Dipeptidyl peptidase-4 (DPP-4) inhibitors for the treatment of type 2 diabetes mellitus

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All topics are updated as new evidence becomes available and our peer review process is complete.
Literature review current through: Feb 2018. | **This topic last updated:** Oct 19, 2017.

INTRODUCTION — Current pharmacologic treatments for type 2 diabetes are based upon increasing insulin availability (either through direct insulin administration or through agents that promote insulin secretion), improving sensitivity to insulin, delaying the delivery and absorption of carbohydrate from the gastrointestinal tract, or increasing urinary glucose excretion. Glucagon-like peptide-1 (GLP-1)-based therapies (eg, dipeptidyl peptidase-4 [DPP-4] inhibitors, GLP-1 receptor agonists) affect glucose control through several mechanisms, including enhancement of glucose-dependent insulin secretion, slowed gastric emptying, and reduction of postprandial glucagon and of food intake (table 1).

This topic will review the mechanism of action and therapeutic utility of DPP-4 inhibitors for the treatment of type 2 diabetes mellitus. GLP-1 receptor agonists are discussed separately. A general discussion of the initial management of blood glucose and the management of persistent hyperglycemia in adults with type 2 diabetes is also presented separately. (See "Glucagon-like peptide-1 receptor agonists for the treatment of type 2 diabetes mellitus" and "Initial management of blood glucose in adults with type 2 diabetes mellitus" and "Management of persistent hyperglycemia in type 2 diabetes mellitus".)

MECHANISM OF ACTION — Glucagon-like peptide-1 (GLP-1) is produced from the proglucagon gene in L-cells of the small intestine and is secreted in response to nutrients (figure 1) [1]. GLP-1 exerts its main effect by stimulating glucose-dependent insulin release from the pancreatic islets [2]. It has also been shown to slow gastric emptying [3] and inhibit inappropriate post-meal glucagon release [1,4] (table 1). GLP-1-based therapies, including the DPP-4 inhibitors, do not usually cause hypoglycemia unless combined with therapies that can cause hypoglycemia [5]. GLP-1 is considered an incretin and is one of a family of naturally occurring gut hormones that is released in the setting of a meal, but not with intravenous carbohydrate, and stimulates insulin synthesis and secretion. (See "Glucagon-like peptide-1 receptor agonists for the treatment of type 2 diabetes mellitus", section on 'Glucagon-like peptide-1'.)

DPP-4 inhibitors are a class of oral diabetes drugs that inhibit the enzyme DPP-4 [6]. DPP-4 is a ubiquitous enzyme expressed on the surface of most cell types that deactivates a variety of other bioactive peptides, including glucose-dependent insulinotropic polypeptide (GIP) and GLP-1; therefore, its inhibition could potentially affect glucose regulation through multiple effects. However, DPP-4 inhibitors have a modest effect on GLP-1 levels and activity compared with giving GLP-1 receptor agonists. (See "Glucagon-like peptide-1 receptor agonists for the treatment of type 2 diabetes mellitus".)

CANDIDATES — DPP-4 inhibitors are not considered as initial therapy for the majority of patients with type 2 diabetes. Initial therapy in most patients with type 2 diabetes should begin with diet, weight reduction, exercise, and metformin (in the absence of contraindications). DPP-4 inhibitors can be considered as monotherapy in patients who are intolerant of or have contraindications to metformin, sulfonylureas, or thiazolidinediones, such as patients with chronic kidney disease or who are at particularly high risk for hypoglycemia. DPP-4 inhibitors can be considered as add-on drug therapy for patients who are inadequately

controlled on metformin, a thiazolidinedione, or a sulfonylurea. However, their modest glycemia-lowering effectiveness and expense temper our enthusiasm for these drugs. Therapeutic options for initial and subsequent therapy are reviewed in detail separately. (See "Initial management of blood glucose in adults with type 2 diabetes mellitus", section on 'Choice of initial therapy' and "Management of persistent hyperglycemia in type 2 diabetes mellitus", section on 'Treatment options'.)

There are inadequate data to support the use of DPP-4 inhibitors in combination with prandial insulin.

CHOICE OF DPP-4 INHIBITORS — Sitagliptin, saxagliptin, linagliptin, and alogliptin are the dipeptidyl peptidase-4 (DPP-4) inhibitors available for the treatment of type 2 diabetes in the United States and many other countries. Vildagliptin is available in several countries but not in the United States. Among the DPP-4 inhibitors, patient preference and payer coverage are considerations for selecting a specific agent. If DPP-4 inhibitors are going to be used in patients with chronic kidney disease (estimated glomerular filtration rate [eGFR] <30 mL/min), we prefer linagliptin because it is primarily eliminated via the enterohepatic system. (See 'Use in chronic kidney disease' below.).

