

# Overview of the Gliptin Class (Dipeptidyl Peptidase-4 Inhibitors) in Clinical Practice

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**Abstract:** Dipeptidyl peptidase-4 inhibitors (DPP-4s), also commonly called gliptins, are a relatively new class of drugs for the treatment of type 2 diabetes. These agents work in a unique way to improve insulin secretion from the  $\beta$ -cells of the pancreas in response to an increase in blood sugar and simultaneously decrease glucagon output from the  $\alpha$ -cells of the pancreas, which results in decreased hepatic glucose output. Specifically, gliptins decrease the breakdown of glucagon-like peptide-1 (GLP-1) such that the circulating levels reach the high normal physiologic GLP-1 range. This results in more prompt and appropriate secretion of insulin and suppression of glucagon in response to a carbohydrate-containing meal or snack. The change in glucagon correlates linearly with improvement in glucose tolerance. Since these drugs improve insulin secretion in response to an increase in blood glucose, it seems appropriate to pair them with drugs that have a different mechanism of action, such as insulin sensitizers or metformin. In fact, improvements in fasting and postprandial glucose levels, improved  $\beta$ -cell function, and improvement in HbA<sub>1c</sub> levels have been demonstrated in numerous clinical trials using different gliptins as monotherapy and in combination with various type 2 diabetes medications, including insulin. This article reviews data from a number of clinical trials, presentations, and abstracts indicating the importance of the DPP-4 inhibitors sitagliptin, vildagliptin, and alogliptin both alone and in combination with insulin sensitizers in the treatment of type 2 diabetes.

**Keywords:** type 2 diabetes; DPP4 inhibition; gliptin; pharmacotherapy; review; comparison

## Introduction

Dipeptidyl peptidase-4 inhibitors (DPP-4s), also commonly called gliptins, are a relatively new class of drugs for the treatment of type 2 diabetes. These agents work in a unique way to improve insulin secretion from the  $\beta$ -cells of the pancreas in response to an increase in blood sugar and simultaneously decrease glucagon output from the  $\alpha$ -cells of the pancreas, which results in decreased hepatic glucose output. In order to understand how gliptins work, it is essential to understand the normal physiology of glucose homeostasis in both the fasting and fed states.

When a person is fasting, the tissues extract glucose from the bloodstream to use as fuel. If this extraction were to continue without glucose being replaced into the circulation, that person would die of hypoglycemia within a matter of hours. The blood glucose does not fall to hypoglycemic levels during fasting, however, because the liver replaces glucose to maintain normal glycemia. It does so under the influence of glucagon, a hormone that is produced from the  $\alpha$ -cells of the pancreas. Glucagon signals the liver to release glucose into the circulation, either from glycogenolysis or from gluconeogenesis. Normally, this balance of blood glucose works very well to maintain normal glycemia in the range of 60 to 90 mg/dL in the fasting state.

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Basal insulin is necessary at all times to maintain normal metabolism, including metabolism of fat and protein, as well as glucose. Similarly, basal glucagon secretion is necessary to maintain normal fasting glucose levels. When a person eats, a neural stimulus from the act of eating triggers the brain to send signals to the gut which leads to the release of intestinal hormones, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP). At the islets of Langerhans, they influence the secretion of glucagon and insulin by the  $\alpha$ - and  $\beta$ -cells in response to changes in blood sugar.

After a meal, as the glucose begins to rise, the GLP-1 and GIP levels should have already increased in response to the ingestion of the food, and have sensitized the  $\beta$ -cells, which immediately begin to secrete insulin. At the same time as the blood sugar is rising, the  $\alpha$ -cells significantly decrease glucagon secretion, which, in conjunction with the rising insulin level, results in suppression of hepatic glucose output (HGO).

Suppression of HGO in the postprandial state is necessary in order to prevent an even higher rise in glycemia after ingesting food. The lack of suppression of HGO after meals, together with inadequate insulin secretion, leads to abnormally high post-meal blood glucose values in diabetics. Patients with type 2 diabetes also have decreased  $\alpha$ -cell sensitivity to glucose, so their glucagon secretion is not appropriately suppressed as blood glucose rises postprandially,<sup>1</sup> and it may even be paradoxically stimulated. The importance of suppressing glucagon has been recognized for many years<sup>2,3</sup> but not until recently have drugs with a potent effect on postprandial glucagon secretion become available.

