohort)</p> <p>vs</p> <p>saxagliptin 5 mg Daily (low-dose cohort)</p> <p>vs</p> <p>saxagliptin 10 mg Daily</p>	<p>DB, MC, PC, PG, RCT</p> <p>Men and non-breastfeeding, non-pregnant women ≥21 to ≤70 years of age, with type 2 diabetes and a baseline HbA_{1C} ≥6.8% to ≤9.7%, a BMI ≤37 kg/m²,</p>	<p>N=338</p> <p>12 weeks (saxagliptin 2.5, 5, 10, 20, and 40 mg)</p> <p>6 weeks (saxagliptin 100 mg)</p>	<p>Primary: Analysis for a dose-related trend in lowering of HbA_{1C} from baseline across the saxagliptin doses in the low-dose cohort</p> <p>Secondary: Analyses of each dose vs placebo</p>	<p>Primary: In the low-dose cohort, the test for log-linear trend across the treatment groups did not demonstrate a statistically significant dose-response relationship in the lowering of HbA_{1C} after 12 weeks of treatment. Placebo-subtracted adjusted mean changes from baseline to week 12 for saxagliptin ranged from -0.45% to -0.63% with no apparent significant dose-response relationship (<i>P</i>=0.9888).</p> <p>Secondary: After 12 weeks, HbA_{1C} was significantly reduced from baseline in all saxagliptin doses in the low-dose cohort compared with placebo (all doses <i>P</i><0.007) with similar and clinically meaningful reductions in HbA_{1C} achieved with all doses of saxagliptin. Adjusted mean reductions from baseline exceeded 0.70% for each of the saxagliptin doses vs 0.27% for placebo. In the high-dose cohort, HbA_{1C}</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
(low-dose cohort) vs saxagliptin 20 mg Daily (low-dose cohort) vs saxagliptin 40 mg Daily (low-dose cohort) vs saxagliptin 100 mg Daily (high-dose cohort) vs placebo	and a screening fasting or random C-peptide >0.5 ng/mL; patients <35 years of age had to test negative for anti-glutamic acid decarboxylate antibodies		for lowering HbA _{1c} , FSG, and PPG at 60 minutes from baseline	was also significantly reduced from baseline relative to placebo. An adjusted mean change following six weeks of treatment was -1.09% vs -0.36% (<i>P</i> value not reported). In both treatment cohorts for all saxagliptin groups, FSG reductions from baseline were evident after two weeks of treatment. Adjusted mean FSG changes from baseline ranged from -11.0 mg/dL to -22.0 mg/dL for the low-dose cohort vs 3.0 mg/dL for placebo and -26.3 mg/dL for the high-dose cohort vs -3.3 mg/dL for placebo (<i>P</i> values not reported). In the low-dose cohort, adjusted mean changes from baseline in PPG at 60 minutes during a liquid meal tolerance test ranged from -24.0 mg/dL to -41.0 mg/dL vs -1.0 mg/dL for placebo (<i>P</i> value not reported). In the high-dose cohort it was -45.0 mg/dL vs -17.0 mg/dL for placebo (<i>P</i> value not reported).
Nonaka et al ¹³ Sitagliptin 100 mg Daily vs placebo	DB, MC, PC, RCT Japanese patients with type 2 diabetes with an HbA _{1c} ≥6.5% to <10% and FPG ≥126 mg/dL to ≤240 mg/dL	N=151 12 weeks	Primary: Change from baseline HbA _{1c} , FPG, PPG, body weight changes, adverse effects Secondary: Not reported	Primary: Sitagliptin demonstrated a least squares mean change from baseline HbA _{1c} of -0.65% (95% CI, -0.80 to -0.50) compared to placebo (0.41%; 95% CI, 0.26 to 0.56). The between group difference was -1.05% (95% CI, -1.27 to -0.84; <i>P</i> <0.001). A greater proportion of patients on sitagliptin achieved an HbA _{1c} level of <7% than placebo (<i>P</i> <0.001). Patients in the sitagliptin group experienced a least squares mean change of -22.5 mg/dL (95% CI, -28.0 to -17.0). The least squares mean change of FPG in the placebo group was 9.4 mg/dL (95% CI, 3.9 to 14.9). The between group difference was -31.9 mg/dL (95% CI, -39.7 to -24.1; <i>P</i> <0.001). Patients in the sitagliptin group had a least squares mean difference from baseline in 2-hour PPG level of -69.3 mg/dL (95% CI, -85.3 to -53.4) compared

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				<p>to 12.0 mg/dL (95% CI, -6.5 to 30.5) with placebo. The between group difference was -81.3 mg/dL (95% CI, -105.8 to -56.9; $P<0.001$). A 0.1 kg decrease in weight was seen in the sitagliptin group compared to a reduction of 0.7 kg in the placebo group ($P<0.01$). No notable difference in adverse events, including hypoglycemia, was shown between the comparators.</p> <p>Secondary: Not reported</p>
<p>Aschner et al¹⁴</p> <p>Sitagliptin 100 mg Daily vs sitagliptin 200 mg Daily vs placebo</p> <p>Metformin was used as rescue therapy if defined glycemic goals were not met.</p>	<p>DB, MC, PC, RCT</p> <p>Patients 18 to 75 years of age with type 2 diabetes, either on or naïve to an oral antihyperglycemic agent, with an average baseline HbA_{1c} of 8%</p> <p>Patients with significant renal impairment were excluded.</p>	<p>N=741</p> <p>24 weeks</p>	<p>Primary: Change from baseline HbA_{1c}, FPG, PPG, fasting insulin, proinsulin, and fasting lipids, and assessment of β-cell function and insulin resistance</p> <p>Secondary: Safety and tolerability assessments</p>	<p>Primary: Sitagliptin 100 and 200 mg significantly reduced HbA_{1c} compared with placebo ($P<0.001$), by -0.79% for 100 mg vs placebo (95% CI, -0.96 to -0.62) and -0.94% for 200 mg vs placebo (95% CI, -1.11 to -0.77). At the conclusion of the study, 41% of patients in the sitagliptin 100 mg group and 45% in the sitagliptin 200 mg group achieved an HbA_{1c}<7% vs 17% in the placebo group ($P<0.001$ for active treatment vs placebo).</p> <p>Sitagliptin demonstrated significance between treatment differences vs placebo in FPG change from baseline of -17.1 mg/dL and -21.3 mg/dL for the 100 and 200 mg doses, respectively ($P<0.001$).</p> <p>The reduction in two-hour PPG from baseline was significantly ($P<0.001$) greater with sitagliptin 100 mg (-48.9 mg/dL) and 200 mg (-56.3 mg/dL) than with placebo (-2.2 mg/dL).</p> <p>There were no statistically significant effects on fasting insulin and proinsulin. Sitagliptin also had no significant effects on fasting lipids.</p> <p>HOMA-β was significantly increased and the proinsulin to insulin ratio was significantly decreased with sitagliptin treatment, indicating improved β-cell function ($P\leq 0.001$ and $P\leq 0.01$, respectively, for active treatment vs placebo).</p> <p>There were fewer patients in the active treatment groups than in the placebo group that required rescue therapy (8.8% for sitagliptin 100 mg, 4.8% for 200 mg and 20.6% for placebo; $P<0.001$ for sitagliptin vs placebo).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>Raz et al¹⁵</p> <p>Sitagliptin 100 mg Daily</p> <p>vs</p> <p>sitagliptin 200 mg Daily</p> <p>vs</p> <p>placebo</p> <p>Metformin was used as rescue therapy if defined glycemic goals were not met.</p>	<p>DB, MC, PC, PG, RCT</p> <p>Patients 18 to 75 years of age with type 2 diabetes with an HbA_{1c} level between 7% to 10%</p> <p>Patients with significant renal or hepatic disease were excluded.</p>	<p>N=521</p> <p>18 weeks</p>	<p>Primary: Change from baseline HbA_{1c}</p> <p>Secondary: Changes in FPG, fasting insulin, proinsulin, and lipids, safety and tolerability assessments</p>	<p>Secondary: No meaningful differences in clinical adverse effects were noted between groups. The incidence of hypoglycemia was similar among groups yet did not exhibit marked severity. Both sitagliptin doses were well tolerated in this study.</p> <p>Primary: Treatment with both sitagliptin 100 and 200 mg doses led to a significant ($P<0.001$) reduction in HbA_{1c} from baseline compared to placebo. In the sitagliptin 100 mg group, HbA_{1c} was reduced by -0.60% (95% CI, -0.82 to -0.39) and by -0.48% (95% CI, -0.70 to -0.26) in the 200 mg group.</p> <p>Secondary: Treatment with sitagliptin led to significant ($P<0.001$) reductions in FPG compared to placebo throughout the treatment period. FPG was reduced by -1.1 mmol/L (95% CI, -1.7 to -0.5) and by -0.9 mmol/L (95% CI, -1.5 to -0.3) for sitagliptin 100 and 200 mg, respectively.</p> <p>There were no statistically significant effects on fasting insulin, proinsulin or on fasting lipids.</p> <p>Rescue therapy was required for 8.8% of the sitagliptin 100 mg treatment group, 11.7% of patients on sitagliptin 200 mg, and 17.3% of the placebo group (no P value reported).</p> <p>Treatment with sitagliptin was well tolerated. There were no statistically significant differences between treatment groups in the incidence of adverse effects. The incidence of hypoglycemia and gastrointestinal side effects was not significantly different among all treatment groups.</p>
<p>Hanefeld et al¹⁶</p> <p>Sitagliptin 25 mg Daily</p> <p>vs</p> <p>sitagliptin 50 mg Daily</p>	<p>DB, MC, PC, PG, RCT</p> <p>Patients 23 to 74 years of age with a mean baseline HbA_{1c} of 7.6% to 7.8%</p>	<p>N=555</p> <p>12 weeks</p>	<p>Primary: Change from baseline HbA_{1c}, FPG, mean daily glucose, HOMA-β, QUICKI and HOMA-IR</p>	<p>Primary: Sitagliptin significantly reduced HbA_{1c} levels by -0.39% to -0.56% relative to placebo ($P<0.05$).</p> <p>FPG was also significantly reduced by -11.0 to -17.2 mg/dL as compared to placebo ($P<0.05$) and the largest decrease was found in the 100 mg Daily group. Additionally a significant improvement in mean daily glucose was observed throughout all active treatment groups (-14.0 to -22.6 mg/dL;</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs sitagliptin 50 mg BID vs sitagliptin 100 mg Daily vs placebo			Secondary: Adverse events, baseline body weight change	P<0.05). HOMA-β was significantly increased (11.3 to 15.2; P<0.05) with sitagliptin, whereas there was no significant change in QUICKI and HOMA-IR compared to placebo. There were no significant differences noted between sitagliptin 100 mg Daily as opposed to 50 mg BID for any end point. Secondary: Overall, there was a low frequency of hypoglycemia observed in the active treatment groups. There was no change in baseline body weight noted.
Frederich et al ¹⁷ Saxagliptin 2.5 to 10 mg Daily vs glyburide, metformin, or placebo	SR Eight phase two or three studies evaluating saxagliptin in patients with inadequately controlled type 2 diabetes	N=4,607 16 to 116 weeks	Primary: Reported cardiovascular events and cardiovascular death, myocardial infarction and/or stroke Secondary: Not reported	Primary: There were 38 (1.1%) cardiovascular events reported by investigators in the saxagliptin treated patients and 23 (1.8%) in the comparator groups (RR, 0.59; 95% CI, 0.35 to 1.00). There were 23 (0.7%) cardiovascular death/myocardial infarction/stroke events in the saxagliptin group and 18 (1.4%) in the comparator groups (RR, 0.44; 95% CI, 0.24 to 0.82). Cardiovascular death occurred in 7 (0.2%) of saxagliptin treated patients and 10 (0.8%) in the comparator groups (RR, 0.24; 95% CI, 0.09 to 0.63). Secondary: Not reported
Scott et al ¹⁸ Sitagliptin 5 mg BID vs sitagliptin 12.5 mg BID vs sitagliptin 25 mg BID	AC, DB, PC, RCT Male and female patients 21 to 75 years of age with type 2 diabetes inadequately controlled (mean HbA _{1c} of 7.9%) with diet and exercise	N=743 12 weeks	Primary: Change from baseline in HbA _{1c} , FPG and mean daily glucose, changes in weight and adverse effects Secondary: Not reported	Primary: All sitagliptin treatment groups demonstrated a significant reduction in HbA _{1c} over placebo (-0.38% to -0.77%; P<0.001). Sitagliptin at a dose of 50 mg BID resulted in the largest decrease. The placebo subtracted difference in HbA _{1c} of glipizide was -1.00%. Sitagliptin, at all doses, also demonstrated significant reductions in FPG and mean daily glucose. No significant changes in baseline body weight were observed in the sitagliptin groups compared to placebo, whereas the glipizide group demonstrated modest weight gain vs placebo (no P value reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs sitagliptin 50 mg BID vs glipizide 5 mg/day electively titrated up to 20 mg/day vs placebo				The incidence of hypoglycemia was highest in the glipizide-treated group (17%) as compared to placebo (2%) and sitagliptin (0% to 4%, not dose dependent). Secondary: Not reported
Hollander et al ¹⁸ Saxagliptin 2.5 mg Daily and OL TZD (pioglitazone or rosiglitazone) vs saxagliptin 5 mg Daily and OL TZD (pioglitazone or rosiglitazone) vs placebo and OL TZD (pioglitazone or rosiglitazone) Eligible patients entered a 2-week, single-blind, dietary and exercise placebo and TZD lead-in	DB, MC, RCT Patients 18 to 77 years of age with type 2 diabetes and inadequate glycemic control (HbA _{1C} ≥7% and ≤10.5%) taking stable doses of TZD monotherapy (pioglitazone 30 or 45 mg Daily or rosiglitazone 4 or 8 mg Daily or 4 mg BID for at least 12 weeks) and with fasting C-peptide ≥0.3 nmol/L and BMI ≤45 kg/m ²	565 24 weeks	Primary: Change from baseline in HbA _{1C} Secondary: Change from baseline in FPG, proportion of patients achieving HbA _{1C} <7%, change from baseline in PPG area under the curve from 0 to 180 minutes in response to a 75 g OGTT	Primary: At week 24, statistically significant reductions in HbA _{1C} from baseline were demonstrate for saxagliptin 2.5 mg (-0.36%; <i>P</i> <0.0007) and 5 mg (-0.63%; <i>P</i> <0.0001) vs placebo. Baseline vs week 24 HbA _{1C} mean values were 8.3% vs 7.6%, 8.4% vs 7.4%, and 8.2% vs 7.9% for saxagliptin 2.5 and 5 mg and placebo respectively. Adjusted mean change in HbA _{1C} from baseline was -0.66% (<i>P</i> <0.0007) and -0.94% in the saxagliptin 5 mg group (<i>P</i> <0.0001) vs -0.30% in the placebo group. Reductions were observed starting at week 4 with the greatest reductions in the saxagliptin 5 mg group. Sensitivity analysis demonstrated that a switch from rosiglitazone to pioglitazone did not affect results. Secondary: At week 24, statistically significant greater mean reductions in FPG at week 24 were demonstrated for saxagliptin 2.5 mg (-0.8 mmol/L; <i>P</i> <0.0053) and 5 mg (-1.0 mmol/L; <i>P</i> =0.0005) vs placebo (-0.2 mmol/L). FPG reductions were observed starting at week two with the greatest reductions in the saxagliptin 5 mg group. At 24 weeks, 42.2% (<i>P</i> =0.0010) and 41.8% (<i>P</i> =0.0013) of patients in the saxagliptin 2.5 and 5 mg groups, respectively, achieved an HbA _{1C} <7% compared to 25.6% of patients in the placebo group.