Glycemic efficacy — The DPP-4 inhibitors appear to have similar glycemic efficacy. They result in modest improvement in glycated hemoglobin (A1C). However, there are few head-to-head trials and no clinical trial data on long-term (greater than two-year) safety, mortality, diabetic complications, or health-related quality of life. In an 18-week trial of saxagliptin (5 mg) versus sitagliptin (100 mg) in 800 patients inadequately controlled on a stable dose of metformin, there were similar reductions in A1C (-0.52 versus -0.62 percentage points) [7]. In addition, the results from a meta-analysis of studies comparing sitagliptin with placebo or vildagliptin with placebo suggest similar efficacy (weighted mean difference in A1C values of -0.74 and -0.73 percent, 95% CI -0.84 to -0.63 and -0.94 to -0.52, for sitagliptin and vildagliptin compared with placebo, respectively) [8]. A second meta-analysis of sitagliptin and vildagliptin trials reported similar findings [9].

The glycemic efficacy of the individual drugs is reviewed below (see individual headings).

Cardiovascular effects — There are a growing number of trials evaluating the cardiovascular effects of DPP-4 inhibitors. These studies have been performed to satisfy US Food and Drug Administration (FDA) cardiovascular disease (CVD) safety requirements. Although these data are reassuring in that there does not appear to be an increased risk of adverse coronary heart disease outcomes with short-term use of DPP-4 inhibitors used in combination with another oral agent, there may be an increased risk of heart failure with specific DPP-4 inhibitors. Longer-term clinical trials are needed to definitively assess the cardiovascular safety of DPP-4 inhibitors. The preliminary claims that DPP-4 inhibitors have a beneficial effect on CVD risk have not been borne out by the studies to date. Of note, the cardiovascular studies to date have been carried out in very high-risk populations, presumably to increase the hazard rate for major CVD events and complete the studies in a relatively brief period of time. Therefore, there are few data on CVD safety or putative benefits in lower-risk patients.

In trials with median follow-up of 18 to 36 months, the following findings were reported:

- In one trial, 16,492 patients with type 2 diabetes and either a history of CVD or multiple risk factors for vascular disease were randomly assigned to saxagliptin or placebo, in addition to other diabetes medications (predominantly metformin, sulfonylurea, insulin). After a median follow-up of two years, the primary endpoint (a composite endpoint of cardiovascular death, nonfatal myocardial infarction, or nonfatal ischemic stroke) occurred in a similar proportion of patients (7.3 and 7.2 percent in the saxagliptin and placebo groups, respectively; hazard ratio [HR] 1.00, 95% CI 0.89-1.12) [10]. Significantly more patients in the saxagliptin group were hospitalized for heart failure (3.5 versus 2.8 percent; HR 1.27, 95% CI 1.07-1.51). Known risk factors for heart failure, including baseline natriuretic peptides, prior heart failure, and chronic kidney disease were risk factors for heart failure hospitalizations [11].

- In a similarly designed trial, 5380 patients with type 2 diabetes and either an acute myocardial infarction or unstable angina requiring recent hospitalization were randomly assigned to alogliptin or placebo, in

addition to other diabetes medications (predominantly metformin, sulfonylurea, insulin) [12]. After a median follow-up of 18 months, the primary endpoint (a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) occurred in a similar proportion of patients (11.3 and 11.8 percent in the alogliptin and placebo groups, respectively; HR 0.96, upper boundary of the one-sided CI 1.16). In a post hoc analysis of the data, there was no significant difference in the rate of hospital admission for heart failure (3.1 and 2.9 percent in the alogliptin and placebo groups, respectively; HR 1.07, 95% CI 0.79-1.46) [13].

- In a third trial, 14,735 patients with type 2 diabetes and established CVD (history of major coronary artery disease, ischemic cerebrovascular disease, or atherosclerotic peripheral arterial disease) were randomly assigned to sitagliptin or placebo, in addition to other diabetes medications (predominantly metformin, sulfonylurea, insulin) [14]. After a median follow-up of three years, the primary composite cardiovascular outcome (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina) occurred in a similar proportion of patients (11.4 and 11.6 percent in the sitagliptin and placebo groups, respectively; HR 0.98, 95% CI 0.89-1.08). There was no significant difference in any of the individual components of the composite endpoint. There was no significant difference in the rate of hospitalization for heart failure (3.1 percent in each group).

The clinical significance of the finding of increased hospitalization for heart failure in the saxagliptin study is unclear [15-19]. A systematic review and meta-analysis of randomized trials and observational studies examining the association between DPP-4 inhibitors and heart failure outcomes (risk of heart failure or hospital admission for heart failure) reported the following findings [20]:

- A meta-analysis of 38 trials provided low-quality evidence of no significant difference in risk of heart failure between DPP-4 inhibitor treatment and control (placebo or active comparator) (event rates 0.27 and 0.26 percent). Observational studies provided effect estimates similar to the randomized trials but were limited by heterogeneity with variation in types of patients (ie, with or without CVD) and comparators.

- A meta-analysis of five trials provided moderate-quality evidence of increased risk of hospitalization for heart failure in DPP-4 inhibitor users compared with placebo (event rate 3.4 versus 3.0 percent; odds ratio [OR] 1.13, 95% CI 1.00-1.26). The patients in these trials, specifically designed to assess the cardiovascular safety of DPP-4 inhibitors, had CVD or multiple risk factors for CVD. Observational studies provided effect estimates similar to the randomized trials but with very-low-quality evidence. In the observational studies, results varied with type of control (active comparator or placebo).