## Incretins

Glucagon-like peptide-1 and GIP are among the class of hormones called incretins. The “incretin effect” on insulin secretion is seen primarily in response to a rise in glucose, and therefore is termed a glucose-dependent effect.

In one study, the difference in endogenous insulin secretion in response to oral intake of glucose compared with endogenous insulin secretion in response to an intravenous (IV) glucose infusion that reproduced the same glucose levels, was demonstrated in healthy nondiabetic subjects who ingested 50 g of glucose and had C-peptide (a measurement of insulin secretion) measured.<sup>4</sup> The C-peptide levels achieved in response to the IV glucose were far lower than those achieved in response to the same glycemia when glucose had been taken orally. The cause of the difference between these 2 insulin secretory responses was termed the

“incretin effect.” The class of intestinal factors released in response to oral food intake that led to the increased insulin secretion was named the incretins.<sup>4</sup>

The existence of incretins has been known for many years, but until recently there have been no clinical therapeutic implications. Recent research has shown their importance in the maintenance of normal carbohydrate tolerance. The incretin effect in nondiabetics is responsible for about 70% of the insulin secretion in response to oral glucose. In patients with type 2 diabetes, it's only about 30%. Suppression of endogenous glucose production is impaired in patients with type 2 diabetes<sup>5</sup> and  $\alpha$ -cell sensitivity to glucose is reduced.<sup>1</sup>

Patients with type 2 diabetes tend to have low incretin levels postprandially.<sup>6</sup> However, diminished insulin secretion and reduced suppression of glucose production are already evident in individuals with impaired glucose tolerance,<sup>7</sup> and they have further deteriorated by the time of being diagnosed with type 2 diabetes.<sup>8</sup>

Studies have shown that an improvement in glycemia can be achieved by increasing circulating GLP-1 via an infusion of native GLP-1. Unfortunately, native GLP-1 has an extremely short half-life in the circulation and, being a peptide hormone, needs to be given by continuous intravenous infusion in order to maintain normal physiologic levels.

Classes of drugs that mimic or increase the incretins have now become available for therapeutic use. The first one available was an incretin mimetic, exenatide, which is a peptide with 52% molecular homology with native GLP-1. Exenatide needs to be given by subcutaneous injection twice daily. Other, even longer-acting GLP-1 analogs and/or mimetics are being developed for once daily, once weekly, or even twice monthly injection, but are not yet therapeutically available.

Glucagon-like peptide-1 and GIP have short circulating half-lives because peptidase enzymes rapidly break them down. The primary degrading enzymes are DPP-4s, located on the vascular endothelium. Fifty percent of the GLP-1 secreted is destroyed before it reaches the general circulation<sup>9</sup> and another 40% is destroyed before it reaches the  $\alpha$ - and  $\beta$ -cells.<sup>10</sup> Intravenous infusion of a DPP-4 enzyme inhibitor results in higher GLP-1 levels, improved insulin secretion, and improved glucose tolerance in patients with type 2 diabetes.<sup>11</sup> Since patients with type 2 diabetes have lower levels of circulating GLP-1,<sup>6</sup> inhibition of the DPP-4 enzymes would be expected to increase GLP-1 levels, resulting in improved insulin secretion and more appropriate suppression of glucagon, which is what is seen therapeutically in patients with type 2 diabetes.

Exenatide, the GLP-1 mimetic drug, is not susceptible to degradation by the DPP-4 enzyme and therefore has a much

longer duration of action. It is also more potent in its appetite suppression and weight loss effects than the native hormone and also causes significant slowing of gastric emptying, which frequently leads to nausea early in therapy, though that symptom usually subsides with continued treatment. However, because it's a peptide molecule, it must be delivered by subcutaneous injection rather than orally.

One way to produce higher levels of circulating endogenous GLP-1 is to decrease its destruction by inhibiting the activity of the DPP-4 enzyme. The gliptin class of drugs does just that. By decreasing the breakdown of GLP-1, the circulating levels are doubled or tripled, which brings them into the high normal physiologic GLP-1 range, resulting in more prompt and appropriate secretion of insulin and suppression of glucagon in response to an oral carbohydrate-containing meal or snack. The change in glucagon correlates linearly with improvement in glucose tolerance.