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<p>period during which they received OL pioglitazone or rosiglitazone according to their current regimen and continued for the study duration.</p> <p>Due to recent safety concerns with rosiglitazone, a switch from rosiglitazone was permitted during lead-in period if medically appropriate.</p>				<p>A statistically significant reduction from baseline to week 24 was seen in PPG area under the curve during the OGTT for the saxagliptin 2.5 and saxagliptin 5 mg vs placebo (both $P<0.0001$). In addition, the 120-minute PPG demonstrated significantly greater reductions for 2.5 and 5 mg compared to placebo (both $P<0.0001$).</p> <p>Overall, the addition of saxagliptin to TZD therapy was well tolerated. The proportion of patients experiencing any adverse effect was 68.0% in the saxagliptin groups and 66.8% in the placebo group with the highest frequency in the saxagliptin 5 mg group (74.2%). The frequency of hypoglycemic events was similar with saxagliptin (3.4%) compared to placebo (3.8%). The most common adverse effects reported were upper respiratory tract infection, peripheral edema, and headache.</p>
<p>Jadzinsky et al²⁰</p> <p>Saxagliptin 5 mg Daily and metformin IR 500 mg/day in divided doses</p> <p>vs</p> <p>saxagliptin 10 mg Daily and metformin IR 500 mg/day in divided doses</p> <p>vs</p> <p>saxagliptin 10 mg Daily and placebo</p> <p>vs</p> <p>metformin IR 500 mg/day in divided doses and</p>	<p>AC, DB, MC, RCT</p> <p>Patients 18 to 77 years of age with type 2 diabetes, HbA_{1C} ≥8% and ≤12% at screening, fasting C-peptide concentration ≥1.0 ng/mL, and a BMI ≤40 kg/m²</p>	<p>N=1,306</p> <p>24 weeks</p>	<p>Primary: Change from baseline in HbA_{1C}</p> <p>Secondary: Change from baseline in FPG, proportion of patients achieving HbA_{1C} <7%, change from baseline in area under the curve from 0 to 180 minutes for PPG response to an OGTT, proportion of patients achieving a HbA_{1C} ≤6.5%, and proportion of</p>	<p>Primary: Statistically significant reductions in HbA_{1C} from baseline were seen in patients randomized to saxagliptin 5 mg and metformin or saxagliptin 10 mg and metformin at 24 weeks compared to patients randomized to either monotherapy. Baseline vs week 24 HbA_{1C} means were 9.4% vs 6.9%, 9.5% vs 7.0%, 9.6% vs 7.9%, and 9.4% vs 7.5% for the four treatment arms. Adjusted mean change in HbA_{1C} from baseline was -2.5% in both the saxagliptin 5 mg and metformin and the saxagliptin 10 mg and metformin groups vs -1.7% for saxagliptin 10 mg and -2.0% for metformin, respectively (all $P<0.0001$ vs monotherapy).</p> <p>Secondary: Statistically significant greater mean reductions in FPG at week 24 were observed for saxagliptin 5 mg and metformin vs saxagliptin 10 mg ($P=0.0002$) and for saxagliptin 10 mg and metformin vs saxagliptin 10 mg and vs metformin (both $P<0.0001$ vs monotherapy).</p> <p>The proportion of patients achieving an HbA_{1C} <7% was statistically significantly greater for both combination treatment groups compared to either monotherapy group (60.3% and 59.7% vs 32.2% and 41.1%; all $P<0.0001$ vs monotherapy).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>placebo</p> <p>At week 1, all patients randomized to metformin, either as monotherapy or in combination with saxagliptin, were titrated to 1,000 mg/day of metformin.</p> <p>From weeks 2 to 5, metformin was uptitrated based on predefined FPG levels in 500 mg/day increments as tolerated to 2,000 mg/day maximum in the saxagliptin 5 mg and metformin, saxagliptin 10 mg and metformin, and metformin and placebo arms.</p>			<p>patients requiring rescue for failing to achieve prespecified glycemic targets or discontinuing for lack of efficacy at 24 weeks</p>	<p>A statistically significant reduction in glucose exposure from baseline to week 24 was seen in PPG area under the curve during the OGTT for both combination treatment groups vs both monotherapy treatment groups (all $P<0.0001$ vs monotherapy).</p> <p>The proportion of patients with an $HbA_{1C} \leq 6.5\%$ at week 24 was 45.3%, 40.6%, 20.3%, and 29.0 % for the four treatment groups. The proportion was statistically significantly greater for saxagliptin 5 mg and metformin vs saxagliptin 10 mg and vs metformin (both $P<0.0001$) and for saxagliptin 10 mg and metformin vs saxagliptin 10 mg and vs metformin ($P<0.0001$, $P=0.0026$).</p> <p>At week 24, 7.5% of patients in the saxagliptin 5 mg and metformin group and 21.2% of the saxagliptin 10 mg group were discontinued or rescued for lack of glycemic control ($P<0.0001$). No statistical significance was observed when the saxagliptin 5 mg and metformin group was compared to the metformin group (10.1%; $P=0.2693$). Similar results were observed with the saxagliptin 10 mg and metformin group compared to either monotherapy ($P<0.0001$ vs saxagliptin 10 mg and $P=0.0597$ vs metformin).</p>
<p>DeFronzo et al²¹</p> <p>Saxagliptin 2.5 mg Daily and metformin 1,500 to 2,500 mg/day</p> <p>vs</p> <p>saxagliptin 5 mg Daily and metformin 1,500 to 2,500 mg/day</p> <p>vs</p>	<p>DB, PC, RCT</p> <p>Patients 18 to 77 years of age with type 2 diabetes and inadequate glycemic control ($HbA_{1C} \geq 7\%$ and $\leq 10\%$) taking stable doses of metformin for eight weeks ($\geq 1,500$ mg/day</p>	<p>N=743</p> <p>24 weeks</p>	<p>Primary: Change from baseline in HbA_{1C}</p> <p>Secondary: Change from baseline in FPG, PPG three-hour area under the curve, and percentage of patients at the glycemic target</p>	<p>Primary: Saxagliptin (2.5, 5 and 10 mg) plus metformin demonstrated statistically significant adjusted mean decreases from baseline to week 24 vs placebo in HbA_{1C} (-0.59%, -0.69%, -0.58% vs 0.13%; all $P<0.0001$). All saxagliptin treatment groups demonstrated reductions in HbA_{1C} compared to metformin plus placebo starting at week four with a maximal reduction at week 12 that was sustained through week 24.</p> <p>Secondary: Saxagliptin (2.5, 5 and 10 mg) plus metformin demonstrated statistically significant adjusted mean decreases from baseline to week 24 vs placebo in FPG (-14.31 mg/dL, -22.03 mg/dL, -20.50 mg/dL vs 1.24 mg/dL; all $P<0.0001$) and PPG three-hour area under the curve (-8,891 mg·minute/dL, -9,586</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>saxagliptin 10 mg Daily and metformin 1,500 to 2,500 mg/day</p> <p>vs</p> <p>placebo and metformin 1,500 to 2,500 mg/day</p>	<p>and <2,550 mg/day), fasting C-peptide concentration ≥ 1.0 ng/mL, and BMI ≤ 40 kg/m²</p>		<p>(HbA_{1C}<7%),</p>	<p>mg-minute/dL, -8,137 mg-minute/dL vs -3,291 mg-minute/dL; all $P < 0.0001$).</p> <p>There was a statistically significant greater percentage of patients that achieved HbA_{1C}<7% with saxagliptin (2.5, 5 and 10 mg) plus metformin at week 24 vs placebo (37.1%, 43.5%, 44.4% vs 16.6%; all $P < 0.0001$).</p> <p>Other measures also demonstrated statistically significant differences at all doses of saxagliptin compared to placebo (PPG at two hours, postprandial glucagon area under the curve, postprandial insulin area under the curve, and postprandial C-peptide area under the curve).</p>
<p>Chacra et al²²</p> <p>Saxagliptin 2.5 mg Daily and glyburide 7.5 mg/day in divided doses</p> <p>vs</p> <p>saxagliptin 5 mg Daily and glyburide 7.5 mg/day in divided doses</p> <p>vs</p> <p>placebo and glyburide 7.5 mg/day in divided doses</p> <p>Eligible patients entered a 4-week, single-blind, dietary and exercise placebo lead-in period during which they discontinued their current sulfonylurea therapy and received OL glyburide 7.5</p>	<p>DB, MC, RCT</p> <p>Patients 18 to 77 years of age with type 2 diabetes and inadequate glycemic control (HbA_{1C} screening value $\geq 7.5\%$ to $\leq 10\%$) on a submaximal sulfonylurea dose (defined as less than the maximum approved dose for each sulfonylurea) for ≥ 2 months before screening and with fasting C-peptide ≥ 1.0 ng/mL and BMI ≤ 40 kg/m²</p>	<p>N=768</p> <p>24 weeks</p>	<p>Primary: Change from baseline in HbA_{1C}</p> <p>Secondary: Change from baseline in FPG, proportion of patients achieving HbA_{1C}<7%, change from baseline in PPG area under the curve from 0 to 180 minutes in response to a 75 g OGTT, safety</p>	<p>Primary: At week 24, patients randomized to saxagliptin 2.5 or 5 mg demonstrated statistically significant reductions in HbA_{1C}. Baseline vs week 24 HbA_{1C} mean values were 8.4% vs 7.8%, 8.5% vs 7.8%, and 8.4% vs 5.8% for saxagliptin 2.5 and 5 mg and uptitrated glyburide. Adjusted mean change in HbA_{1C} from baseline was -0.54% and -0.64% in the saxagliptin 2.5 and 5 mg groups vs 0.08% for the uptitrated glyburide group (both $P < 0.0001$). Greater HbA_{1C} mean reductions were observed with saxagliptin vs uptitrated glyburide by week 4 and the greatest HbA_{1C} reductions were demonstrated in the saxagliptin 5 mg group.</p> <p>Secondary: At week 24, statistically significant greater mean reductions in FPG at week 24 were observed for saxagliptin 2.5 and 5 mg ($P=0.0218$, $P=0.002$) vs uptitrated glyburide. Adjusted mean change from baseline was -7, -10, and 1 mg/dL in the saxagliptin 2.5 mg, saxagliptin 5 mg, and uptitrated glyburide groups.</p> <p>At 24 weeks, 22.4% and 22.8% of patients in the saxagliptin 2.5 and 5 mg groups achieved an HbA_{1C} <7.0% compared to 9.1% of patients in the uptitrated glyburide group (both $P < 0.0001$).</p> <p>A statistically significant reduction in glucose exposure from baseline to week 24 was seen in PPG area under the curve during the OGTT for the saxagliptin 2.5 mg (-4,296 mg-minute/dL) and 5 mg (-5,000 mg-minute/dL) groups vs the uptitrated glyburide group (1,196 mg-minute/dL; both $P < 0.0001$).</p>

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<p>mg Daily.</p> <p>A one-time decrease in OL glyburide to 5 mg/day was permitted for patients who developed hypoglycemia.</p> <p>Uptitration of blinded glyburide was permitted at weeks 2 and 4 in the uptitrated glyburide treatment group for patients satisfying prespecified glycemic criteria to a maximum total daily dose of 15 mg.</p>				<p>Overall saxagliptin added to glyburide therapy was well tolerated. The proportion of patients reporting any adverse events was similar across all treatment groups; with no evidence of a dose-response relationship. The percentage 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% in the saxagliptin 2.5 mg, saxagliptin 5 mg, and uptitrated glyburide groups. No events of Stevens-Johnson syndrome or angioedema were reported. Cardiac disorder events were: 2.0% (5/248) for saxagliptin 2.5 mg, 4.0% (10/253) for saxagliptin 5 mg, and 3.7% (10/267) for uptitrated glyburide. Adverse events of hypertension were reported for 3.6% (9/248), 6.3% (16/253), and 2.2% (6/267) for saxagliptin 2.5 mg, saxagliptin 5 mg, and uptitrated glyburide, however, mean SBP and DBP decreased in all treatment groups. There were no statistically significant difference in the incidence of reported and confirmed hypoglycemic events in the saxagliptin treatment groups vs uptitrated glyburide ($P>0.05$). Confirmed hypoglycemia occurred in 2.4%, 0.8%, and 0.7% of patients in the 2.5 mg and 5 mg saxagliptin groups and uptitrated glyburide group.</p>
<p>Goldstein et al²³</p> <p>Sitagliptin 50 mg BID and metformin 500 mg BID</p> <p>vs</p> <p>sitagliptin 50 mg BID and metformin 1,000 mg BID</p> <p>vs</p> <p>sitagliptin 100 mg Daily</p> <p>vs</p> <p>metformin 500 mg BID</p>	<p>DB, MC, PC, PG, RCT</p> <p>Patients 18 to 78 years of age with type 2 diabetes and an HbA_{1c} of 7.5% to 11%</p> <p>Patients with significant renal dysfunction were excluded.</p>	<p>N=1,091</p> <p>24 weeks</p>	<p>Primary: Change from baseline in HbA_{1c}</p> <p>Secondary: FPG, fasting serum insulin, fasting serum proinsulin, fasting lipids, assessment of β-cell function (change in baseline proinsulin to insulin ratio, HOMA-β), assessment of</p>	<p>Primary: Changes in baseline HbA_{1c} were statistically significant in all active treatment groups 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 placebo-subtracted HbA_{1c} changes for the combination of sitagliptin 100 mg and metformin 1,000 mg, the combination of sitagliptin 100 mg and metformin 2,000 mg, sitagliptin monotherapy, metformin 1,000 mg monotherapy and metformin 2,000 mg monotherapy treatment groups were -1.57%, -2.07%, -0.83%, -0.99% and -1.30%, respectively.</p> <p>The percentage of patients who reached an HbA_{1c} level $<7\%$ was significantly greater within all active treatment groups vs placebo ($P<0.001$). Sitagliptin in combination with metformin 2,000 mg demonstrated the highest rate at 66%. In comparison to the 43% of patients in the sitagliptin in combination with metformin 1,000 mg group, 38% of patients in the metformin 2,000 mg monotherapy group, 23% in metformin 1,000 mg monotherapy group, 20% in sitagliptin monotherapy group and 9% in the placebo group achieved an</p>