This analysis suggests a small increased risk of admission for heart failure with DPP-4 inhibitor use in patients with type 2 diabetes who have existing CVD or multiple risk factors for it. It is unclear if the risk is specific to certain DPP-4 inhibitors and whether it extends to patients without CVD. The FDA recommends discontinuation specifically of saxagliptin and alogliptin in patients who develop heart failure and monitoring to determine if alternative therapy for diabetes is required [21].

Retrospective, population-based studies with follow-up of one to three years have not shown a higher risk for hospitalization for heart failure in users of saxagliptin or sitagliptin compared with other agents (sulfonylureas, pioglitazone, insulin) [22,23]. These observational studies may supplement but cannot replace the more persuasive findings of controlled clinical trials, as the observational study design and analyses cannot completely address potential confounding factors, such as level of glycemic control and other unmeasured factors that influenced choice of therapy. A causal mechanism for the association of DPP-4 inhibitors with heart failure has not been established.

Mortality — DPP-4 inhibitors do not appear to have any effect on overall mortality. In a systematic review and meta-analysis of 189 trials, there was no difference in all-cause mortality between any incretin drug versus control [24]. The results of the meta-analysis were heavily weighted by six large, randomized trials in which 92 percent of all deaths occurred. In a subgroup analysis of the DPP-4 cardiovascular outcomes trials,

there was no difference in all-cause mortality between a DPP-4 inhibitor and placebo (6.1 versus 6.0 percent, OR 1.02, 95% CI 0.91-1.14) [24].

Use in chronic kidney disease — Sitagliptin, saxagliptin, alogliptin, and vildagliptin require dose adjustment in patients with chronic kidney disease. Linagliptin is primarily eliminated via the enterohepatic system, and therefore, no dose adjustment is necessary. Although DPP-4 inhibitors are not considered as initial therapy for the majority of patients with type 2 diabetes, they can be used as monotherapy or add-on therapy in patients with type 2 diabetes who are intolerant of, have contraindications to, or who are inadequately controlled on metformin, sulfonylureas, or thiazolidinediones. In particular, linagliptin might be a good choice as initial therapy in a patient with chronic kidney disease at risk for hypoglycemia. Other DPP-4 inhibitors may be used in the setting of chronic kidney disease with proper dose adjustment.

DPP-4 inhibitors appear to be effective in patients with chronic kidney disease [25-29]. As examples:

- In a 54-week trial, 129 patients with end-stage renal disease requiring dialysis were randomly assigned to sitagliptin (reduced dose) or glipizide, in place of their usual oral glucose-lowering agents [25]. There were no significant differences in the reduction in A1C (-0.72 versus -0.87 percentage points) or in the rate of symptomatic hypoglycemia (6.3 versus 10.8 percent). Severe hypoglycemia was more common with glipizide (7.7 versus 0 percent), whereas headache and cellulitis were more frequent with sitagliptin (6.3 versus 0 percent).

- In another trial, 133 patients with type 2 diabetes and eGFR <30 mL/min (but not requiring dialysis) were randomly assigned to receive linagliptin or placebo, in addition to their previous background glucose-lowering therapy [26]. At 12 weeks, A1C decreased significantly more with linagliptin compared with placebo (-0.76 versus -0.15 percentage points). The A1C-lowering effect was sustained up to one year. The magnitude of glycemia lowering was similar to that seen in patients with normal renal function. Hypoglycemia tended to be more common in the linagliptin group, but this was largely in patients taking background insulin therapy and was limited to the first 12 weeks of the study, when background therapy was adjusted. Average eGFR did not decrease significantly in either group.

SITAGLIPTIN — Sitagliptin is a DPP-4 inhibitor that is approved for the treatment of type 2 diabetes (as monotherapy; as a second agent in those who do not respond to a single agent, such as a sulfonylurea, metformin, or a thiazolidinedione; and as a third agent when dual therapy with metformin and a sulfonylurea does not provide adequate glycemic control). The usual dose of sitagliptin is 100 mg once daily, with reduction to 50 mg for moderate-to-severe renal insufficiency (glomerular filtration rate [GFR] 30 to 50 mL/min) and 25 mg for severe renal insufficiency (<30 mL/min) [30].

The glycemic efficacy of sitagliptin monotherapy was demonstrated in the following studies:

- In an 18-week randomized trial of patients with type 2 diabetes and an average baseline A1C of 8.1 percent, sitagliptin 100 mg compared with placebo resulted in an absolute A1C reduction of 0.6 percentage points [31].

- In a 24-week trial of sitagliptin (100 or 200 mg) in 741 patients with type 2 diabetes, there were similar improvements in A1C values and fasting plasma glucose concentrations in both sitagliptin groups compared with placebo [32]. Patients with baseline A1C values ≥9 percent had greater reductions in A1C values compared with those with baseline A1C values <8 percent (-1.52 versus -0.57 percentage points). The incidence of hypoglycemia was similar among groups, but the proportion of patients reporting gastrointestinal side effects was significantly higher in the sitagliptin group.