Since these drugs improve insulin secretion in response to an increase in blood glucose, it seems appropriate to pair them with drugs that have a different mechanism of action, such as insulin sensitizers or metformin. When studies were done with gliptin/metformin combination therapy it was apparent that this was an excellent pairing, addressing 2 of the major defects found in patients with type 2 diabetes.

## Gliptin Availability

In many countries gliptins are available in combination tablets with metformin, which is likely to enhance adherence and decrease the number of copays for the patient. Approximate retail cost from Drugstore.com for a 30-day supply of sitagliptin 100 mg (1 bottle, 30 ea) is \$181.09. Sitagliptin/metformin 50 to 500 mg (1 bottle, 60 ea) is \$184.25 and the 50 to 1000 mg dose (1 bottle, 60 ea) is \$183.19.<sup>12</sup> Both doses are taken twice daily. Glimepiride, a sulfonylurea, is \$13.00 to \$19.00 depending on dose. Metformin immediate release 1000 mg bid is \$31.97 and pioglitazone 30 mg is \$203.31 for 30 tablets.<sup>12</sup>

The gliptins currently on the market are also weight neutral, which is very important to physicians and patients. They are both primarily excreted in urine and there are no drug-drug interactions with commonly used drugs. Vildagliptin has been found to be as effective as pioglitazone 30 mg, without the weight gain and with low risk of hypoglycemia or gastrointestinal side effects (similar to placebo).<sup>13</sup> There were no statistically significant changes in lipids in the fast-ing state,<sup>13</sup> however vildagliptin has been shown to augment postprandial lipid mobilization and oxidation in patients with type 2 diabetes.<sup>14</sup>

## Gliptins: Clinical Trial Data

### Sitagliptin

In an 18-week study of sitagliptin monotherapy, placebo-adjusted HbA<sub>1c</sub> and fasting plasma glucose (FPG) results showed a statistically significant difference ( $P < 0.001$  for both) of  $-0.6\%$  in HbA<sub>1c</sub> and  $-20$  mg/dL in FPG.<sup>15</sup>

In one study on 24-week treatment with sitagliptin 100 mg daily, the significant improvement in HbA<sub>1c</sub> over placebo was  $0.8\%$  ( $P < 0.001$ ) and was not affected by gender, age, race, or baseline body mass index (BMI). Sitagliptin treatment provided a significant improvement in FPG with adjusted mean difference from placebo of  $-17$  mg/dL and in 2-hour postprandial glucose of  $-47$  mg/dL at 24 weeks (both  $P < 0.001$ ).<sup>16</sup>

Sitagliptin versus placebo added to metformin over 26 weeks in 677 subjects showed an improvement in HbA<sub>1c</sub> compared with placebo of  $0.65\%$  ( $P < 0.001$ ) for sitagliptin.<sup>17</sup> In both add-on studies (to metformin or pioglitazone), sitagliptin provided significant improvements in HbA<sub>1c</sub> and FPG (both  $P < 0.001$ ), and in the metformin study in which it was measured, it also reduced 2-hour postprandial glucose versus placebo by  $51$  mg/dL.<sup>18</sup>

In a study in which combination therapy with sitagliptin and metformin was compared with metformin alone or sitagliptin alone, in which mean baseline HbA<sub>1c</sub> was  $8.8\%$ , the placebo-subtracted HbA<sub>1c</sub> change from baseline was  $-2.07\%$  (sitagliptin 100 mg/metformin 2000 mg),  $-1.57\%$  (sitagliptin 100 mg/metformin 1000 mg),  $-1.3\%$  (metformin 2000 mg),  $-0.99\%$  (metformin 1000 mg), and  $-0.83\%$  (sitagliptin 100 mg) ( $P < 0.001$  for comparisons vs placebo and for coadministration vs respective monotherapies). The percent of patients achieving HbA<sub>1c</sub>  $< 7\%$  and  $< 6.5\%$  was  $66\%$  and  $44\%$ , respectively, in the S100/M2000 group ( $P < 0.001$  vs S100 or M2000). Substantial and additive glycemic improvement achieved with initial combination therapy and was generally well tolerated in patients with type 2 diabetes.<sup>19</sup>