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<p>vs metformin 1,000 mg BID vs placebo</p> <p>Glyburide was used as rescue therapy if defined glycemic goals were not met.</p> <p>Doses of metformin alone or in combination with sitagliptin were titrated up by 500 mg/week to reach target dose and reduce potential for gastrointestinal upset.</p> <p>Sitagliptin was titrated to mimic the currently available fixed-dose combination product.</p>			<p>insulin resistance (change in baseline HOMA-IR and QUICKI) and adverse events</p>	<p>HbA_{1c}<7%.</p> <p>Secondary: Statistically significant changes in FPG were found between the combination and monotherapy groups as well as all active treatment groups vs placebo ($P<0.001$). The placebo-subtracted FPG changes for the combination of sitagliptin 100 mg and metformin 1,000 mg, the combination of sitagliptin 100 mg and metformin 2,000 mg, sitagliptin monotherapy, metformin 1,000 mg monotherapy and metformin 2,000 mg monotherapy treatment groups were -52.9 mg/dL, -69.7 mg/dL, -23.3 mg/dL, -33.1mg/dL and -35.1 mg/dL respectively.</p> <p>Combination therapy also demonstrated an additive effect, as compared to treatment with the individual agents in regards to improvement in β-cell function. Significant improvement in the proinsulin to insulin ratio was observed with all active treatment groups compared to placebo ($P<0.05$). The differences between the combined therapy groups and the monotherapy groups (sitagliptin and metformin) were also significant ($P<0.05$). Changes were -0.08 for the sitagliptin monotherapy group, -0.08 for the metformin 1,000 mg monotherapy group, -0.12 for the metformin 2,000 mg monotherapy group, -0.14 for the combination of sitagliptin and metformin 1,000 mg group and -0.20 for the combination of sitagliptin and metformin 2,000 mg group from placebo.</p> <p>HOMA-β was increased with all active treatments from baseline as compared with placebo. HOMA-β was significantly improved in the combined therapy groups, 27.3% for the combination of sitagliptin and metformin 1,000 mg and 29.3% for the combination of sitagliptin and metformin 2,000 mg (both $P\leq 0.001$) as well as in the higher dose metformin monotherapy group (10.6%; $P\leq 0.05$). The combination of sitagliptin and metformin also significantly increased HOMA-β relative to sitagliptin monotherapy (7.1%) and the lower metformin monotherapy dose (7.3%) group ($P\leq 0.001$).</p> <p>The results of changes in fasting serum insulin and lipids were not reported.</p> <p>The incidence of adverse events was similar among combination treatments</p>

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				<p>and metformin monotherapy. Gastrointestinal adverse events including diarrhea, nausea, and abdominal pain and vomiting were most frequently seen in the higher dose metformin groups (both alone and in combination). A low frequency of hypoglycemia was reported and was similar among all groups (0.6% to 2.2%). No change in weight was reported in the sitagliptin monotherapy group as compared to all other active treatment groups, where there was a significant reduction in body weight (-0.6 kg to -1.3 kg; $P<0.05$) and placebo (-0.9 kg; $P<0.01$).</p> <p>Data on efficacy, changes in body weight and rates of hypoglycemia was excluded if patients received any doses of rescue therapy.</p>
<p>Brazg et al²⁴</p> <p>Sitagliptin 50 mg BID and metformin $\geq 1,500$ mg daily</p> <p>vs</p> <p>placebo and metformin $\geq 1,500$ mg daily</p> <p>Patients received 1 drug regimen for 4 weeks then XO to the comparator group for 4 weeks.</p>	<p>DB, PC, RCT, XO</p> <p>Patients 25 to 75 years of age with type 2 diabetes with inadequate glycemic control on metformin monotherapy and a baseline HbA_{1c} of 6.5% to 9.6%</p>	<p>N=28</p> <p>8 weeks</p>	<p>Primary: 24-hour weighted mean glucose</p> <p>Secondary: Change in FPG, MDG, fructosamine and β-cell function</p>	<p>Primary: There was a significant least-squares mean decrease in 24-hour weighted mean glucose of 32.8 mg/dL in the sitagliptin and metformin treatment group as compared to placebo and metformin ($P<0.05$).</p> <p>Secondary: Despite a carryover effect from period 1 to period 2, the combined period 1 and period 2 results for glycemic measurements were statistically significant for sitagliptin vs placebo when added to continuing metformin therapy. The period 1 outcomes were also compared between the groups, in consideration of any carryover.</p> <p>Following period 1, there were significant least-squares mean reductions in FPG of 20.3 mg/dL, MDG of 28 mg/dL, and fructosamine of 33.7 mmol/L in patients treated with combination sitagliptin and metformin relative to placebo and metformin ($P<0.05$).</p> <p>Sitagliptin, in addition to metformin, demonstrated significantly improved parameters of β-cell function relative to placebo.</p> <p>Weight gain, gastrointestinal adverse events and hypoglycemia were not reported during the course of treatment with sitagliptin, as compared to placebo, in combination with metformin.</p>