Sitagliptin is also effective when used in combination with metformin [33-35], thiazolidinediones [36], or sulfonylureas [37], and in one study, it had similar A1C-lowering efficacy as glipizide [35]. As examples:

- In a 24-week randomized trial in 701 patients with type 2 diabetes inadequately controlled with metformin, the addition of sitagliptin improved A1C (-0.6 percentage points from baseline), fasting

glucose, and two-hour postprandial glucose concentrations compared with placebo [33].

- In a 24-week randomized trial in 353 patients with type 2 diabetes, the addition of sitagliptin to pioglitazone improved A1C (-0.85 percentage points from baseline) and fasting plasma glucose [36]. The between-treatment difference (sitagliptin versus placebo) was -0.70 percent. There were more gastrointestinal side effects with sitagliptin compared with placebo (13.7 versus 6.2 percent).

- In a 52-week randomized trial in 1172 patients inadequately controlled with metformin, the addition of sitagliptin versus glipizide resulted in a similar reduction in A1C of 0.7 percent [35]. However, the addition of glipizide was associated with more hypoglycemia and weight gain.

Sitagliptin-metformin is available in a single tablet (50 mg/500 mg and 50 mg/1000 mg of sitagliptin and metformin, respectively) that is taken twice daily with meals [38]. Sitagliptin is also available combined with extended-release metformin (50 mg/500 mg, 50 mg/1000 mg, 100 mg/1000 mg of sitagliptin and extended-release metformin, respectively) that is taken once daily with the evening meal [39].

SAXAGLIPTIN — Saxagliptin is approved as initial pharmacologic therapy for the treatment of type 2 diabetes or as a second agent in those who do not respond to a single agent, such as a sulfonylurea, metformin, or a thiazolidinedione. The usual dose of saxagliptin is 2.5 or 5 mg once daily, with the 2.5 mg dose recommended for patients with moderate to severe chronic kidney disease (glomerular filtration rate [GFR] ≤50 mL/min) and for patients taking strong cytochrome P450 3A4/5 inhibitors (eg, ketoconazole) [40].

Saxagliptin monotherapy reduces A1C [41,42]. As an example, in an 24-week randomized trial of saxagliptin (2.5, 5, or 10 mg daily) versus placebo in 401 patients with treatment-naive type 2 diabetes and an average baseline A1C of 7.9 percent, saxagliptin resulted in A1C reductions of 0.4, 0.5, and 0.5 percentage points, respectively, compared with an increase of 0.2 percentage points in the placebo group [42].

Saxagliptin is also effective when used in combination with metformin [43,44], sulfonylureas [45], or thiazolidinediones [40]. As an example, in a 24-week trial of 743 patients inadequately controlled with metformin monotherapy (1500 to 2500 mg/day), the addition of saxagliptin (2.5 or 5 mg once daily) versus placebo improved A1C (-0.6 and -0.7 versus +0.1 percentage points from baseline) [43].

Saxagliptin-metformin is available in a single tablet (5 mg/500 mg, 5 mg/1000 mg, 2.5 mg/1000 mg of saxagliptin and extended-release metformin, respectively) that is taken once daily [46].

VILDAGLIPTIN — Vildagliptin is another DPP-4 inhibitor available for use in some countries, although it has not been approved by the US Food and Drug Administration (FDA). The usual dose is 50 mg twice daily when used as monotherapy, with metformin, or with a thiazolidinedione and 50 mg once daily (in the morning) when used with a sulfonylurea [47]. No dose adjustment is necessary in patients with mild renal impairment (creatinine clearance ≥50 mL/min). In patients with moderate or severe renal impairment, the dose is 50 mg once daily.

It is effective as monotherapy [48-51] or in combination with metformin [52,53], thiazolidinediones [54], or insulin [55], as illustrated by the following studies:

- In a 12-week trial, 279 patients with type 2 diabetes were randomly assigned to one of four doses of vildagliptin or placebo [48]. The higher doses of vildagliptin (50 or 100 mg daily) were associated with significant reductions in A1C compared with placebo (between-treatment differences of -0.43 and -0.40 percentage points, respectively).

- In two randomized trials, the addition of vildagliptin (50 or 100 mg daily) compared with placebo improved A1C in patients with type 2 diabetes inadequately controlled with metformin (between-group differences of -0.6 to -1.1 percentage points) [52,53]. In the patients with the highest A1C values at baseline (>8.5 percent), only 7.5, 16.3, and 2.1 percent of patients receiving 50 mg vildagliptin, 100 mg vildagliptin, or placebo, respectively, achieved an A1C of <7.0 percent [53].

- In a 24-week trial of vildagliptin versus placebo in 296 patients with type 2 diabetes suboptimally treated with insulin, the addition of vildagliptin (50 mg twice daily) significantly, but modestly, improved A1C (between-group difference -0.3 percentage points) [55].