### Vildagliptin

In a study on 24-week treatment with 50-mg vildagliptin daily, 100-mg vildagliptin daily, or placebo in patients continuing a stable metformin dose  $\geq 1500$  mg/day but inadequate control (HbA<sub>1c</sub>  $7.5\%$ – $11\%$ ), the between-treatment difference (vildagliptin vs placebo) in HbA<sub>1c</sub> from baseline to end-point was  $-0.7$  ( $P < 0.001$ ) and  $-1.1$  ( $P < 0.001$ ) in patients receiving 50 or 100 mg vildagliptin daily, respectively. Gastrointestinal adverse events were reported by

9.6% ( $P = 0.022$  vs placebo), 14.8%, and 18.2% of patients receiving 50 mg vildagliptin daily, 100 mg vildagliptin daily, or placebo, respectively. One patient in each treatment group experienced 1 mild hypoglycemic event. Vildagliptin is well tolerated and produces clinically meaningful, dose-related decreases in HbA<sub>1c</sub> and FPG as add-on therapy in patients with type 2 diabetes inadequately controlled by metformin.<sup>20</sup>

In a head-to-head study of vildagliptin versus glimepiride as add-on therapy in patients with type 2 diabetes inadequately controlled with metformin monotherapy, a 52-week interim analysis of the planned 2-year randomized double-blind multicenter study was recently announced. It involved 3789 patients with initial baseline HbA<sub>1c</sub> levels of 6.5% to 8.5% and showed a 0.4% reduction in HbA<sub>1c</sub> with vildagliptin 50 mg bid plus metformin and a 0.5% reduction in A<sub>1c</sub> with glimepiride (up to 6 mg QD) plus metformin, not a significant difference. In those subjects > 65 years, the HbA<sub>1c</sub> reduction was exactly the same, -0.6%, in both cohorts, and in those with baseline BMI  $\geq 30$  kg/m<sup>2</sup>, the reduction was 0.44% with vildagliptin and 0.53% with glimepiride, both in conjunction with metformin therapy. In those subjects with baseline in HbA<sub>1c</sub> > 8%, the mean decrease in HbA<sub>1c</sub> was -0.92% for vildagliptin and -0.95% for glimepiride. In both groups, 54% (vildagliptin) and 56% (glimepiride) reached the target HbA<sub>1c</sub> of  $\leq 7.0\%$ . Fasting plasma glucose reduction at week 52 was not clinically significant between the 2 groups, nor was change in postprandial glucose area under the curve. There was no weight gain with vildagliptin, as opposed to glimepiride, when either was added to baseline metformin. There was a 1.8-kg difference with glimepiride gaining weight and vildagliptin losing weight.<sup>19</sup>

Importantly, in a single-center, double-blind, placebo-controlled, randomized crossover study assessing glucagon response to hyperglycemic and hypoglycemic stimuli in 30 patients with type 2 diabetes treated with either 100 mg of vildagliptin or placebo qd for 30 days, vildagliptin was shown to improve  $\alpha$ -cell glucose sensing to both hyperglycemic and hypoglycemic stimuli in patients with type 2 diabetes.<sup>21</sup>

Vildagliptin is safe and well tolerated in patients with mild or moderate renal impairment. Nine hundred twenty-seven patients with mild or moderate renal failure were studied with 50 mg vildagliptin once or twice daily. The HbA<sub>1c</sub> lowering in those with mildly impaired renal function was the same as in those with normal renal function and the adverse event rates in those with mild or moderate impairment was the same as with comparators (pioglitazone, rosiglitazone or placebo) in similar subjects, though greater than in nonimpaired subjects.<sup>22</sup>

Improved glycemic control occurred when vildagliptin was administered either as a morning or evening dose added to metformin.<sup>23</sup> Vildagliptin has been shown to be as effective as thiazolidinediones (TZDs) in metformin failures.<sup>13</sup>

Because of recent concerns about cardiovascular effects of antidiabetic drugs, the vildagliptin trials database (3784 treated patients) was analyzed for cardiovascular and cerebrovascular side effects. The incidence rates of cardio- and cerebrovascular adverse events was lower with vildagliptin than with placebo.<sup>24</sup>

## Alogliptin

At the American Diabetes Association Annual Scientific Assembly in June 2008, multiple studies were presented in which alogliptin (ALO) was compared with other agents or placebo to evaluate efficacy and safety in patients with type 2 diabetes. Almost 50% of subjects inadequately controlled on lifestyle and/or antidiabetic medications were able to achieve HbA<sub>1c</sub> levels  $\leq 7\%$  with the addition of ALO.<sup>25,26</sup>