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<p>Charbonnel et al²⁵</p> <p>Sitagliptin 100 mg Daily, and metformin ≥1,500 mg/day</p> <p>vs</p> <p>placebo and metformin ≥1,500 mg/day</p> <p>Pioglitazone was used as rescue therapy if defined glycemic goals were not met.</p>	<p>DB, MC, PC, PG, RCT</p> <p>Patients 18 to 78 years of age with type 2 diabetes and inadequate glycemic control (HbA_{1c} ≥7% and ≤10%) on metformin monotherapy (≥1,500 mg/day)</p>	<p>N=701</p> <p>24 weeks</p>	<p>Primary: Change from baseline in HbA_{1c}</p> <p>Secondary: Changes from baseline in FPG, PPG, insulin, C-peptide concentrations, β-cell function, and lipid panel and safety</p>	<p>Primary: Sitagliptin added to metformin therapy led to a significant ($P<0.001$) reduction from baseline in HbA_{1c} compared with placebo. Placebo subtracted HbA_{1c} reduction was -0.65% with sitagliptin at 24 weeks ($P\leq 0.001$). Significantly more patients reached an HbA_{1c} <7% with sitagliptin 100 mg (47%) than with placebo (18.3%; $P<0.001$). Significantly more patients also reached an HbA_{1c} <6.5% with sitagliptin (17.2%) than with placebo (4.9%; $P<0.001$).</p> <p>Secondary: FPG was significantly reduced from baseline with the sitagliptin combination group compared with placebo plus metformin group. Placebo subtracted FPG was -25.4 mg/dL ($P<0.001$).</p> <p>Placebo subtracted two-hour PPG was -50.6 mg/dL with sitagliptin ($P\leq 0.001$). There were significant increases in the sitagliptin group relative to the placebo plus metformin group in fasting insulin ($P<0.050$), and fasting C-peptide ($P<0.010$). Conversely, there was no observed between group difference in LDL-cholesterol. There was observed improvement in fasting proinsulin to insulin ratio ($P<0.010$) and HOMA-β ($P<0.001$) consistent with improved β-cell function in the sitagliptin treatment group.</p> <p>There were no differences between treatment groups in the incidence 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 ($P<0.050$). The between group difference was not significant ($P=0.835$).</p>
<p>Raz et al²⁶</p> <p>Sitagliptin 100 mg Daily and metformin ≥1,500 mg/day</p> <p>vs</p>	<p>DB, MC, PC, PG, RCT</p> <p>Patients 18 to 78 years of age with type 2 diabetes and an HbA_{1c} of 7% to 10% that</p>	<p>N=190</p> <p>30 weeks</p>	<p>Primary: Reduction in HbA_{1c} at 18 weeks of sitagliptin therapy</p> <p>Secondary: Reduction in FPG</p>	<p>Primary: At week 18 the sitagliptin and metformin group significantly reduced HbA_{1c} from baseline ($P<0.001$). The between group difference in mean change from baseline was -1.0% (95% CI, -1.4 to -0.7; $P<0.001$). Numerically greater HbA_{1c} reductions from baseline were observed in patients with higher baseline HbA_{1c} values.</p> <p>The proportion of patients in the sitagliptin and metformin group who achieved</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>placebo and metformin $\geq 1,500$ mg/day</p>	<p>were on metformin or other oral antihyperglycemic agents as monotherapy or being treated with metformin in combination with other oral antihyperglycemic agents</p>		<p>at 18 weeks, reduction in two-hour PPG at 18 weeks, reduction in HbA_{1c} at 30 weeks, safety and tolerability</p>	<p>an HbA_{1c} <7% was 13.7% at week 18 and 22.1% at week 30. For the placebo group this goal was reached by 3.3% of patients at both time periods.</p> <p>Secondary: Treatment with sitagliptin resulted in significant reductions from baseline in FPG compared to placebo at week 18. The between group mean difference from baseline was -1.4 mmol/L (95% CI, -2.1 to -0.7; <i>P</i><0.001).</p> <p>The sitagliptin and metformin group had a significantly improved two-hour PPG at week 18 (<i>P</i><0.001). The between group mean difference was -3.0 mmol/L (95% CI, -4.2 to -1.9) and this was significant (<i>P</i><0.001).</p> <p>At week 30 the sitagliptin and metformin group significantly reduced HbA_{1c} from baseline (<i>P</i><0.001). The between group difference in mean change from baseline was -1.0% (95% CI, -1.4 to -0.6; <i>P</i><0.001).</p> <p>The incidence of adverse events was similar in both treatment groups. No serious adverse events or discontinuations due to clinical adverse events were reported in the sitagliptin group. In the placebo group there were six serious clinical adverse events that resulted in one death and two discontinuations. None of the adverse events however, were deemed to be drug related. There were no statistically significant differences between the two treatment groups in the incidence of hypoglycemia or in the incidence of gastrointestinal adverse events (abdominal pain, nausea, vomiting, and diarrhea). Over the 30 week period a small decrease in mean weight of 0.5 kg was seen in both groups.</p>
<p>Rosenstock et al²⁷</p> <p>Sitagliptin 100 mg Daily in addition to pioglitazone 30 or 45 mg Daily (SIT+PIO)</p> <p>vs</p> <p>pioglitazone 30 or 45 mg</p>	<p>DB, MC, PC, PG, RCT</p> <p>Patients ≥ 18 years of age with type 2 diabetes and inadequate glycemic control (HbA_{1c} $\geq 7\%$ and $\leq 10\%$) on</p>	<p>N=353</p> <p>24 weeks</p>	<p>Primary: Change from baseline in HbA_{1c}</p> <p>Secondary: Change from baseline in FPG, fasting insulin, proinsulin and lipid parameters,</p>	<p>Primary: There were significant decreases in HbA_{1c} with the SIT+PIO-treated group compared to the PBO+PIO group (<i>P</i><0.001). The mean HbA_{1c} change from baseline was -0.70% (95% CI, -0.85 to -0.54). Forty five percent of patients in the SIT+PIO treated group achieved an HbA_{1c}<7% compared to 23.0% in the PBO+PIO group (<i>P</i><0.001).</p> <p>Secondary: FPG significantly decreased in the SIT+PIO group relative to baseline and PBO+PIO (-17.7 mg/dL; 95% CI, -24.3 to -11.0; <i>P</i><0.001).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>Daily in addition to placebo (PBO+PIO)</p> <p>Metformin was used as rescue therapy if defined glycemic goals were not met.</p>	<p>pioglitazone monotherapy</p>		<p>safety and tolerability</p>	<p>SIT+PIO treatment, compared with PBO+PIO, reduced fasting serum proinsulin levels ($P=0.009$) and the proinsulin to insulin ratio ($P<0.001$).</p> <p>TG significantly decreased with SIT+PIO treatment compared with PBO+PIO, with a mean difference of -11.2% (95% CI, -22.0 to -0.4; $P<0.041$). However, there were no significant differences in the other lipid parameters.</p> <p>SIT+PIO were well tolerated with no increased risk of hypoglycemia compared to PBO+PIO. There was a small significant increase in the incidence of abdominal pain in the SIT+PIO group compared to the PBO+PIO group. There was no statistically significant difference in change of body weight from baseline observed between groups.</p>
<p>Hermansen et al²⁸</p> <p>Sitagliptin 100 mg Daily in addition to glimepiride 4 to 8 mg/day</p> <p>vs</p> <p>sitagliptin 100 mg Daily in addition to glimepiride 4 to 8 mg/day and metformin 1,500 to 3,000 mg/day</p> <p>vs</p> <p>glimepiride 4 to 8 mg/day and placebo</p> <p>vs</p> <p>glimepiride 4 to 8 mg/day,</p>	<p>DB, MC, PG, RCT</p> <p>Patients 18 to 75 years of age with type 2 diabetes with a baseline HbA_{1c} level between 6.7% to 10.6%</p> <p>Patients with renal dysfunction were excluded.</p>	<p>N=441</p> <p>24 weeks</p>	<p>Primary: Change from baseline in HbA_{1c}</p> <p>Secondary: Change from baseline in FPG, plasma lipids, assessment of β-cell function (HOMA-β, proinsulin to insulin ratio) and insulin resistance (HOMA-IR, QUICKI), safety and tolerability</p>	<p>Primary: The addition of sitagliptin significantly decreased HbA_{1c} ($P<0.001$) from baseline with a least squares mean change of -0.74% (95% CI, -0.90 to -0.57) compared to placebo.</p> <p>A larger placebo subtracted decrease in HbA_{1c} of -0.89% (95% CI, -1.10 to -0.68) was observed in the patients on triple active therapy, compared to the dual active treatment group (-0.57%; 95% CI, -0.82 to -0.32). For the overall study population, there was a significantly higher proportion of patients achieving an HbA_{1c}<7% with sitagliptin treatment (17.1%) than with placebo (4.8%; $P<0.001$). More patients in the triple active treatment group achieved an HbA_{1c}<7% than patients in the glimepiride, metformin and placebo group (22.6% vs 1.0%; $P<0.001$). No significant difference was noted between glimepiride and sitagliptin vs glimepiride and placebo in the number of patients who reached an HbA_{1c} level <7% (10.8% vs 8.7%; $P<0.638$).</p> <p>Secondary: Sitagliptin led to significant ($P<0.001$) reductions in baseline FPG compared to placebo with overall least squares mean change from baseline of -20.1 mg/dL (95% CI, -28.4 to -11.8).</p> <p>There was an overall significant increase in fasting insulin with sitagliptin (1.8</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>metformin 1,500 to 3,000 mg/day and placebo</p> <p>Pioglitazone 30 mg daily was used as rescue therapy if defined glycemic goals were not met.</p>				<p>$\mu\text{IU/mL}$; 95% CI, 0.8 to 2.9) relative to placebo (0.1 $\mu\text{IU/mL}$; 95% CI, -1.1 to 1.2; $P<0.001$).</p> <p>A significant increase in HOMA-β was also observed in the sitagliptin groups 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 significant differences in fasting proinsulin, proinsulin to insulin ratio, HOMA-IR and QUICKI between the treatments (specific figures not reported).</p> <p>Sitagliptin showed neutral effects on plasma lipids compared to placebo (specific figures not reported).</p> <p>Sitagliptin was essentially well tolerated, both with glimepiride alone and in combination with metformin. There was a higher incidence of overall adverse events (difference of 8.0%; 95% CI, 2.2 to 13.9) observed in the sitagliptin group relative to placebo, with the majority of that difference due to rates of hypoglycemia. None of these hypoglycemic events were considered severe.</p> <p>A slight, statistically significant increase in body weight of 0.8 kg (95% CI, 0.4 to 1.2) was noted in the sitagliptin group as compared to a slight decrease in weight for the placebo group (-0.4 kg; 95% CI, -0.8 to 0.1).</p>
<p>Scott et al²⁹</p> <p>Sitagliptin 100 mg Daily, in addition to existing metformin therapy</p> <p>vs</p> <p>rosiglitazone 8 mg Daily, in addition to existing metformin therapy</p> <p>vs</p>	<p>DB, MC, PG, RCT (1:1:1)</p> <p>Patients 18 to 75 years of age with type 2 diabetes taking stable metformin doses ($\geq 1,500$ mg/day for ≥ 10 weeks) and inadequate glycemic control (HbA_{1c} $\geq 7\%$ and $\leq 11\%$)</p>	<p>N=273</p> <p>18 weeks</p>	<p>Primary: Change from baseline in HbA_{1c}</p> <p>Secondary: Change from baseline in FPG, fasting serum insulin, fasting serum proinsulin, fasting plasma lipids, β-cell function (proinsulin to</p>	<p>Primary: Compared to placebo, there was a significant reduction in HbA_{1c} from baseline with sitagliptin (least squares mean difference, -0.50%; 95% CI, -0.87 to -0.60; $P\leq 0.001$). There was also a significant reduction in HbA_{1c} from baseline in the rosiglitazone group (least squares mean difference, -0.57%; 95% CI, -0.76 to -0.37; P value not reported). The difference in change from baseline of HbA_{1c} between sitagliptin and rosiglitazone was not clinically significant (least squares mean difference, -0.06%; 95% CI, -0.25 to 0.14).</p> <p>The proportion of patients achieving an HbA_{1c} $< 7\%$ was significantly higher in the sitagliptin group (55%; $P=0.006$) and rosiglitazone group (63%; P value not reported) compared to placebo (38%). The difference between sitagliptin and rosiglitazone in proportion of patients achieving HbA_{1c} was similar (least squares mean difference, 8%; 95% CI, -6 to 22; P value not reported).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>placebo, in addition to existing metformin therapy</p>			<p>insulin ratio and HOMA-β) and insulin resistance (HOMA-IR)</p>	<p>Secondary: There was a significant reduction in FPG from baseline compared with placebo in the sitagliptin group (least squares mean difference, -17.8 mg/dL; 95% CI, -27.6 to -8.1; $P \leq 0.001$) and rosiglitazone group (least squares mean difference, -30.6 mg/dL; 95% CI, -40.6 to -20.7; P value not reported). There was a greater reduction in FPG in the rosiglitazone group compared to the sitagliptin group (least squares mean difference, -12.8 mg/dL; 95% CI, -22.6 to -3.0; P value not reported).</p> <p>Sitagliptin and rosiglitazone had significant increases in HOMA-β compared to placebo (least squares mean difference, 16.3; 95% CI, 2.3 to 30.3; $P \leq 0.05$; and least squares mean difference, 15.3; 95% CI, 1.0 to 29.6; P value not reported, respectively). The increase in HOMA-β was not significantly different between sitagliptin and rosiglitazone.</p> <p>Rosiglitazone had greater reductions in HOMA-IR compared to placebo (least squares mean difference, -2.4; 95% CI, -3.4 to -1.4; P value not reported) or sitagliptin (least squares mean difference, -1.6; 95% CI, -2.6 to -0.7; P value not reported). There reduction in HOMA-IR was similar between sitagliptin and placebo (least squares mean difference, -0.7; 95% CI, -1.7 to 0.2; P value not reported).</p> <p>Rosiglitazone had a greater reduction of fasting serum insulin compared to placebo (least squares mean difference, -3.4 μIU/mL; 95% CI, -5.5 to -1.4; P value not reported) and sitagliptin (least squares mean difference, -3.53 μIU/mL; 95% CI, -5.5 to -1.4; P value not reported). The ratio of proinsulin to insulin was similar across groups.</p> <p>There was an increase in LDL for all treatment groups; however, compared to placebo, LDL decreased with sitagliptin (least squares mean difference, -5.3 mg/dL; 95% CI, -14.5 to 3.9; P value not reported) and increased with rosiglitazone (least squares mean difference, 9.5 mg/dL; 95% CI, 0.2 to 18.7; P value not reported). There was an increase in total cholesterol for all treatment groups; however, compared to placebo, total cholesterol decreased with</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				<p>sitagliptin (least squares mean difference, -6.3 mg/dL; 95% CI, -11.8 to -0.9; $P \leq 0.05$) and increased with rosiglitazone (least squares mean difference, 5.1 mg/dL; 95% CI, -0.3 to 10.6; P value not reported). Compared to placebo, TG decreased with sitagliptin (least squares mean difference, -16.7 mg/dL; 95% CI, -27.9 to 5.5; $P \leq 0.05$) and increased with rosiglitazone (least squares mean difference, 1.2 mg/dL; 95% CI, -10.1 to 12.6; P value not reported). In the rosiglitazone group, there was a greater increase in LDL (least squares mean difference, 14.8 mg/dL; 95% CI, 5.7 to 23.9; P value not reported), total cholesterol (least squares mean difference, 11.5 mg/dL; 95% CI, 6.0 to 16.9 23.9; P value not reported), HDL (least squares mean difference, 4.9 mg/dL; 95% CI, 0.6 to 9.2; P value not reported) and TG (least squares mean difference, 17.9 mg/dL; 95% CI, 6.7 to 29.2; P value not reported) compared to sitagliptin.</p>
<p>Derosa et al³⁰</p> <p>Metformin 850 mg BID plus pioglitazone 15 mg BID</p> <p>vs</p> <p>sitagliptin 100 mg Daily plus pioglitazone 30 mg Daily</p>	<p>DB, MC, RCT</p> <p>Patients ≥ 18 years of age with type 2 diabetes uncontrolled (HbA_{1c} $> 7.5\%$) with diet, exercise and pioglitazone 30 mg/day</p>	<p>N=151</p> <p>12 months</p>	<p>Primary: Change from baseline at 3, 6, 9 and 12 months in body weight and BMI</p> <p>Secondary: Change from baseline at 3, 6, 9 and 12 months in HbA_{1c}, FPG, PPG, fasting plasma insulin, insulin resistance and β-cell function (HOMA-β and HOMA-IR), fasting plasma proinsulin, proinsulin to fasting plasma insulin ratio,</p>	<p>Primary: There was no significant difference in BMI or body weight at 3, 6, 9 and 12 months in the sitagliptin group compared to baseline. In the metformin group body weight and BMI were decreased significantly at 12 months compared to baseline and sitagliptin (both $P < 0.05$).</p> <p>Secondary: The sitagliptin and metformin groups had significant improvement in HbA_{1c} compared to baseline at 9 and 12 months ($P < 0.05$ and $P < 0.01$, respectively for both groups). There was no significant difference comparing the sitagliptin group and metformin group.</p> <p>The sitagliptin and metformin groups had significant decrease in FPG compared to baseline at 9 and 12 months ($P < 0.05$ and $P < 0.01$, respectively for both groups). There was no significant difference comparing the sitagliptin group and metformin group.</p> <p>The sitagliptin and metformin groups had significant decrease in PPG compared to baseline at 9 and 12 months ($P < 0.05$ and $P < 0.01$, respectively for both groups). There was no significant difference comparing the sitagliptin group and metformin group.</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			adiponectin, resistin, TNF- α and high-sensitivity CRP	<p>The sitagliptin group had a significant decrease in fasting plasma insulin compared to baseline at 12 months ($P<0.05$). The metformin group had a significant decrease in fasting plasma insulin compared to baseline at 9 and 12 months ($P<0.05$ and $P<0.01$, respectively) At 12 months, the fasting plasma insulin was significantly lower in the metformin group compared to sitagliptin ($P<0.05$).</p> <p>The sitagliptin group had a significant increase in HOMA-β compared to baseline at 9 and 12 months ($P<0.05$ and $P<0.01$, respectively). The metformin group had a significant increase in HOMA-β compared to baseline at 12 months ($P<0.05$). There was no significant difference comparing the sitagliptin group and metformin group.</p> <p>The sitagliptin group had a significant decrease in fasting plasma proinsulin compared to baseline at 12 months ($P<0.05$). The metformin group had a significant decrease in fasting plasma proinsulin compared to baseline at 9 and 12 months ($P<0.05$ and $P<0.01$, respectively). At 12 months, the decrease was significantly greater in the metformin group compared to sitagliptin ($P<0.05$).</p> <p>The sitagliptin group had a significant decrease in proinsulin to fasting plasma insulin ratio compared to baseline at 12 months ($P<0.05$). The metformin group had a significant decrease in plasma proinsulin to fasting plasma insulin ratio compared to baseline at 6, 9 and 12 months ($P<0.05$, $P<0.02$ and $P<0.01$, respectively). At 12 months, the proinsulin to fasting plasma insulin ratio was lower in the metformin group compared to sitagliptin ($P<0.05$).</p> <p>The sitagliptin group had a significant decrease in HOMA-IR compared to baseline at 12 months ($P<0.05$). The metformin group had a significant decrease in HOMA-IR compared to baseline at 9 and 12 months ($P<0.05$ and $P<0.01$, respectively). At 12 months, the HOMA-IR was significantly lower in the metformin group compared to sitagliptin ($P<0.05$).</p> <p>There was no significant difference in adiponectin at any time points in the sitagliptin group compared to baseline. The metformin group had a significant increase in adiponectin compared to baseline 12 months ($P<0.05$). At 12</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				<p>months, the adiponectin was significantly higher in the metformin group compared to sitagliptin ($P<0.05$).</p> <p>There was no significant difference in resistin at any time points in the sitagliptin group compared to baseline. The metformin group had a significant decrease in resistin compared to baseline 12 months ($P<0.05$). At 12 months, the resistin was significantly lower in the metformin group compared to sitagliptin ($P<0.05$).</p> <p>There was no significant difference in TNF-α at any time points in the sitagliptin group compared to baseline. The metformin group had a significant decrease in TNF-α compared to baseline 12 months ($P<0.05$). At 12 months, the decrease in TNF-α was significantly higher in the metformin group compared to sitagliptin ($P<0.05$).</p> <p>The sitagliptin and metformin groups had significant decrease in high-sensitivity CRP compared to baseline at 12 months ($P<0.05$ for both groups). There was no significant difference comparing the sitagliptin group and metformin group.</p>
<p>DeFronzo et al³¹ (abstract)</p> <p>Exenatide 5 μg BID for 1 week then 10 μg BID for 1 week, in addition to existing metformin therapy</p> <p>vs</p> <p>sitagliptin 100 mg Daily for 2 weeks</p> <p>Patients received 1 drug regimen for 2 weeks then</p>	<p>DB, MC, RCT, XO</p> <p>Patients with type 2 diabetes treated with metformin</p>	<p>N=61</p> <p>4 weeks</p>	<p>Primary: Change in two-hour PPG, insulin and glucagon secretion, gastric emptying and caloric intake</p> <p>Secondary: Not reported</p>	<p>Primary: After 2 weeks, the two-hour PPG was lower in the exenatide group compared to sitagliptin (133\pm6 mg/dL vs 208\pm6 mg/dL; $P<0.0001$). There was an increase in two-hour PPG of 73\pm11 mg/dL after switching from exenatide to sitagliptin and a further reduction of 76\pm10 mg/dL after switching from sitagliptin to exenatide.</p> <p>Exenatide improved insulinogenic index (ratio exenatide to sitagliptin 1.50\pm0.26; $P=0.0239$), reduced postprandial glucagon (area under the curve ratio exenatide to sitagliptin 0.88\pm0.03; $P=0.0011$), reduced postprandial TG (area under the curve ratio exenatide to sitagliptin, 0.90\pm0.04; $P=0.0118$) and gastric emptying (acetaminophen area under the curve ratio exenatide to sitagliptin, 0.56\pm0.05; $P<0.0001$) compared to sitagliptin.</p> <p>Compared to sitagliptin, exenatide reduced total caloric intake (-134\pm97 kcal vs 130\pm97 kcal; $P=0.0227$).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
XO to the comparator group for 2 weeks.				<p>There was no significant difference in the reduction in fasting glucose between the exenatide group (-15±4 mg/dL) and sitagliptin group (-19±4 mg/dL; <i>P</i>=0.3234).</p> <p>Secondary: Not reported</p>
<p>Pratley et al³²</p> <p>Liraglutide 1.2 mg SC Daily in addition to existing metformin therapy</p> <p>vs</p> <p>liraglutide 1.8 mg SC Daily in addition to existing metformin therapy</p> <p>vs</p> <p>sitagliptin 100 mg Daily in addition to the existing metformin therapy</p>	<p>MC, OL, PG, RCT</p> <p>Type 2 diabetic patients 18 to 80 years of age with HbA_{1c} 7.5% to 10%, BMI ≤45 kg/m² and had been treated with metformin (≥1,500 mg/day) for ≥3 months</p>	<p>N=665</p> <p>26 weeks</p>	<p>Primary: Change in HbA_{1c} from baseline to week 26</p> <p>Secondary: Proportions of patients reaching HbA_{1c} targets <7.0% or ≤6.5%, FPG, PPG, body weight, β-cell function, fasting lipid profile, cardiovascular risk markers, blood pressure, heart rate, physical measures, treatment satisfaction, adverse events and a composite endpoint of proportions of patients with a HbA_{1c} <7.0% with</p>	<p>Primary: In the superiority comparison, greater lowering of mean HbA_{1c} (8.5% at baseline) was achieved with liraglutide 1.8 mg (-1.5%; 95% CI, -1.63 to -1.37) and 1.2 mg (-1.24%; 95% CI, -1.37 to -1.11) than with sitagliptin (-0.90%; 95% CI, -1.03 to -0.77). Estimated mean treatment differences for liraglutide vs sitagliptin were -0.60% (95% CI, -0.77 to -0.43; <i>P</i><0.0001) for 1.8 mg and -0.34% (95% CI, -0.51 to -0.16; <i>P</i><0.0001) for 1.2 mg liraglutide.</p> <p>Secondary: Significantly more patients achieved the HbA_{1c} targets (<7% and ≤6.5%) with liraglutide than with sitagliptin (<7%: liraglutide 1.8 mg OR, 4.50; 95% CI, 2.90 to 6.71; liraglutide 1.2 mg OR, 2.75; 95% CI, 1.78 to 4.25; ≤6.5%: liraglutide 1.8 mg OR, 4.25; 95% CI, 2.55 to 7.08; liraglutide 1.2 mg OR, 2.11; 95% CI, 1.24 to 3.59; <i>P</i> values not reported).</p> <p>After 26 weeks, mean decreases in FPG were significantly greater with liraglutide than with sitagliptin (liraglutide 1.8 mg, -2.14 mmol/L; 95% CI, -2.43 to -1.84; liraglutide 1.2 mg, -1.87; 95% CI, -2.16 to -1.57 and sitagliptin, -0.83; 95% CI, -1.13 to -0.54; <i>P</i> values not reported). Estimated least squares mean treatment differences were -1.31 mmol/L (95% CI, -1.70 to -0.91; <i>P</i> value not reported) for liraglutide 1.8 mg vs sitagliptin and -1.04 mmol/L (95% CI, -1.43 to -0.64; <i>P</i> value not reported) for liraglutide 1.2 mg vs sitagliptin.</p> <p>Mean reductions in the area under the curve for PPG is not reported because data were difficult to interpret.</p> <p>Mean weight loss after 26 weeks was significantly greater with liraglutide than with sitagliptin (liraglutide 1.8 mg, -3.38 kg; 95% CI, -3.7 to -2.84; liraglutide 1.2</p>