In studies of previously untreated patients, vildagliptin had similar A1C-lowering efficacy as rosiglitazone but was less effective than metformin [56,57]. As an example, in a 52-week noninferiority study of vildagliptin (100 mg daily) versus metformin (titrated to 2000 mg daily) in 780 patients with previously untreated type 2 diabetes, metformin was superior (vildagliptin was not found to be noninferior) in reducing A1C values (between-group difference 0.4 percentage points, 95% CI 0.28-0.65) [57]. Goal A1C (<7.0 percent) was achieved by 45 and 35 percent of those who received metformin and vildagliptin, respectively.

LINAGLIPTIN — Linagliptin is available for use as an adjunct to diet and exercise in adults with type 2 diabetes. The usual dose of linagliptin is 5 mg once daily, taken with or without food. It is primarily eliminated via the enterohepatic system. No dose adjustment is necessary in patients with renal or hepatic impairment. Inducers of CYP3A4 or P-glycoprotein (eg, rifampin) may decrease the efficacy of linagliptin. Therefore, patients requiring such drugs should receive an alternative to linagliptin.

The efficacy of linagliptin as monotherapy [58] and in combination with metformin [59,60], glimepiride [61], combined metformin and sulfonylurea [62], or pioglitazone [63] is illustrated by the following trials:

- In one trial, 503 patients with diabetes were randomly assigned to linagliptin (5 mg daily) or placebo [58]. After 24 weeks, A1C decreased by 0.44 percentage points in the linagliptin group compared with an increase of 0.25 percentage points in the placebo group.

- In a 24-week trial, the addition of linagliptin (5 mg daily) versus placebo improved A1C in patients with type 2 diabetes inadequately controlled with metformin (mean change from baseline -0.49 versus +0.15 percentage points) [60].

- In a 24-week trial, 1058 patients with type 2 diabetes inadequately controlled with metformin and a sulfonylurea were randomly assigned to the addition of linagliptin (5 mg) or placebo [62]. The reduction in A1C was significantly greater in the linagliptin group (mean change from baseline -0.72 versus -0.10 percentage points).

There are few head-to-head trials comparing linagliptin with other agents. In a two-year, noninferiority study of glimepiride (1 to 4 mg, mean dose 3 mg) versus linagliptin (5 mg), both administered once daily, in 1551 patients with type 2 diabetes inadequately controlled on metformin (mean baseline A1C 7.7 percent), the adjusted mean change in A1C was better with glimepiride (-0.36 versus -0.16 percentage points), although linagliptin was not found to be statistically inferior to glimepiride [64]. The A1C reduction for both drugs in this long-term study was small. This may be related to adjustment for baseline factors (baseline A1C, treatment arm, and prior antidiabetic drugs) or to the high dropout rate (approximately 40 percent) as missing data were imputed via the last-observation-carried-forward method. The addition of glimepiride was associated with more hypoglycemia (36 versus 7 percent of patients) and weight gain (+1.3 versus -1.4 kg with linagliptin). There were too few cardiovascular events to draw any meaningful conclusions.

Linagliptin-metformin is available in a single tablet (2.5 mg/500 mg, 2.5 mg/850 mg, 2.5 mg/1000 mg of linagliptin and metformin, respectively) that is taken twice daily with meals [39].

Empagliflozin-linagliptin is available as a combination pill (10 mg/5 mg and 25 mg/5 mg of empagliflozin and linagliptin, respectively) taken once daily [65].

ALOGLIPTIN — Alogliptin is available for use as an adjunct to diet and exercise in adults with type 2 diabetes [66]. The usual dose of alogliptin is 25 mg once daily, with dose reductions to 12.5 mg once daily in patients with creatinine clearance between 30 and 60 mL/min and to 6.25 mg daily in patients with creatinine clearance <30 mL/min or undergoing dialysis [67,68].

Alogliptin is effective as monotherapy [69] and in combination with metformin [70], pioglitazone [71], pioglitazone plus metformin [72], sulfonylureas [73], or insulin [74]. As examples:

- In a 12-week trial of alogliptin (12.5 or 25 mg once daily) versus placebo in 288 patients with type 2 diabetes inadequately controlled with metformin (500 or 750 mg daily), there were greater reductions in A1C in the active treatment group (-0.55, -0.64, and +0.22 percent for 12.5, 25 mg, and placebo, respectively) [70].

- In similarly-designed 26-week trials of alogliptin (12.5 or 25 mg once daily) versus placebo in patients with type 2 diabetes inadequately controlled with a stable dose of glyburide (n = 500) [73] or insulin (monotherapy or in combination with metformin, n = 390) [74], there were greater reductions in A1C in the alogliptin groups (mean change in A1C from baseline -0.39, -0.53, and +0.01 percentage points for the 12.5, 25 mg, and placebo groups, respectively, in the glyburide trial and -0.63, -0.71, and -0.13 percentage points, respectively, in the insulin trial).

For initial therapy in patients with type 2 diabetes, alogliptin has not been shown to be superior to short-term dietary intervention. In a three-month trial comparing alogliptin with a traditional Japanese diet (unspecified low fat-low calorie) in 50 patients with newly diagnosed type 2 diabetes, there were similar reductions in A1C in both groups (-1.77 and -1.62 percentage points) [75]. Patients randomly assigned to the traditional Japanese diet lost significantly more weight (change in body mass index [BMI] -0.9 versus -0.1 kg/m^2).

