

# Profile of vildagliptin in type 2 diabetes: efficacy, safety, and patient acceptability

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**Abstract:** Vildagliptin is a selective and potent dipeptidyl peptidase-4 inhibitor that improves glycemic control by inhibiting the degradation of both endogenous glucagon-like peptide-1 and glucose-dependent insulinotropic peptide. This article is a comprehensive review of the safety and efficacy of vildagliptin in patients with type 2 diabetes. Clinical evidence has proven that it effectively decreases hemoglobin A<sub>1c</sub> with a low risk of hypoglycemia and is weight neutral. The addition of vildagliptin to metformin improves glucose control and significantly reduces gastrointestinal adverse events, particularly in patients inadequately controlled with metformin monotherapy. Its long-term advantages include preservation of  $\beta$ -cell function, reduction in total cholesterol, decrease in fasting lipolysis in adipose tissue, and triglyceride storage in non-fat tissues. Vildagliptin is well tolerated with a low incidence of AEs, and it does not increase the risk of cardiovascular/cerebrovascular (CCV) events. It can be taken before or after meals, and has little drug interaction, thus it will be well accepted.

**Keywords:** dipeptidyl peptidase-4, incretin hormones, vildagliptin, efficacy, safety, patient acceptability

## Introduction

The prevalence of type 2 diabetes mellitus (T2DM) among adults aged 20–79 years in 2010 was approximately 285 million worldwide. It is estimated that this figure will increase to 430 million by the year 2030.<sup>1</sup> Many antidiabetic agents are available, including sulfonylureas (SUs), metformin,  $\alpha$ -glucosidase inhibitors, thiazolidinediones (TZDs), prandial glucose regulators, insulin, and so on.

Recently, a new therapeutic approach for the treatment of type 2 diabetes that targets the incretin hormones has been developed. These peptide hormones, glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP), are released from the intestine after a meal and stimulate insulin secretion in a glucose-dependent fashion.<sup>2</sup> However, their action is limited by rapid inactivation by the enzyme dipeptidyl peptidase (DPP)-4. In addition, patients with T2DM usually do not respond well to GIP and GLP-1.<sup>3,4</sup> Inhibition of DPP-4 will increase active incretins; therefore, DPP-4 has become a target in diabetes control.<sup>5–7</sup> To date, several DPP-4 inhibitors are available, including sitagliptin, vildagliptin, saxagliptin, and linagliptin. Their pharmacokinetics/pharmacodynamics, efficacy, safety, and tolerability have been assessed in numerous clinical studies.<sup>8</sup>

Recently, the American Diabetes Association and the European Association for the Study of Diabetes published a joint position statement on the management of hyperglycemia in type 2 diabetes.<sup>9</sup>

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Key points of this statement include:

- Glycemic targets and glucose-lowering therapies must be individualized.
- Diet, exercise, and education remain the foundation for any type 2 diabetes treatment program.
- Unless there are prevalent contraindications, metformin is the optimal first-line drug.
- After metformin, there are limited data to guide us. Combination therapy with additional 1–2 oral or injectable agents is reasonable, aiming to minimize side effects where possible.
- Ultimately, many patients may require insulin therapy alone or in combination with other agents to maintain glucose control.
- All treatment decisions, where possible, should be made in conjunction with the patient, focusing on his/her preferences, needs, and values.

According to this position statement, in most patients, it is important to begin with lifestyle changes; metformin monotherapy is added at, or soon after, diagnosis (unless there are explicit contraindications). If the hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) target is not achieved after about 3 months, consider one of the five treatment options combined with metformin: a SU, TZD, DPP-4 inhibitor, GLP-1 receptor agonist, or basal insulin. Some studies have shown advantages of adding a third noninsulin agent to a two-drug combination that is not yet or no longer achieving the glycemic target. If combination therapy that includes basal insulin has failed to achieve the HbA<sub>1c</sub> target after 3–6 months, proceed to a more complex insulin strategy, usually in combination with one or two noninsulin agents. In patients intolerant of, or with contraindications for, metformin, select initial drugs from other classes (such as SUs/glinide, pioglitazone, or a DPP-4 inhibitor; in occasional cases where weight loss is seen as an essential aspect of therapy, initial treatment with a GLP-1 receptor agonist might be helpful), and proceed accordingly.

Vildagliptin is a selective and potent DPP-4 inhibitor that inhibits rapid degradation of endogenous GLP-1 and GIP, and increases  $\alpha$ - and  $\beta$ -cell responsiveness to glucose, thereby improving glycemic control in T2DM.<sup>10</sup> Having a strong binding ability to DPP-4 and a long half-life, vildagliptin is more potent than other DPP-4 inhibitors such as sitagliptin in suppressing glucagon, and causes less glycemic variation.<sup>8</sup>

This paper provides the efficacy, safety, and acceptability of vildagliptin in treating patients with type 2 diabetes.