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			no hypoglycemia and weight change of ≤0 kg	<p>mg, -2.86 kg; 95% CI, -1.50 to -0.42; sitagliptin; -0.96 kg; 95% CI, -1.50 to -0.42; <i>P</i> values not reported). Estimated mean treatment differences were -2.42 kg (95% CI, -3.14 to -1.70; <i>P</i> value not reported) for liraglutide 1.8 mg vs sitagliptin and -1.90 kg (95% CI, -2.61 to -1.18; <i>P</i> value not reported) for liraglutide 1.2 mg.</p> <p>Both liraglutide doses were associated with significant improvements in HOMA-β, C-peptide concentration and proinsulin to insulin ratio compared with sitagliptin, but no treatment-related differences were recorded for HOMA-IR or fasting insulin concentration.</p> <p>Changes in the lipid profile between liraglutide and sitagliptin were not significant, apart from the decrease in total cholesterol which was significantly greater with liraglutide 1.8 mg than with sitagliptin.</p> <p>Data on cardiovascular markers were not reported.</p> <p>Both liraglutide and sitagliptin had a small effect on SBP and DBP; lowering of DBP with sitagliptin seemed to be significant compared to liraglutide 1.8 mg, but not compared to liraglutide 1.2 mg (<i>P</i> values not reported).</p> <p>Heart rate increased with liraglutide, and decreased slightly with sitagliptin; differences were small but significant for both doses of liraglutide vs sitagliptin.</p> <p>Both liraglutide doses were associated with significantly greater reductions in waist circumference than sitagliptin, but no significant treatment-related differences of waist to hip ratios were noted.</p> <p>Improvements were seen in all DTSQ items for all treatment groups. The increase in patients' treatment satisfaction from baseline was significantly higher with liraglutide 1.8 mg than with sitagliptin (difference, 1.39; 95% CI, 0.13 to 2.64; <i>P</i> value not reported), but the increase with liraglutide 1.2 mg compared to sitagliptin was not significant (<i>P</i> value not reported).</p> <p>Most treatment-emergent adverse events were reported with liraglutide than</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				<p>with sitagliptin. Two deaths occurred, neither of which was judged as likely to be related to the study drug. The most common adverse events were gastrointestinal symptoms, especially with liraglutide, and infections and infestations, which occurred with similar frequency in all treatment groups.</p> <p>Forty six percent of liraglutide 1.8 mg, 37% of liraglutide 1.2 mg and 14% of sitagliptin achieved the composite secondary endpoint. Measurements scheduled to be taken after baseline were missing for some patients. The ORs vs sitagliptin were 5.46 (95% CI, 3.37 to 8.85; $P<0.0001$) for liraglutide 1.8 mg and 3.45 (95% CI, 2.12 to 5.61; $P<0.0001$) for liraglutide 1.2 mg.</p>
<p>Bergenstal et al³³</p> <p>Exenatide 2 mg SC once weekly plus placebo, in addition to existing metformin therapy</p> <p>vs</p> <p>sitagliptin 100 mg Daily plus placebo, in addition to existing metformin therapy</p> <p>vs</p> <p>pioglitazone 45 mg Daily plus placebo, in addition to existing metformin therapy</p>	<p>DB, DD, RCT</p> <p>Type 2 diabetic patients ≥ 18 years of age treated with a stable metformin regimen for ≥ 2 months before screening, HbA_{1c} 7.1% to 11% and a BMI 25 to 45 kg/m²</p>	<p>N=491</p> <p>26 week</p>	<p>Primary: Change from baseline in HbA_{1c}</p> <p>Secondary: Proportion of patients achieving the HbA_{1c} target $<6.5\%$ or $<7\%$; proportion of patients achieving a FPG target ≤ 7 mmol/L; six-point self-monitored blood glucose profile; body weight; fasting lipid profile; fasting insulin profile; SBP and DBP; cardiovascular risk markers; patient-reported outcomes</p>	<p>Primary: Exenatide resulted in a significantly greater reduction in HbA_{1c} compared to pioglitazone by week four ($P<0.05$) or sitagliptin by week six ($P<0.05$); statistical significance was maintained throughout the remainder of the study.</p> <p>After 26 weeks of treatment, mean HbA_{1c} was 7.2% (SE, 0.1) for exenatide, 7.7% (SE, 0.1) for sitagliptin and 7.4% (SE, 0.1) for pioglitazone.</p> <p>Between baseline and week 26, the reduction in HbA_{1c} with exenatide (-1.5%; 95% CI, -1.7 to -1.4) was significantly greater compared to sitagliptin (-0.9%; 95% CI, -1.1 to -0.7) or pioglitazone (-1.2%; 95% CI, -1.4 to -1.0). Treatment differences were -0.6% (95% CI, -0.9 to -0.4; adjusted $P<0.0001$ vs sitagliptin) and -0.3% (95% CI, -0.6 to -0.1; adjusted $P=0.0165$ vs pioglitazone).</p> <p>When data were stratified by baseline HbA_{1c}, exenatide was associated with a significantly greater reduction in HbA_{1c} than sitagliptin in all patients, but when compared to pioglitazone, the difference was significant only in patients with baseline HbA_{1c} $\geq 9\%$ (P values not reported).</p> <p>Secondary: Significantly more patients achieved HbA_{1c} targets of $<7\%$ and $<6.5\%$ with exenatide than with sitagliptin ($P<0.0001$ and $P<0.0001$) or pioglitazone ($P=0.0015$ and $P=0.0120$).</p> <p>All treatments improved FPG, with exenatide resulting in a significantly greater</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			<p>(IWQOL, PGWB, DTSQ and EQ-5D) and safety</p>	<p>reduction (-1.8 mmol/L; 95% CI, -2.2 to -1.3) compared to sitagliptin (-0.9 mmol/L; 95% CI, -1.3 to -0.5), but not pioglitazone (-1.5 mmol/L; 95% CI, -1.9 to -1.1). Treatment differences were -0.9 mmol/L (95% CI, -0.3 to -1.4; adjusted $P=0.0038$ vs sitagliptin) and -0.2 mmol/L (-0.8 to 0.3; adjusted $P=0.3729$ vs pioglitazone). The percentage of patients who achieved the target of ≤ 7 mmol/L with exenatide (60%) was significantly greater than with sitagliptin (35%; adjusted $P<0.0001$) and was similar to pioglitazone (52%; adjusted $P=0.1024$).</p> <p>In all measurements of the six-point self-monitored blood glucose profile, reductions at week 26 were significantly greater with exenatide than with sitagliptin, but not pioglitazone (P value not reported).</p> <p>Exenatide resulted in a significantly greater reduction in body weight compared to pioglitazone by week one ($P<0.05$) and sitagliptin by week four ($P<0.05$). At week 26, weight loss with exenatide (-2.3 kg; 95% CI, -2.9 to -1.7) was significantly greater compared to sitagliptin (-0.8 kg; 95% CI, -1.4 to -0.1) or pioglitazone (2.8 kg; 95% CI, 2.2 to 3.4). Treatment differences were -1.5 kg (95% CI, -2.4 to -0.7; adjusted $P=0.0002$ vs sitagliptin) and -5.1 kg (-5.9 to -4.3; adjusted $P<0.001$ vs pioglitazone).</p> <p>Improvements in SBP were recorded within a few weeks of starting all treatments. After 26 weeks of treatment, the reduction in SBP was significantly greater with exenatide compared to sitagliptin in all patients (difference, -4 mm Hg; 95% CI, -6 to -1; P value not reported) but not pioglitazone (P value not reported). Change in DBP at week 26 did not differ significantly between groups (P values not reported).</p> <p>Significant improvements in HDL cholesterol were recorded with all treatments, which was significantly greater with pioglitazone compared to exenatide (difference, 0.11 mmol/L; 95% CI, 0.07 to 0.15; $P<0.0001$). Pioglitazone was the only treatment associated with a significant reduction in TG (-16%; 95% CI, -21 to -11; P value not reported) and increase in total cholesterol (0.16 mmol/L; 95% CI, 0.04 to 0.28; P value not reported), the former of which was significantly different from changes with exenatide (-5%; 95% CI, -11 to 0;</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				<p>$P=0.0062$).</p> <p>All treatments were associated with significant improvements in high-sensitivity CRP and adiponectin. Exenatide was the only treatment associated with significantly improved BNP and albumin to creatinine ratio; BNP was also significantly greater than sitagliptin or pioglitazone (P values not reported). Pioglitazone was associated with a significantly greater increase in adiponectin compared to exenatide, and was the only treatment associated with significantly improved PAI-1 and significant worsening of BNP (P values not reported).</p> <p>All five domains of the weight-related quality of life and IWQOL total score were significantly improved with exenatide (IWAOL 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. Significantly greater improvements in IWQOL total score were recorded for exenatide compared to pioglitazone (difference, 3.94; 95% CI, 1.28 to 6.61; $P=0.0038$), consistent with differences in body weight change. All groups showed significant improvements in all domains of the PGWB and the DTSQ total scores; greater improvement in overall treatment satisfaction was recorded with exenatide (3.96; 95% CI, 2.78 to 5.15) compared to sitagliptin (2.35; 95% CI, 1.19 to 3.51; difference, 1.61; 95% CI, 0.07 to 3.16; $P=0.0406$). Results for the EQ-5D were not reported.</p> <p>For patients treated with exenatide and sitagliptin, the most common treatment-emergent adverse events were nausea and diarrhea, whereas upper respiratory tract infection and peripheral edema were most common in those on pioglitazone. Vomiting was more common with exenatide than with sitagliptin or pioglitazone. There were no episodes of major hypoglycemia.</p>
<p>Nauck et al³⁴</p> <p>Sitagliptin 100 mg Daily in addition to metformin $\geq 1,500$ mg/day (SIT+MET)</p>	<p>AC, DB, MC, NI, PG, RCT</p> <p>Patients 18 to 78 years of age with type 2 diabetes</p>	<p>N=1,172</p> <p>52 weeks</p>	<p>Primary: NI of sitagliptin to glipizide (change in baseline HbA_{1c})</p> <p>Secondary:</p>	<p>Primary: In both the SIT+MET and GLI+MET groups, the least squares mean HbA_{1c} change from baseline was -0.67% (95% CI, -0.75 to -0.59). The upper limit of the two-sided 95% CI for the between group least squares mean difference of 0.08% was less than the prespecified NI margin of 0.3%.</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>vs</p> <p>glipizide Daily (5 mg titrated to a maximum of 20 mg) in addition to metformin $\geq 1,500$ mg/day (GLI+MET)</p>	<p>who were inadequately controlled ($HbA_{1c} \geq 6.5\%$ and $\leq 10\%$) on metformin monotherapy</p>		<p>FPG, fasting insulin, proinsulin, and lipid parameters, β-cell function, insulin resistance and sensitivity, safety and tolerability, change in body weight</p>	<p>A similar proportion of patients reached an HbA_{1c} level $<7\%$ in each group (63% for SIT+MET and 59% for GLI+MET; difference of 3.9%; 95% CI, -2.8 to 10.7). Sitagliptin showed NI to glipizide.</p> <p>Secondary: The change in FPG was not significantly different between groups. The least squares change from baseline for SIT+MET was -0.56 mmol/L (95% CI, -0.81 to -0.30) and -0.42 mmol/L for GLI+MET (95% CI, -0.67 to -0.17). SIT+MET treatment led to a decrease in fasting proinsulin compared with an increase with GLI+MET (<i>P</i> value not reported).</p> <p>Patients in the GLI+MET treatment group demonstrated a higher rate of hypoglycemia as compared to the SIT+MET group (32% vs 5%; <i>P</i><0.001). No meaningful differences in overall serious clinical adverse events were observed between the SIT+MET and the GLI+MET group.</p> <p>Body weight significantly decreased with SIT+MET. The least squares mean change from baseline was -1.5 kg (95% CI, -2 to -0.9). Body weight significantly increased in the GLI+MET group with a least squares mean change from baseline of 1.1 kg (95% CI, 0.5 to 1.6) with between-treatment difference of -2.5 kg (95% CI, -3.1 to -2.0; <i>P</i><0.001).</p>
<p>Rigby et al³⁵ (abstract)</p> <p>Colesevelam 3.75 g Daily, in addition to existing metformin therapy</p> <p>vs</p> <p>rosiglitazone 4 mg Daily, in addition to existing metformin therapy</p>	<p>MC, OL, RCT (1:1:1)</p> <p>Patients with inadequately controlled type 2 diabetes (HbA_{1c} 7% to 10%) on stable metformin regimen (1,500 to 2,550 mg Daily for ≥ 3 months)</p>	<p>N=169</p> <p>16 weeks</p>	<p>Primary: Change in HbA_{1c} at week 16 from baseline</p> <p>Secondary: Not reported</p>	<p>Primary: At week 16, all groups had a statistically significant reduction in HbA_{1c} from baseline (colesevelam, -0.3%; <i>P</i><0.031; rosiglitazone, -0.6%; <i>P</i><0.001; sitagliptin, -0.4%; <i>P</i><0.009).</p> <p>There was a statistically significant reduction in LDL from baseline in the colesevelam group (11.6%; <i>P</i> value not reported) and a statistically significant increase in LDL in the rosiglitazone and sitagliptin groups (7.8% and 7.7%; <i>P</i> value not reported).</p> <p>Secondary: Not reported</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs sitagliptin 100 mg Daily, in addition to existing metformin therapy				
Schwarz et al ³⁶ Scenario 1: Rosiglitazone added to metformin vs sitagliptin added to metformin Scenario 2: glipizide added to metformin vs sitagliptin added to metformin Scenario 3: glipizide added to metformin then change to rosiglitazone and metformin if glipizide failure vs sitagliptin added to	Cost-Effectiveness Patients with type 2 diabetes not at target HbA _{1c} (>6.5%) Cost-effectiveness analysis based on cost inputs from six countries and clinical data from Nauck et al ³⁴ and Scott et al ²⁹	N/A	Primary: Costs of adding sitagliptin to metformin compared with 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
metformin then change to rosiglitazone and metformin if sitagliptin failure				
<p>Richter et al³⁷</p> <p>Dipeptidyl peptidase-4 inhibitors (sitagliptin or vildagliptin*) as monotherapy or in combination with other hypoglycemic agents</p> <p>vs</p> <p>other hypoglycemic agents as monotherapy combination or lifestyle interventions</p>	<p>MA</p> <p>Patients ≥ 18 years of age with type 2 diabetes</p>	<p>N=12,684</p> <p>12 to 52 weeks</p>	<p>Primary: Change from baseline in HbA_{1c} and adverse events</p> <p>Secondary: Weight gain or weight loss and β-cell function</p>	<p>Primary:</p> <p>There was substantial heterogeneity in the studies evaluating HbA_{1c} with sitagliptin vs placebo, and the removal of one study caused the heterogeneity to significantly decrease. There was a significant mean HbA_{1c} difference between placebo and sitagliptin of -0.7% in favor of sitagliptin (95% CI, -0.8 to -0.6; <i>P</i><0.00001). There was substantial heterogeneity in the 6 studies that evaluated HbA_{1c} with vildagliptin vs placebo, and the removal of two studies study caused the heterogeneity to significantly decrease. There was a significant mean HbA_{1c} difference between placebo and vildagliptin of -0.6% in favor of vildagliptin (95% CI, -0.7 to -0.5; <i>P</i><0.00001). The studies evaluating sitagliptin monotherapy vs another hypoglycemic agent monotherapy had significant heterogeneity and pooled analysis could not be performed. When comparing vildagliptin to another hypoglycemic agent, the mean HbA_{1c} difference was 0.3% in favor of the control interventions (95% CI, 0.1 to 0.5; <i>P</i>=0.0002). There was substantial heterogeneity when comparing sitagliptin or vildagliptin combination therapy with another combination of hypoglycemic agents and a pooled analysis could not be performed.</p> <p>There was not statistically significant difference between the groups in severe adverse events, discontinuation due to adverse events and hypoglycemic episodes. All cause infections was significantly increased in the sitagliptin group compared to placebo and other hypoglycemic agents (RR, 1.15, 95% CI, 1.02 to 1.31, <i>P</i>=0.03). There was no significant difference in all cause infections between vildagliptin vs placebo and other hypoglycemic agents.</p> <p>The mean difference in weight between sitagliptin and placebo and other hypoglycemic agents was 0.66 kg (95% CI, 0.37 to 0.94; <i>P</i><0.00001) in favor of the comparators. When comparing vildagliptin to placebo and other hypoglycemic agents, the mean difference was 1.32 kg (95% CI, 1.02 to 1.63; <i>P</i><0.00001) in favor of the comparators.</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				<p>Pooling of data on the effects of dipeptidyl peptidase-4 inhibitors on β-cell function was not performed due to lack of data and differing methods used in the studies to evaluate the outcome.</p> <p>Health-related quality of life, mortality, morbidity and costs were listed as outcomes; however, they were not analyzed due to insufficient data.</p>
<p>Amori et al³⁸</p> <p>Incretin-based therapies (exenatide, liraglutide, sitagliptin, and vildagliptin*)</p> <p>vs</p> <p>non-incretin-based therapy (placebo or hypoglycemic agent)</p>	<p>MA</p> <p>29 RCTs reporting HbA_{1c} levels in nonpregnant type 2 diabetic patients</p>	<p>N=12,996</p> <p>Duration varied from 12 to 52 weeks</p>	<p>Primary: Change from baseline in HbA_{1c}</p> <p>Secondary: Treatment group difference in FPG and the proportion of patients achieving HbA_{1c} <7%</p>	<p>Primary: The dipeptidyl peptidase-4 inhibitors as a class significantly decreased HbA_{1c} compared with placebo (-0.74%; 95% CI, -0.85% to -0.62%) with similar efficacy as monotherapy or combination. Both sitagliptin and vildagliptin were shown to cause a similar decrease in HbA_{1c} vs placebo (-0.74% vs -0.73%). No clinical trials have been performed directly comparing these agents. Dipeptidyl peptidase-4 inhibitors (4 trials) demonstrated slightly less efficacy in regards to glycemic outcomes when compared to other hypoglycemic agents (0.21%; 95% CI, 0.02% to 0.39%). Sitagliptin was determined to be as effective as glipizide in 1 trial.</p> <p>Patients in dipeptidyl peptidase-4 inhibitor groups achieved an HbA_{1c} level <7% at a greater rate vs placebo (43% vs 17%; risk ratio, 2.5%; 95% CI, 2.1 to 2.8). No difference was found between sitagliptin and vildagliptin. Overall, there was a larger decrease in HbA_{1c} noted in patients with higher levels at baseline.</p> <p>Pooled analysis of trials comparing GLP-1 analogues to placebo showed a statistically significant difference in reducing HbA_{1c} from baseline favoring the GLP-1 analogues (WMD, -0.97; 95% CI, -1.13 to -0.81).</p> <p>Specifically, no difference in the HbA_{1c} was found in OL NI trials between exenatide and insulin glargine or biphasic aspart (WMD, -0.06; 95% CI, -0.22 to 0.10). Liraglutide showed similar HbA_{1c} efficacy compared with OL glimepiride titrated to glycemic goals or DB maximum dose metformin (data not reported).</p> <p>Secondary: A greater improvement in FPG with the dipeptidyl peptidase-4 inhibitors was determined when compared to placebo (-18 mg/dL; 95% CI, -22 to -14 mg/dL),</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				<p>with sitagliptin providing a greater decrease than vildagliptin. Statistically significant decreases in PPG were shown with sitagliptin at 2 hours after a meal. Sitagliptin did not show an overall change in lipid profile as compared to placebo.</p> <p>In 13 trials dipeptidyl peptidase-4 inhibitors demonstrated a small increase in weight as compared to placebo (0.5 kg; 95% CI, 0.3 to 0.7 kg). In 1 trial comparing it to glipizide, sitagliptin provided a decrease in body weight compared to an increase with glipizide (-2.5 vs 1.0 kg, respectively).</p> <p>Only 2 patients experienced severe hypoglycemia while on dipeptidyl peptidase-4 inhibitors. An increased risk of infection (nasopharyngitis, urinary tract infection) and headache was observed with the dipeptidyl peptidase-4 inhibitors; however, they had a much lower rate of gastrointestinal side effects relative to comparators.</p> <p>Only data from patients taking the maximum dose of sitagliptin, 100 mg, was used in the MA to calculate dose-dependent outcomes such as glycemic efficacy. Reported data from patients taking the entire range of doses was evaluated for side effects.</p> <p>Exenatide-treated patients were more likely to achieve HbA_{1c} <7.0% than placebo-treated patients (45% vs 10%, respectively; RR, 4.2; 95% CI, 3.2 to 5.5) while no difference in the proportion of patients achieving this goal was seen between exenatide or insulin therapy in noninferiority trials (39% vs 35%, respectively; RR, 1.1; 95% CI, 0.8 to 1.5). No information was reported for liraglutide for this secondary outcome. Compared to placebo, FPG was reduced with GLP-1 analogues (WMD, -27 mg/dL; 95% CI, -33 to -21).</p>
<p>Fakhoury et al³⁹</p> <p>Incretin-based therapies (exenatide, liraglutide, sitagliptin or vildagliptin) vs</p>	<p>MA</p> <p>RCTs comparing incretin-based therapies to placebo in type 2 diabetics ≥18</p>	<p>N=Not reported (38 RCTs; 8, exenatide; 7, liraglutide; 12, sitagliptin;</p>	<p>Primary: Change from baseline HbA_{1c}, weight and BMI</p> <p>Secondary: Not reported</p>	<p>Primary: Both sitagliptin (WMD, -0.79; 95% CI, -0.93 to -0.65; <i>P</i><0.001) and vildagliptin (WMD, -0.67; 95% CI, -0.83 to -0.52; <i>P</i><0.001) were shown to produce a statistically significant reductions in HbA_{1c} compared with placebo.</p> <p>Both exenatide (WMD, -0.75; 95% CI, -0.83 to -0.67; <i>P</i><0.001) and liraglutide (WMD, -1.03; 95% CI, -1.16 to -0.90; <i>P</i><0.0010) showed a statistically</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo	years of age	11, vildagliptin Duration varied from 4 to 52 weeks		<p>significant difference in HbA_{1c} decrease from baseline. 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; <i>P</i><0.001). In the adjusted analyses for liraglutide, no covariates were found to be statistically significant.</p> <p>There was a statistically significant weight gain with sitagliptin (WMD, 0.60; 95% CI, 0.33 to 0.87; <i>P</i><0.001) and vildagliptin (WMD, 0.56; 95% CI, 0.27 to 0.84; <i>P</i><0.001) compared with placebo. Exenatide (WMD, -1.10; 95% CI, -1.32 to -0.88; <i>P</i><0.001) and liraglutide (WMD, -0.82; 95% CI, -1.92 to -0.27; <i>P</i>=0.142) both exhibited reduction in weight. The most remarkable result is the average weight reduction of 1.10 kg observed with exenatide.</p> <p>A nonstatistically significant increase in the number of vildagliptin-treated patients who reported hypoglycemic episodes in comparison to those who received a placebo was observed (RR, 1.52; 95% CI, 0.80 to 2.88; <i>P</i>=0.196). Sitagliptin-treated patients were 156% more likely to experience some hypoglycemia in comparison to placebo patients (RR, 2.56; 95% CI, 1.23 to 5.33; <i>P</i>=0.01). When adjusted for covariates, age was the only variable found to be statistically significant (RR, 1.84; 95% CI, 1.02 to 3.34; <i>P</i>=0.044). Exenatide-treated patients were 140% more likely to experience some hypoglycemia than patients treated with placebo, and this difference was statistically significant (RR, 2.40; 95% CI, 1.39 to 4.11; <i>P</i>=0.002). Patients treated with liraglutide were 69% more likely to experience some hypoglycemia compared to placebo (RR, 1.69; 95% CI, 1.00 to 2.86; <i>P</i>=0.050).</p> <p>Secondary: Not reported</p>