Studies have been done with ALO as monotherapy, as addition to pioglitazone, as an add-on to sulfonylurea, as add-on to combinations, and as add-on to insulin.<sup>27,28</sup> Alogliptin added to ongoing insulin, with or without metformin therapy, significantly improved glycemic control in patients with type 2 diabetes who had been inadequately controlled on insulin, and did so without increasing weight or hypoglycemia.<sup>29</sup>

In a study presented at the 44th Annual Meeting of the European Association for the Study of Diabetes, after a 4-week, single-blind, placebo run-in/stabilization period, 500 patients were assigned to receive ALO 12.5 mg ( $n = 203$ ), ALO 25 mg ( $n = 198$ ), or placebo ( $n = 99$ ) once daily in addition to their ongoing glyburide regimen (mean dose = 12 mg/day) for 26 weeks.<sup>30</sup> Mean changes from baseline in HbA<sub>1c</sub> were significantly greater ( $P < 0.001$ ) for ALO 12.5 mg (-0.38%) and ALO 25 mg (-0.52%) compared with placebo (+0.01%) at week 26. There were similar mean changes from baseline in HbA<sub>1c</sub> regardless of age ( $\leq 65$  years), BMI ( $\leq 30$  kg/m<sup>2</sup>), or ethnicity (Hispanic or non-Hispanic), and were greater in patients with higher baseline HbA<sub>1c</sub> levels. Mean changes from baseline in FPG were greater for ALO versus placebo at week 26 and a greater proportion of patients achieved HbA<sub>1c</sub> < 7% for ALO versus placebo. Alogliptin added to ongoing glyburide monotherapy significantly improved glycemic control in patients with type 2 diabetes without increasing weight or the incidence of hypoglycemia.<sup>31</sup>

In one study, 527 patients received ALO 12.5 mg or 25 mg ( $n = 210$ ) or placebo once daily in addition to their ongoing metformin regimen for 26 weeks. At week 26 mean changes

from baseline HbA<sub>1c</sub> were significantly ( $P < 0.001$ ) greater for ALO 12.5 mg (−0.6%) and ALO 25 mg (−0.6%) compared with placebo (−0.1%).<sup>32</sup> Alogliptin was well tolerated. The proportion of patients with less than 1 gastrointestinal symptom was similar across groups.<sup>32</sup> The incidence of hypoglycemia was negligible. Alogliptin added to ongoing metformin monotherapy improved glycemic control without changing weight or increasing the incidence of gastrointestinal symptoms or hypoglycemia in patients with type 2 diabetes.<sup>32</sup>

In another study, 493 patients with type 2 diabetes inadequately controlled on a TZD alone or on a TZD with metformin or a sulfonylurea were studied.<sup>28</sup> The mean baseline HbA<sub>1c</sub> was 8%. Patients already taking metformin (56%) or a sulfonylurea (21%) continued this therapy at a stable dose throughout the study. At week 26, changes from baseline in HbA<sub>1c</sub> were significantly ( $P < 0.001$ ) greater for ALO 12.5 mg (−0.66%) and ALO 25 mg (−0.80%) versus placebo (−0.19%), and were similar regardless of age ( $\leq 65$  years), BMI ( $\leq 30$  mg/kg<sup>2</sup>), ethnicity (Hispanic or non-Hispanic), or background therapy (metformin, sulfonylurea, or none) and were greater in patients with higher baseline HbA<sub>1c</sub> levels. The incidences of edema, infections, and gastrointestinal symptoms were similar across groups. Alogliptin added to ongoing pioglitazone therapy (with or without metformin or a sulfonylurea) significantly improved glycemic control in patients with type 2 diabetes, without increasing weight gain or hypoglycemia.

## Summary

The principal mechanisms of action for the gliptin class include both reducing glucagon secretion from the  $\alpha$ -cells of the islets of Langerhans and increasing insulin secretion from the  $\beta$ -cells, both of which are achieved in a glucose-dependent manner. This results in improvements in fasting and postprandial glucose levels, improved  $\beta$ -cell function, and improvement in HbA<sub>1c</sub> levels, as has been demonstrated in numerous clinical trials using different gliptins as monotherapy and in combination with various type 2 diabetes medications, including insulin.

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