Alogliptin is also available in combination with metformin and pioglitazone [66].

ADVERSE EFFECTS — The DPP-4 inhibitors were well tolerated in short-term studies. There are no effects on body weight or risk of hypoglycemia (in the absence of concomitant treatment with insulin or sulfonylureas) [5]. Commonly reported side effects include headache, nasopharyngitis, and upper respiratory tract infection [8,40,58,76,77]. Some [32,36], but not all [31,33,53], studies have reported a slight increased risk of gastrointestinal side effects with sitagliptin. The long-term safety with DPP-4 inhibitors has not been established.

Immune function — Although the DPP-4 inhibitors are relatively specific for glucagon-like peptide-1 (GLP-1), the long-term consequences of DPP-4 inhibition and its effects on other DPP-4 substrates are unknown. Due to the ubiquitous nature of dipeptidyl peptidase substrates and the variable specificity of DPP-4 inhibitors, each agent within this class will need to be scrutinized individually for drug-specific side effects [78]. It is possible that the risk of side effects may be higher with less selective DPP-4 inhibitors. Residual crossover with other substrates of DPP-4, particularly with respect to immune function, remains a concern, although this has not been reported in short-term clinical trials. However, a meta-analysis of sitagliptin and vildagliptin studies with available side effect data reported a small increased risk of nasopharyngitis (relative risk [RR] 1.2, 95% CI 1.0-1.4), urinary tract infection (RR 1.5, 95% CI 1.0-2.2), and headache (RR 1.4, 95% CI 1.1-1.7) [8]. A subsequent meta-analysis of trials (18 to 104 weeks' duration) comparing a DPP-4 inhibitor (sitagliptin, saxagliptin, vildagliptin, linagliptin, alogliptin) with placebo (44 trials), a comparator from another class of antidiabetic agents (20 trials), or another DPP-4 inhibitor (three trials) showed a small increased risk of nasopharyngitis compared with placebo (6 versus 5.3 percent, RR 1.13, 95% CI 0.99-1.29), which was predominantly driven by the sitagliptin subgroup (5.3 versus 4.1 percent; RR 1.35, 95% CI 1.03-1.77) [76]. The risk of upper respiratory and urinary tract infections was not significantly elevated, whereas the risk of dizziness and headache was slightly elevated (8.2 versus 7.5 percent; RR 1.14, 95% CI 1.02-1.26). In the three head-to-head trials, there were no clinically significant differences in adverse effects among DPP-4 inhibitors. There were too few events to report meaningful data on cardiovascular or mortality outcomes.

Pancreas — Acute pancreatitis has been reported in association with DPP-4 inhibitors. At the current time, there are insufficient data to know if there is a causal relationship [79-84]. Pancreatitis should be considered in patients with persistent severe abdominal pain (with or without nausea), and DPP-4 inhibitors should be discontinued in such patients. If pancreatitis is confirmed, a DPP-4 inhibitor should not be restarted. In addition, DPP-4 inhibitors should not be initiated in a patient with a history of pancreatitis.

There have been postmarketing case reports of acute pancreatitis in patients using sitagliptin, saxagliptin, and alogliptin [85-87]. This finding is similar to case reports describing pancreatitis in patients treated with GLP-1 receptor agonists. (See "Glucagon-like peptide-1 receptor agonists for the treatment of type 2 diabetes mellitus", section on 'Pancreas'.)

Observational studies have reported conflicting results, with some showing no difference in risk of pancreatitis in patients taking GLP-1-based therapies compared with other oral agents [79,83,88] and another showing an increased risk in users versus nonusers [80]. As examples:

- In a retrospective, cohort study of a claims database, the incidence of acute pancreatitis in sitagliptin users was 5.6 cases per 1000 patient-years, which was similar to the incidence in the diabetic control group [79].
- In a population-based, case-control study, compared with nonuse, use of GLP-1-based therapy (sitagliptin and exenatide) was associated with an increased risk of hospitalization for acute pancreatitis (adjusted odds ratio [OR] 2.07, 95% CI 1.36-3.13) [80].

Meta-analyses of randomized trials did not identify an increased risk [81,82]. The overall incidence of pancreatitis was low (35 cases among 68,318 patients, 20 in patients taking DPP-4 inhibitors and 15 in the comparator groups) [82]. More carefully designed observational studies are warranted to definitively establish risk.

There have also been reports of an increased risk of subclinical pancreatic inflammation, pancreatic cancer, and neuroendocrine tumors in sitagliptin users [85,89-91]. A causal relationship has not been established. After a review of currently available data, the US Food and Drug Administration (FDA) and the European Medicines Agency agreed that there was insufficient evidence to confirm an increased risk of pancreatic cancer with use of GLP-1-based therapies [92-94]. However, concerns remain [95], and monitoring for and reporting of pancreatic adverse effects will continue [92,94,96].