*Agent is not available in the United States.

Drug regimen abbreviations: BID=twice daily, IU=international units, SC=subcutaneous

Study abbreviations: AC=active-controlled, DB=double-blind, DD=double dummy, MA=meta-analysis, MC=multicenter, NI=noninferiority, OL=open-label, PC=placebo controlled, PG=parallel-group, RCT=randomized controlled trial, XO=crossover, SR=systematic review

Miscellaneous abbreviations: BMI=body mass index, BNP= brain natriuretic peptide, CI=confidence interval, CRP=C-reactive protein, DBP=diastolic blood pressure, DTSQ=Diabetes Treatment Satisfaction Questionnaire, EQ-5D=EuroQoL Quality of Life, FPG=fasting plasma glucose, FSG=fasting serum glucose, GLP-1=glucagon-like-peptide-1, HbA_{1c}=hemoglobin A_{1c}, HDL=high-density lipoprotein, HOMA-β=homeostasis model assessment-β-cell function, HOMA-IR=homeostasis model assessment-insulin resistance, IR=immediate-release, IWQOL=Impact of Weight on Quality of Life Questionnaire, LDL=low-density lipoprotein, MDG=mean of 7 daily self-blood glucose, mm Hg=millimeter of mercury, NS=not significant, OGTT=oral glucose tolerance test, OR=odds ratio, PAI-

1=plasminogen activator inhibitor-1, PGWB=Psychological General Well-being index, PPG=postprandial glucose, QALY=quality-adjusted life year, RR=relative risk, SBP=systolic blood pressure, SE=standard error, TG=triglycerides, TNF- α =tumor necrosis factor- α , TZD=thiazolidinedione, QUICKI=quantitative insulin sensitivity check index, WMD=weighted mean difference

Special Populations

Table 5. Special Populations^{1,7,8}

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Single Entity Products					
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 required in moderate or severe renal impairment, or end-stage renal disease (creatinine clearance ≤ 50 mL/minute).	No dosage adjustment required.	B	Unknown
Sitagliptin	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Safety and efficacy in children have not been established.	Renal dose adjustment is required; for creatinine clearances of ≥ 30 to < 50 mL/minute; a dose of 50 mg once daily is recommended. Renal dose adjustment is required; for creatinine clearances of < 30 mL/minute (or end-stage renal disease requiring dialysis); a dose of 25 mg once daily is recommended.	No dosage adjustment required.	B	Unknown
Combination Product					
Sitagliptin/ metformin hydro- chloride	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients with sitagliptin. Safety and efficacy in children have not been established.	Should not be used in patients with renal disease or renal dysfunction.	Should be avoided in patients with clinical or laboratory evidence of hepatic disease.	B	Unknown

Adverse Drug Events

The most common adverse reactions, as reported in the manufacturer prescribing information, are noted in Table 6. The data comes from controlled clinical studies with single entity dipeptidyl peptidase-4 inhibitor monotherapy and in combination with a thiazolidinedione, glyburide, glimepiride or metformin hydrochloride. There was an increased risk of hypoglycemia when administered in combination with a sulfonylurea. The overall incidence of the other adverse events was similar to placebo.