Hepatic function — Although uncommon, cases of hepatic dysfunction (liver enzyme elevations, hepatitis) have been reported in patients taking vildagliptin and alogliptin [77,97]. As a result, liver function tests should be evaluated prior to initiation of vildagliptin and alogliptin and at three-month intervals during the first year of therapy [97]. If an increase in aspartate aminotransferase (AST) or alanine aminotransferase (ALT) of three times the upper limit of normal or greater persists, the drugs should be discontinued.

Skin — Some DPP-4 inhibitors, including vildagliptin and saxagliptin, have been associated with serious skin reactions during preclinical studies in animals (red discoloration and swelling, blistering and flaking of skin with necrosis at higher doses) [98,99]. Skin lesions also occurred in normal volunteers given four to six times the proposed therapeutic dose of vildagliptin [100]. In postmarketing reports, sitagliptin, saxagliptin, linagliptin, and alogliptin have been associated with hypersensitivity reactions, including anaphylaxis, angioedema, and blistering skin conditions, including Stevens-Johnson syndrome [66,101]. DPP-4 inhibitors are contraindicated in patients with a history of a serious hypersensitivity reaction after previous exposure [102]. Reports of angioedema in association with DPP-4 inhibitors are reviewed separately. (See "ACE inhibitor-induced angioedema", section on 'Dipeptidyl peptidase-4 inhibitors'.)

Musculoskeletal — Some DPP-4 inhibitors (sitagliptin, vildagliptin, saxagliptin) have been associated with severe joint pain [103,104]. Other reported musculoskeletal side effects include myalgias, muscle weakness, and muscle spasms. Symptoms have been reported from two days to five months after initiating DPP-4 inhibitors. In most patients, symptoms resolved within a month after discontinuing the drug [105]. Some patients developed recurrent severe joint pain after restarting the same or a different DPP-4 inhibitor [104,105]. If a patient develops severe and persistent joint pain while taking a DPP-4 inhibitor, the drug should be discontinued and the patient assessed for resolution of symptoms. If symptoms resolve, a different class of diabetes medication should be prescribed. If symptoms do not resolve after one month of drug discontinuation, they are unlikely the result of DPP-4 inhibitor use, and alternative causes for the symptoms should be sought.

SOCIETY GUIDELINE LINKS — Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Diabetes mellitus in adults".)

SUMMARY AND RECOMMENDATIONS

- Dipeptidyl peptidase-4 (DPP-4) inhibitors are a class of oral diabetes drugs that inhibit the enzyme DPP-4. DPP-4 is a ubiquitous enzyme expressed on the surface of most cell types that deactivates a variety of other bioactive peptides, including glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1). DPP-4 inhibitors could potentially affect glucose regulation through multiple effects (table 1). (See 'Mechanism of action' above and "Glucagon-like peptide-1 receptor agonists for the treatment of type 2 diabetes mellitus", section on 'Glucagon-like peptide-1'.)

- The exact role for DPP-4 inhibitors among the myriad of other agents for management of type 2 diabetes is unclear. There are few long-term studies of DPP-4 inhibitors to assess glycemia-lowering efficacy, clinically important health outcomes (cardiovascular events, mortality), or safety. Many questions remain unanswered regarding clinical use in type 2 diabetes, including long-term benefits and risks and their role in combination with other diabetes medications. Thus, they are not considered as initial therapy for the majority of patients with type 2 diabetes. (See 'Candidates' above and "Initial management of blood glucose in adults with type 2 diabetes mellitus", section on 'Initial pharmacologic therapy'.)

- DPP-4 inhibitors can be considered as monotherapy in patients with type 2 diabetes who are intolerant of or have contraindications to metformin, sulfonylureas, or thiazolidinediones. As an example, linagliptin might be a good choice as initial therapy in a patient with chronic kidney disease or who is at particularly high risk for hypoglycemia. They are, however, more expensive and less potent in lowering glycemia than the glinides, such as repaglinide, which can also be used safely in patients with chronic kidney disease. (See 'Candidates' above and "Sulfonylureas and meglitinides in the treatment of diabetes mellitus", section on 'Meglitinides'.)

- DPP-4 inhibitors can be considered as add-on drug therapy for patients who are inadequately controlled on metformin, a thiazolidinedione, or a sulfonylurea. However, their modest glycemia-lowering effectiveness and expense temper our enthusiasm for these drugs. (See 'Candidates' above and "Management of persistent hyperglycemia in type 2 diabetes mellitus", section on 'Treatment options'.)

- The DPP-4 inhibitors appear to have similar glycemic efficacy. They result in modest improvement in glycated hemoglobin (A1C). Among the DPP-4 inhibitors, patient preference and payer coverage are considerations for selecting a specific agent. For patients with chronic kidney disease (estimated glomerular filtration rate [eGFR] <30 mL/min) in whom a decision has been made to use a DPP-4 inhibitor, we suggest linagliptin (**Grade 2B**). (See 'Choice of DPP-4 inhibitors' above and 'Use in chronic kidney disease' above.)

- The preliminary claims that DPP-4 inhibitors have a beneficial effect on cardiovascular disease (CVD) risk have not been borne out by the studies to date. Although there does not appear to be an increased risk of adverse coronary heart disease outcomes with short-term use of DPP-4 inhibitors used in combination with another oral agent, there may be an increased risk of heart failure with specific DPP-4 inhibitors. (See 'Cardiovascular effects' above.)

- Overall, DPP-4 inhibitors are well tolerated. The use of DPP-4 inhibitors has been associated with a slight increased risk of upper respiratory tract infections. There are insufficient data to know if DPP-4 inhibitors cause acute pancreatitis. (See 'Adverse effects' above.)

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Topic 96015 Version 17.0

GRAPHICS

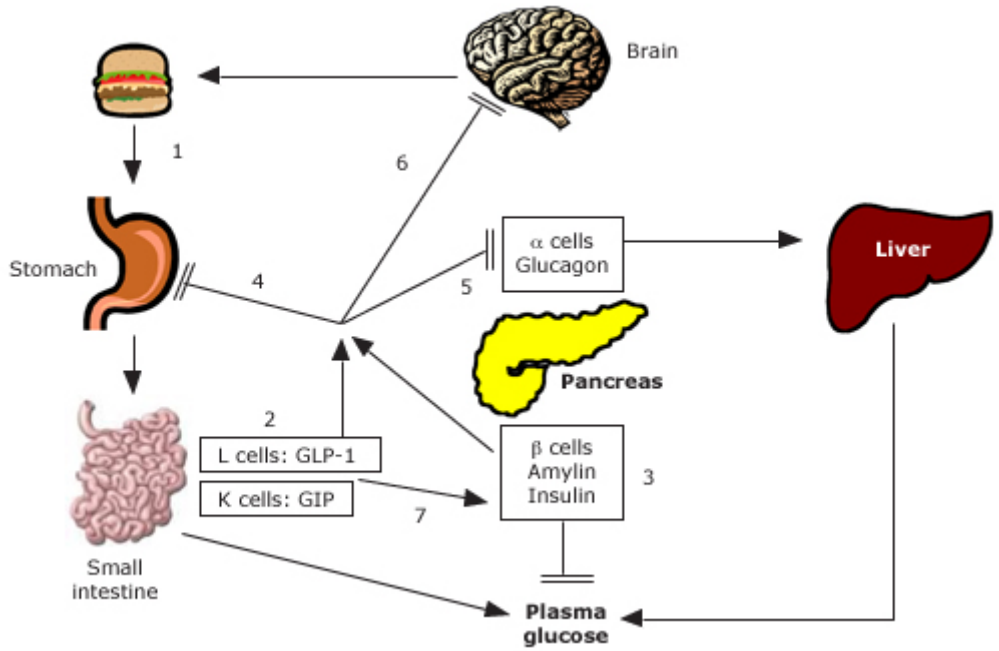
The role of GLP-1 in glucose homeostasis

	GLP-1
Deficiency	Type 2 diabetes, +/− type 1
Site of synthesis	Small intestinal L cells
Glucose-dependent stimulation of insulin secretion	Yes
Reduction of gastric emptying	Yes
Reduction of inappropriate glucagon secretion	Yes
Weight loss	Yes
Beta cell proliferation/regeneration	Yes - in animals

GLP-1: glucagon-like peptide-1.

Graphic 51832 Version 4.0

Multihormonal regulation of glucose



In healthy individuals, (1) ingestion of food results in (2) release of gastrointestinal peptides (GLP-1 and GIP) as well as (3) pancreatic beta cell hormones (insulin and amylin). GLP-1 and amylin, in particular, have inhibitory effects on (4) gastric emptying, (5) glucagon release, and (6) appetite. (7) Following the absorption of food, GLP-1 and GIP promote insulin secretion, otherwise known as the incretin effect. In diabetes, these steps are disrupted.

GLP-1: glucagon-like peptide 1; GIP: glucose-dependent insulinotropic polypeptide, gastric inhibitory peptide.

Graphic 59551 Version 4.0

Contributor Disclosures

Kathleen Dungan, MD Grant/Research/Clinical Trial Support: AstraZeneca/Amylin [Diabetes (Exenatide once weekly, Saxagliptin)]; GlaxoSmithKline [Diabetes (Albiglutide)]; Merck [Diabetes (Sitagliptin)]; Novo Nordisk [Diabetes (Semaglutide)]; Sanofi Aventis [Diabetes (Lixisenatide)]. Consultant/Advisory Boards: Eli Lilly [Diabetes (Dulaglutide)]; GlaxoSmithKline [Diabetes (Albiglutide)], Novo Nordisk [Diabetes (Liraglutide/Semaglutide)]; Sanofi Aventis [Diabetes (Lixisenatide)]. **Anthony DeSantis, MD** Nothing to disclose **David M Nathan, MD** Nothing to disclose **Jean E Mulder, MD** Nothing to disclose

Contributor disclosures are reviewed for conflicts of interest by the editorial group. When found, these are addressed by vetting through a multi-level review process, and through requirements for references to be provided to support the content. Appropriately referenced content is required of all authors and must conform to UpToDate standards of evidence.

Conflict of interest policy