Table 6. Adverse Drug Events^{1,7,8}

Adverse Event	Generic Name	Reported Frequency (%)
Abdominal discomfort	Sitagliptin + metformin hydrochloride	3
Headache	Saxagliptin	6.5
	Sitagliptin + pioglitazone	5.1
	Sitagliptin + glimepiride (+/- metformin hydrochloride)	5.9
	Sitagliptin/metformin hydrochloride	5.9
Diarrhea	Sitagliptin/metformin hydrochloride	7.5
Hypoglycemia	Sitagliptin + glimepiride (+/- metformin hydrochloride)	12.2
Nausea	Sitagliptin/metformin hydrochloride	7 to 26
Nasopharyngitis	Sitagliptin	5.2
	Sitagliptin + glimepiride (+/- metformin hydrochloride)	6.3
	Sitagliptin/metformin hydrochloride	5
Upper respiratory tract infection	Saxagliptin	7.7
	Sitagliptin + pioglitazone	6.3
	Sitagliptin/metformin hydrochloride	4.5 to 6.3
Urinary tract infection	Saxagliptin	6.8

Contraindications/Precautions

The use of sitagliptin is contraindicated in patients with a history of a hypersensitivity reaction to it.⁷ Saxagliptin has no documented contraindications.¹

A dosage adjustment is recommended in patients with moderate to severe renal insufficiency, as well as, in patients with end-stage renal disease on dialysis. When used in combination with a sulfonylurea, a decreased dose of the sulfonylurea is recommended to reduce the risk of hypoglycemia.^{1,7} There have been postmarketing reports of serious hypersensitivity reactions with sitagliptin, including anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome. The exact frequency has not been established due to these reports being self-reported.⁷

The combination product containing sitagliptin and metformin hydrochloride is contraindicated in patients with renal disease or dysfunction, and acute or chronic metabolic acidosis including diabetic ketoacidosis, with or without coma. Patients undergoing radiologic studies with iodinated contrast material should temporarily discontinue the combination product. Due to the metformin hydrochloride component this combination product also contains a black box warning which is outlined below.⁸

Black Box Warning for Sitagliptin and Metformin Hydrochloride⁸

WARNING
<p>Lactic Acidosis: Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin hydrochloride accumulation during treatment with metformin hydrochloride; when it occurs, it is fatal in approximately 50% of cases. Lactic acidosis may also occur in association with a number of pathophysiologic conditions, including diabetes, and whenever there is significant tissue hypoperfusion and hypoxemia. Lactic acidosis is characterized by elevated blood lactate levels (>5 mmol/L),</p>

WARNING

decreased blood pH, electrolyte disturbances with an increased anion gap, and an increased lactate/pyruvate ratio. When metformin hydrochloride is implicated as the cause of lactic acidosis, metformin hydrochloride plasma levels $>5 \mu\text{g/mL}$ are generally found.

The reported incidence of lactic acidosis in patients receiving metformin hydrochloride is very low (approximately 0.03 cases/1,000 patient-years, with approximately 0.015 fatal cases/1,000 patient-years). In more than 20,000 patient-years exposure to metformin hydrochloride in clinical trials, there were no reports of lactic acidosis. Reported cases have occurred primarily in diabetic patients with significant renal insufficiency, including both intrinsic renal disease and renal hypoperfusion, often in the setting of multiple concomitant medical/surgical problems and multiple concomitant medications. Patients with congestive heart failure requiring pharmacologic management, in particular those with unstable or acute congestive heart failure who are at risk of hypoperfusion and hypoxemia, are at increased risk of lactic acidosis. The risk of lactic acidosis increases with the degree of renal dysfunction and the patient's age. The risk of lactic acidosis may, therefore, be significantly decreased by regular monitoring of renal function in patients taking metformin hydrochloride and by use of the minimum effective dose of metformin hydrochloride. In particular, treatment of the elderly should be accompanied by careful monitoring of renal function. Metformin hydrochloride treatment should not be initiated in patients ≥ 80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced, as these patients are more susceptible to developing lactic acidosis. In addition, metformin hydrochloride should be promptly withheld in the presence of any condition associated with hypoxemia, dehydration, or sepsis. Because impaired hepatic function may significantly limit the ability to clear lactate, metformin hydrochloride should generally be avoided in patients with clinical or laboratory evidence of hepatic disease. Patients should be cautioned against excessive alcohol intake, either acute or chronic, when taking metformin hydrochloride, since alcohol potentiates the effects of metformin hydrochloride on lactate metabolism. In addition, metformin hydrochloride should be temporarily discontinued prior to any intravascular radiocontrast study and for any surgical procedure.

The onset of lactic acidosis often is subtle, and accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. There may be associated hypothermia, hypotension, and resistant bradyarrhythmias with more marked acidosis. The patient and the patient's physician must be aware of the possible importance of such symptoms and the patient should be instructed to notify the physician immediately if they occur.

Metformin hydrochloride should be withdrawn until the situation is clarified. Serum electrolytes, ketones, blood glucose, and if indicated, blood pH, lactate levels, and even blood metformin hydrochloride levels may be useful. Once a patient is stabilized on any dose level of metformin hydrochloride, gastrointestinal symptoms, which are common during initiation of therapy, are unlikely to be drug related. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious disease.

Levels of fasting venous plasma lactate above the upper limit of normal but less than 5 mmol/L in patients taking metformin hydrochloride do not necessarily indicate impending lactic acidosis and may be explainable by other mechanisms, such as poorly controlled diabetes or obesity, vigorous physical activity, or technical problems in sample handling.

Lactic acidosis should be suspected in any diabetic patient with metabolic acidosis lacking evidence of ketoacidosis (ketonuria and ketonemia).

Lactic acidosis is a medical emergency that must be treated in a hospital setting. In a patient with lactic acidosis who is taking metformin hydrochloride, the drug should be discontinued immediately and general supportive measures promptly instituted. Because metformin hydrochloride is dialyzable (with a clearance of up to 170 mL/minute under good hemodynamic conditions), prompt hemodialysis is recommended to correct the acidosis and remove the accumulated metformin hydrochloride. Such management often results in prompt reversal of symptoms and recovery.

Drug Interactions

According to the manufacturer's prescribing information, in studies conducted in healthy subjects, saxagliptin did not meaningfully alter the pharmacokinetics of metformin hydrochloride, glyburide, pioglitazone, digoxin, simvastatin, diltiazem, or ketoconazole.¹

Table 7. Drug Interactions^{1,5,7,8}

Generic Name	Interacting Medication or Disease	Potential Result
Sitagliptin, Sitagliptin/metformin hydrochloride	Digoxin	Sitagliptin may increase the concentration of digoxin. Monitor patients receiving digoxin appropriately. No dosage adjustment of digoxin or sitagliptin is recommended.
Saxagliptin	Strong CYP3A4/5 inhibitors (atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin)	Increases in the concentration of saxagliptin may occur when administered concomitantly with strong CYP3A4/5 inhibitors. A reduction in the dose of saxagliptin may be necessary. ¹

Dosage and Administration

Dose adjustment is recommended in patients with moderate-to-severe renal insufficiency, as well as, in patients with end-stage renal disease on dialysis.

Table 8. Dosing and Administration^{1,7,8}

Generic Name	Adult Dose	Pediatric Dose	Availability
Single Entity Products			
Saxagliptin	<u>Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes as either monotherapy or combination therapy:</u> 2.5 or 5 mg Daily regardless of meals	Safety and efficacy in children have not been established.	Tablets: 2.5 mg 5 mg
Sitagliptin	<u>Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes as either monotherapy or combination therapy:</u> Tablet: 100 mg Daily	Safety and efficacy in children have not been established.	Tablet: 25 mg 50 mg 100 mg
Combination Product			
Sitagliptin/metformin hydrochloride	<u>Adjunct to diet and exercise, to improve glycemic control in adult patients with type 2 diabetes when therapy with both metformin hydrochloride and sitagliptin is appropriate:</u> Tablet: initial dose based on the patient's current regimen BID with meals; maximum, 100 mg/2,000 mg/day	Safety and efficacy in children have not been established.	Tablet: 50 mg/500 mg 50 mg/1,000 mg

Drug regimen abbreviations: BID=twice daily

Potential Advantages

- Dipeptidyl peptidase-4 inhibitors provides broader options for treatment using distinct mechanisms of action, especially in patients who continue to have poor glycemic control with adequate trials of first-line antihyperglycemic agents.
- Weight neutral effect.
- Low incidence of documented adverse events (i.e., hypoglycemia).
- No documented cardiovascular-related issues.

Potential Disadvantages/Unanswered Questions

- Lack of long-term safety and efficacy data.
- Safety and efficacy in children under 18 years has not been established.
- Renal dosing is required.
- There have been no head to head trials to date comparing the agents in this class yet.
- Substantially increased costs compared with first-line agents.

Clinical Guidelines

As of 2010, the American Diabetes Association (ADA) endorses the use of a glycosylated hemoglobin (HbA_{1c}) ≥6.5% as a primary criterion for the diagnosis of diabetes.⁴⁰ The ADA made this new recommendation based on data demonstrating that retinopathy occurs in patients with this HbA_{1c} at approximately the same rate (10%) as in individuals who are diagnosed based on current fasting and post-challenge glucose criteria.⁴¹ In addition to the ADA, the American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE) state that the use of HbA_{1c} for the diagnosis of diabetes has several advantages but when used as the primary criterion, approximately 20% fewer people will be indentified compared to if the existing criteria is used (fasting plasma glucose and oral glucose tolerance tests).^{41,42} The ADA also states that, in practice, a large portion of patients with type 2 diabetes remains unaware of their condition so it is conceivable that the lower sensitivity of HbA_{1c} at the designated cut point will be offset by the test’s greater practicality, and that wider application of a more convenient test (HbA_{1c}) may actually increase the number of diagnoses made.⁴¹

While it is now accepted to use HbA_{1c} as an option for the diagnosis of diabetes, additional recommendations from the ADA and AACE/ACE have been made in order to avoid under diagnosing.^{41,42} These additional recommendations include considering HbA_{1c} as an optional criterion; not as the primary criterion for diagnosis, using traditional glucose criteria for diagnosis when feasible, not using HbA_{1c} to diagnosis type 1 or gestational diabetes and to utilize only standardized, validated assays for HbA_{1c}. The recommendations also state that the HbA_{1c} may be misleading in certain ethnic populations, various hemoglobinopathies, iron deficiency, hemolytic anemias, thalassemias, spherocytosis and severe hepatic and renal disease; therefore, appropriate HbA_{1c} assays should be used in these patients. The use of HbA_{1c} is not endorsed as criteria for pre-diabetes or for those at risk for diabetes. However, an HbA_{1c} of 5.5 to 6.4% can be used as a screening test for pre-diabetes if it leads to measurement of fasting glucose or a glucose tolerance test for diagnosis.⁴²

According to the algorithm for glycemic control released by the AACE/ACE, antidiabetic treatment regimens should be based on a patient’s HbA_{1c}.⁹ Specifically, patients with a level ≤7.5% may be able to achieve a goal of 6.5% with monotherapy, while patients with a level of 7.6 to 9.0% should be initiated on combination therapy as they are less likely to achieve glycemic goals with monotherapy. The ADA and AACE/ACE guidelines state that metformin hydrochloride will be the cornerstone of any treatment regimen for most diabetic patients due to its established efficacy and safety.

Table 9. Clinical Guidelines

Clinical Guideline	Recommendation(s)
American Diabetes Association: Standards of Medical Care in Diabetes (2010) ⁴⁰	<p><u>Current criteria for the diagnosis of diabetes</u></p> <ul style="list-style-type: none"> • The following are the criteria for a diagnosis of diabetes: glycosylated hemoglobin (HbA_{1c}) ≥6.5%, OR a fasting plasma glucose (FPG) ≥126 mg/dL, OR a 2-hour plasma glucose ≥200 mg/dL during an oral glucose tolerance test OR patients with classic symptoms of hyperglycemia or hyperglycemic crisis (random plasma glucose ≥200 mg/dL). <p><u>Prevention/delay of type 2 diabetes</u></p> <ul style="list-style-type: none"> • An ongoing support program for weight loss of 5 to 10% of body

Clinical Guideline	Recommendation(s)
	<p>weight and an increase in physical activity, to at least 150 minutes/week of moderate activity, should be encouraged in patients with impaired glucose tolerance or impaired fasting glucose.</p> <ul style="list-style-type: none"> In addition to lifestyle modifications, metformin hydrochloride may be considered in patients at high-risk for developing diabetes, obese patients and patients <60 years of age. <p><u>Glycemic goals in adults</u></p> <ul style="list-style-type: none"> For microvascular disease prevention, the HbA_{1c} goal for nonpregnant adults in general is <7.0%. The general goal of <7.0% is reasonable for many adults for macrovascular risk reduction. <p><u>Treatment of type 2 diabetes</u></p> <ul style="list-style-type: none"> Please see the American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) guideline.³¹
<p>American Diabetes Association/European Association for the Study of Diabetes: Management of Hyperglycemia in Type 2 Diabetes: A Consensus Algorithm for the Initiation and Adjustment of Therapy (2009)¹⁰</p>	<ul style="list-style-type: none"> The goal of the recommended algorithm is to achieve and maintain HbA_{1c} levels <7.0% and to change interventions at as rapid a pace as titration of medications allows when target glycemic goals are not being achieved. The α-glucosidase inhibitors, amylin agonists, dipeptidyl peptidase-4 (DPP-4) inhibitors and glinides are not included in the two tiers of preferred agents in the algorithm due to their lower or equivalent overall glucose-lowering effectiveness compared with the first- and second-tier agents, and/or due to limited clinical data or relative expense. These agents may be appropriate choices in selected patients. <p><u>Tier 1: well-validated core therapies</u></p> <ul style="list-style-type: none"> These interventions represent the best established and most effective and cost-effective therapeutic strategies for achieving target glycemic goals, and are the preferred route of therapy for most type 2 diabetic patients. Step 1: Lifestyle interventions and metformin hydrochloride should be initiated concurrently at diagnosis of type 2 diabetes. Step 2: If lifestyle interventions and the maximal tolerated dose of metformin hydrochloride fail to achieve or sustain glycemic goals after two to three months, insulin or a sulfonylurea should be added. The choice between insulin and a sulfonylurea will be based on the HbA_{1c} levels, with consideration given to insulin (the more effective glycemia-lowering agent) for patients with an HbA_{1c} >8.5%. However, many newly diagnosed type 2 diabetic patients will usually respond to oral medications. Step 3: If lifestyle interventions, metformin hydrochloride and basal insulin or a sulfonylurea do not achieve glycemic goals, insulin therapy should be initiated or intensified. <p><u>Tier 2: less well-validated therapies</u></p> <ul style="list-style-type: none"> In selected clinical settings, the tier 2 algorithm may be considered. Specifically, when hypoglycemia is particularly undesirable, the addition of exenatide or pioglitazone may be considered. Rosiglitazone is not recommended.

Clinical Guideline	Recommendation(s)
	<ul style="list-style-type: none"> • Additionally, if a major consideration is weight loss and the HbA_{1c} level is close to target (<8.0%), then exenatide may be an option (at the time of publication only exenatide had Food and Drug Administration [FDA] approval). • If these interventions do not effectively achieve glycemic goals or if they are not tolerated, the addition of a sulfonylurea could be considered or the tier 2 interventions should be discontinued and basal insulin should be initiated. <p><u>Rationale for selecting specific combinations</u></p> <ul style="list-style-type: none"> • Over time the majority of patients will require more than one medication. • When selecting combination therapy, in general, antihyperglycemic drugs with different mechanisms of action will have the greatest synergy. • Combination insulin and metformin hydrochloride therapy is a particularly effective means of lowering glycemia with limited weight gain. <p><u>Special considerations/patients</u></p> <ul style="list-style-type: none"> • In the setting of severely uncontrolled diabetes with catabolism combination insulin and lifestyle intervention therapy is the treatment of choice.
<p>American Association of Clinical Endocrinologists/ American College of Endocrinology: Statement by an American Association of Clinical Endocrinologists/ American College of Endocrinology Consensus Panel of Type 2 Diabetes Mellitus: An Algorithm for Glycemic Control (2009)⁹</p>	<p><u>Principles underlying the algorithm</u></p> <ul style="list-style-type: none"> • Lifestyle (dietary and exercise) modifications are essential for all patients with diabetes. • Achieving an HbA_{1c} 6.5% is recommended as the primary goal; however, the goal must be customized for individual patients. • If glycemic goals are not achieved, dosages of medications can be titrated, regimens can be changed (add or discontinue medications), or, in certain instances, glycemic goals can be reconsidered and revised. • When using combination therapy it is important to have medications that have complementary mechanisms of action. • Effectiveness of therapy must be re-evaluated frequently, typically every two to three months. <p><u>Stratification by current HbA_{1c}</u></p> <ul style="list-style-type: none"> • Patients with an HbA_{1c} ≤7.5% may be able to achieve a goal of 6.5% with monotherapy; however, if monotherapy fails to achieve this goal, the usual progression is to combination therapy, and then to triple therapy. Insulin therapy, with or without additional agents, should be initiated if goals still fail to be achieved. • Patients with an HbA_{1c} of 7.6 to 9.0% should be initiated on combination therapy as monotherapy in these patients is likely not to achieve glycemic goals. If combination therapy fails, triple therapy and then insulin therapy, with or without additional oral agents, should be administered. • Patients with an HbA_{1c} >9.0% have a small possibility of achieving glycemic goals, even with combination therapy. In these patients, if they are asymptomatic triple therapy based on a combination of metformin hydrochloride and an incretin mimetic or a DPP-4 inhibitor

Clinical Guideline	Recommendation(s)
	<p>combined with either a sulfonylurea or a thiazolidinedione (TZD) should be initiated. If patients are symptomatic or if they have failed therapy with similar agents, insulin therapy with or without additional oral agents should be initiated.</p> <p><u>Management of patients with a HbA_{1c} of 6.5 to 7.5%</u></p> <ul style="list-style-type: none"> • In these patients monotherapy with metformin hydrochloride, an α-glucosidase inhibitor, a DPP-4 inhibitor or a TZD are recommended. Because of the established safety and efficacy of metformin hydrochloride, it is the cornerstone of monotherapy and is usually the most appropriate initial choice for monotherapy. • If monotherapy, even after appropriate dosage titration, is unsuccessful in achieving glycemic goals combination therapy should be initiated. • Because of the established safety and efficacy of metformin hydrochloride, it is considered the cornerstone of combination therapy for most patients. When contraindicated, a TZD may be used as the foundation for combination therapy options. • Due to the mechanism of action (insulin sensitizer) of metformin hydrochloride and TZDs, it is recommended that the second agent in combination therapy be an incretin mimetic, DPP-4 inhibitor or a secretagogue (glinide or sulfonylurea). • The glucagon-like-peptide-1 (GLP-1) receptor agonists (incretin mimetics) and DPP-4 inhibitors are associated with less hypoglycemia compared to the secretagogues. • Despite the gastrointestinal side effects, dosing frequency and injection-based therapy, the GLP-1 agonists are preferred due to its greater effectiveness in reducing postprandial glucose excursions (relative to the DPP-4 inhibitors) and the potential for weight loss. • Combination metformin hydrochloride and TZD therapy is efficacious but carries risks of adverse events associated with both agents. The combination is recommended with a higher priority than a secretagogue because of a lower risk of hypoglycemia and greater flexibility in timing of administration. • The combination therapies of metformin hydrochloride and an α-glucosidase inhibitor and metformin hydrochloride and colesevelam are also included in the algorithm because of their safety and the ability of colesevelam to lower lipid profiles. • If combination therapy fails after each medication has been titrated to its maximally effective dose then triple therapy should be initiated. • The following triple therapy regimens are considered: <ul style="list-style-type: none"> ○ Metformin hydrochloride + GLP-1 agonist + TZD. ○ Metformin hydrochloride + GLP-1 agonist + glinide. ○ Metformin hydrochloride + GLP-1 agonist + sulfonylurea. ○ Metformin hydrochloride + DPP-4 inhibitor + TZD. ○ Metformin hydrochloride + DPP-4 inhibitor + glinide. ○ Metformin hydrochloride + DPP-4 inhibitor + sulfonylurea. • Because of the established safety and efficacy of metformin hydrochloride, it is considered the cornerstone for triple therapy. • The GLP-1 agonist, exenatide, is the second preferred component of triple therapy because of its safety (low risk of hypoglycemia) and its potential for inducing weight loss. It also inhibits glucagon secretion in

Clinical Guideline	Recommendation(s)
	<p>a glucose-dependent manner after consumption of means resulting in increased satiety and delayed gastric emptying.</p> <ul style="list-style-type: none"> • The third component of triple therapy is recommended in order to minimize the risk of hypoglycemia. • The combination with metformin hydrochloride, especially when combined with an incretin mimetic, may counteract the weight gain often associated with glinides, sulfonylureas, and TZDs. • When triple therapy fails to achieve glycemic goals, insulin therapy is needed. <p><u>Management of patients with a HbA_{1c} of 7.6 to 9.0%</u></p> <ul style="list-style-type: none"> • The management of these patients is similar to that just described except patients can proceed directly to combination therapy because monotherapy is unlikely to be successful in these patients. • The following combination therapy regimens are considered: <ul style="list-style-type: none"> ○ Metformin hydrochloride + GLP-1 agonist. ○ Metformin hydrochloride + DPP-4 inhibitor. ○ Metformin hydrochloride + TZD. ○ Metformin hydrochloride + sulfonylurea. ○ Metformin hydrochloride + glinide. • Metformin hydrochloride is again considered the cornerstone of combination therapy. • A GLP-1 agonist or a DPP-4 inhibitor is the preferred second component in view of the safety and efficacy of these agents in combination with metformin hydrochloride. Additionally, a GLP-1 agonist is given higher priority in view of its somewhat greater effect on reducing postprandial glucose excursions and its potential for inducing substantial weight loss. • TZDs are positioned lower due to the risks of weight gain, fluid retention, congestive heart failure and fractures associated with their use. • Glinides and sulfonylureas are relegated to the lowest position because the greater risk of inducing hypoglycemia. • When combination therapy fails to achieve glycemic goals, triple therapy should be started. • The following triple therapy regimens are considered: <ul style="list-style-type: none"> ○ Metformin hydrochloride + GLP-1 agonist + TZD. ○ Metformin hydrochloride + DPP-4 inhibitor + TZD. ○ Metformin hydrochloride + GLP-1 agonist + sulfonylurea. ○ Metformin hydrochloride + DPP-4 inhibitor + sulfonylurea. ○ Metformin hydrochloride + TZD + sulfonylurea. • Metformin hydrochloride is the foundation to which either a TZD or sulfonylurea is added, followed by incretin-based therapy with either a GLP-1 agonist or a DPP-4 inhibitor. • The preference for metformin hydrochloride and the GLP-1 agonist or DPP-4 inhibitor is based on the safety of these agents and minimal associated risks of hypoglycemia. • TZDs are assigned a higher priority than a sulfonylurea because of their lower risk of hypoglycemia. • A GLP-1 agonist is assigned a higher priority than a DPP-4 inhibitor because of its somewhat greater effect on reducing postprandial glucose excursions and the possibility that it might induce

Clinical Guideline	Recommendation(s)
	<p>considerable weight loss.</p> <ul style="list-style-type: none"> • Metformin hydrochloride + TZD + sulfonylurea is relegated to the lowest priority due to an increased risk of weight gain and hypoglycemia. • α-glucosidase inhibitors, colesevelam, and glinides are not considered as options in these patients due to their limited HbA_{1c}-lowering potential. • The considerations for insulin therapy in these patients are similar to those used in patients with an HbA_{1c} of 6.5 to 7.5%. <p><u>Management of patients with a HbA_{1c} >9.0%</u></p> <ul style="list-style-type: none"> • Patients who are drug-naïve with an HbA_{1c} >9.0% are unlikely to achieve glycemic goals with the use of one, two or even three agents (other than insulin). • For patients who are asymptomatic, particularly with a relatively recent onset of diabetes, there is a good chance that some endogenous β-cell function exists; implying that combination or triple therapy may be sufficient. • The following combination and triple therapy regimens are considered: <ul style="list-style-type: none"> ○ Metformin hydrochloride + GLP-1 agonist. ○ Metformin hydrochloride + GLP-1 agonist + sulfonylurea. ○ Metformin hydrochloride + DPP-4 inhibitor. ○ Metformin hydrochloride + DPP-4 inhibitor + sulfonylurea. ○ Metformin hydrochloride + TZD. ○ Metformin hydrochloride + TZD + sulfonylurea. ○ Metformin hydrochloride + GLP-1 agonist + TZD. ○ Metformin hydrochloride + DPP-4 inhibitor + TZD. • Metformin hydrochloride again provides the foundation of treatment in these patients. • An incretin-based therapy can be added with a GLP-1 agonist being preferred due to its greater effectiveness at controlling postprandial glycemia and its potential for inducing weight loss. However the DPP-4 inhibitors in combination with metformin hydrochloride have also demonstrated a robust benefit for drug-naïve patients in this HbA_{1c} range. • A sulfonylurea or a TZD can also be added, with a sulfonylurea being preferred because of its somewhat greater efficacy and more rapid onset of action. • If patients are symptomatic (polydipsia, polyuria and weight loss) or if they have already failed the aforementioned treatment regimens, insulin therapy should be initiated without delay. • Insulin therapy for these patients follows the same principals as outlined previously for patients with different HbA_{1c} levels. • This algorithm favors the use of GLP-1 agonists (at the time of publication only exenatide had FDA approval) and DPP-4 inhibitors with higher priority due to their effectiveness and overall safety profiles. Additionally, due to the increasing amount of literature indicating the serious risks of hypoglycemia, these agents are becoming preferred in most patients in place of secretagogues. • The algorithm moves sulfonylureas to a lower priority due to the risks of hypoglycemia and weight gain associated with their use, as well as the failure of these agents to provide improved glycemic control after

Clinical Guideline	Recommendation(s)
	<p>use for a relatively short period.</p> <ul style="list-style-type: none"> • A TZD is considered a “well-validated” effective agent due to demonstrated extended durability of action, but these agents have a lower priority for many patients in light of their potential side effects. • The three classes of medications; α-glucosidase inhibitors, colesevelam and glinides, are considered in relatively narrow, well-defined clinical situations, due to their limited efficacy.

Conclusions

The single-entity dipeptidyl peptidase-4 (DPP-4) inhibitors are indicated as monotherapy or in combination with other antihyperglycemic agents for adjunct therapy to diet and exercise to improve glycemic control in adult patients with type 2 diabetes.^{1,7} The fixed dose combination product consisting of sitagliptin and metformin hydrochloride is indicated when therapy with both metformin hydrochloride and sitagliptin is appropriate.⁸ Currently, all of the DPP-4 inhibitors are only available as branded products; however, the components of the fixed-dose combination product are available in separate formulations and metformin hydrochloride is available generically. DPP-4 inhibitors represent a novel treatment approach in the management of type 2 diabetes and work by reversibly blocking the inactivation of incretin hormones. Incretin 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.²

Therapy with DPP-4 inhibitors is generally well tolerated with the most common reported adverse events being headache, upper respiratory tract infection, and urinary tract infection.^{1,7} The risk of hypoglycemia associated with these agents is relatively low due to the glucose-dependent nature of incretin hormones. Additionally, it appears that DPP-4 inhibitors do not have the same risk of cardiovascular disease associated with other antidiabetic medications. Several postmarketing reports of hypersensitivity reactions have been reported with sitagliptin.²⁸

In placebo-controlled, randomized trials saxagliptin and sitagliptin have produced significant reductions in baseline glycosylated hemoglobin (HbA_{1c}), fasting plasma glucose (FPG), and postprandial glucose (PPG) levels.^{11,12,14-16,18,38} As add-on therapy to metformin hydrochloride, a sulfonylurea, or a thiazolidinedione, combination treatment with saxagliptin provided significant improvements in HbA_{1c} , FPG, and PPG compared to either monotherapy with any of the agents or placebo add-on therapy.²⁰⁻²² Multiple studies involving sitagliptin in combination with metformin hydrochloride, as individual agents, have demonstrated an additive effect in glycemic control when compared to monotherapy with either sitagliptin or metformin hydrochloride; however, there are no published trials available to date, that assess the fixed-dose combination product.^{23-25,27,28,34} In a trial monitoring the change in HbA_{1c} from baseline, sitagliptin was determined to be as effective as glipizide.³⁴ A systematic review of incretin therapy in type 2 diabetes showed that DPP-4 inhibitors demonstrated a small increase in weight as compared to placebo and provided a decrease in body weight compared to an increase with glipizide.³⁸ The long-term safety and efficacy of these agents have yet to be established.

Current clinical guidelines do not have consistent recommendations regarding the role DPP-4 inhibitors in the management of type 2 diabetes. Until long-term safety and efficacy data become available, it is likely that DPP-4 inhibitors will be utilized as add-on therapy to the current standard antidiabetic agents.

Appendix I: Utilization Within this Drug Class for DVHA: April 1, 2010 to September 30, 2010

Medication	Unique Utilizers	# of Claims	% Marketshare	Amount Paid	Avg Cost/Claim
Januvia	204	365	89.24%	\$139,859.00	\$383.18
Janumet	26	38	9.29%	\$19,496.92	\$513.08
Onglyza	6	6	1.47%	\$1,908.70	\$318.12
Class Total:	236	409	100%	\$161,264.62	\$394.29

Recommendations

In recognition of the established efficacy and safety of the dipeptidyl peptidase-4 (DPP-4) inhibitors for the treatment of type 2 diabetes, the American Diabetes Association and European Association for the Study of Diabetes recommendations which consider metformin to be first-line treatment for type 2 diabetes, and the overall lack of head-to-head evidence demonstrating an advantage of one DPP-4 inhibitor over the other, no changes are recommended to the current Department of Vermont Health Access (DVHA) approval criteria (see below):

Januvia, Onglyza

- The patient has had a documented side effect, allergy, contraindication or treatment failure with metformin.
- Quantity Limit=1 tablet per day

Janumet

- The patient has had an inadequate response with Januvia or metformin monotherapy.
OR
- The patient has been started and stabilized on Januvia and metformin combination therapy.
- Quantity Limit=2 tablets per day

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