## Short-term efficacy

It is well established that hyperglycemia, expressed as elevated HbA<sub>1c</sub>, is associated with the risk of microvascular and macrovascular complications.<sup>11</sup> Reduced rates of microvascular complications in well controlled type 2 diabetic patients were proven by prospective randomized trials.<sup>12,13</sup> Thus the American Diabetes Association's "Standards of Medical Care in Diabetes" recommends lowering HbA<sub>1c</sub> to 7.0% in most patients.<sup>14</sup> Noninsulin agents differ in potency and effective dosages, with a varied expected HbA<sub>1c</sub> improvement of 0.5% to 1.5%.<sup>15</sup> However, some patients failed to reach their HbA<sub>1c</sub> target due to hypoglycemia. In China, insulin secretagogues are the first choice of oral antidiabetic drugs (OADs) (70.2%), which may account for the high incidence of hypoglycemia (odds ratio 1.76, 95% CI 1.20 to 2.57) and poor glycemic control.<sup>16</sup>

DPP-4 inhibitors were said to have an intermediate glucose-lowering effect.<sup>17</sup> A systematic review of numerous clinical trials had profiled the efficacy and safety of incretin-based therapy. Trials were included in that study if they: (1) were randomized controlled trials of >12 weeks' duration; (2) had >10 patients with type 2 diabetes per treatment arm; (3) reported changes in hemoglobin HbA<sub>1c</sub> as the primary endpoint; and (4) studied the effects of adding a single drug (not multiple therapies) in a representative population. That study showed that vildagliptin (50 mg once a day (qd) or twice a day (bid)) is able to reduce HbA<sub>1c</sub> by 0.98% (–1.46% to –0.52%) after adjusting for differences in baseline HbA<sub>1c</sub>.<sup>18</sup> Plenty of evidence has supported that vildagliptin consistently and effectively improves glucose control in patients with mild to moderate hyperglycemia as a monotherapy or as an addition to other antidiabetic agents.

## Monotherapy

The efficacy of vildagliptin has been confirmed in a number of controlled trials.<sup>19–29</sup> Most trials were designed to examine the noninferiority of vildagliptin to the comparator.<sup>26–29</sup> However, the comparison with other active OADs not only validated its efficacy, but also revealed that it is weight-neutral and has low risk of hypoglycemia.

In a 2-year study of 546 patients, Foley and Sreenan<sup>26</sup> compared vildagliptin (50 mg bid) with a SU (gliclazide up to 320 mg/day). Similar reductions in HbA<sub>1c</sub> were found (–0.5% versus –0.6%), but vildagliptin was weight-neutral and posed little risk of hypoglycemia to patients.

Schweizer et al<sup>29</sup> reported a study, in which 780 patients (mean baseline HbA<sub>1c</sub>, 8.7%) were randomized to accept vildagliptin (50 mg bid) or metformin (2 g daily). After 2 years

of treatment, a significant HbA<sub>1c</sub> reduction was noticed both in the vildagliptin (−1.0%) and metformin (−1.4%) groups. However, the metformin group had a twofold higher incidence of gastrointestinal adverse events (AEs).

In another 24-week randomized trial of 786 patients (baseline HbA<sub>1c</sub> 8.7%), vildagliptin (50 mg bid) was compared to rosiglitazone (8 mg qd). Vildagliptin was noninferior to rosiglitazone in reducing HbA<sub>1c</sub> (−1.1% versus −1.3%).<sup>28</sup> It is worth noting that vildagliptin induced a weight loss of 0.3 kg, whereas rosiglitazone caused a weight gain of 1.6 kg ( $P < 0.001$ ). In addition, patients treated with vildagliptin had a lower risk of peripheral edema and a better lipid profile.

We had conducted a head-to-head study in which 661 Chinese patients (HbA<sub>1c</sub> 7.5%–11.0%, mean 8.6%) were randomized to vildagliptin 50 mg bid ( $n = 441$ ) or acarbose up to 100 mg three times a day ( $n = 220$ ) for 24 weeks.<sup>27</sup> The adjusted mean HbA<sub>1c</sub> change (from baseline to the end-point) was −1.4% and −1.3% in the vildagliptin group and acarbose group, respectively, meeting the statistical criterion for noninferiority. Body weight did not change in the vildagliptin group, but it did decrease in the acarbose group.

According to a pooled analysis of data from five clinical trials with 1569 patients, 24 weeks of vildagliptin monotherapy induced a mean change in HbA<sub>1c</sub> of −1.0%. According to baseline HbA<sub>1c</sub> 8.0%, 8.0%–9.0%, 9.0%–10.0% and 10.0%, HbA<sub>1c</sub> decreased 0.6%, 0.9%, 1.6%, and 1.9% from baseline respectively.<sup>30</sup> Similarly, HbA<sub>1c</sub> reduction was more substantial in the more obese patients. In addition, the response to vildagliptin in older patients was similar to younger ones (−1.2% versus −1.0%, respectively,  $P = 0.092$ ). Moreover, the rate of hypoglycemia was low (0.8%).

## Combination therapy

Vildagliptin has been assessed in randomized, double-blind trials as an add-on therapy to metformin, SU, thiazolidinedione, and insulin treatment.

## Vildagliptin as an add-on therapy to metformin

Vildagliptin can work well with metformin. First, vildagliptin improves islet function by increasing the sensitivity of the  $\alpha$ - and  $\beta$ -cells to glucose,<sup>25</sup> whereas metformin reduces hepatic glucose and improves insulin resistance.<sup>31</sup> It is rational to combine an agent primarily targeting insulin sensitivity within the pancreas, like vildagliptin, with an agent primarily targeting insulin resistance, like metformin. Metformin is the optimal first-line drug for patients who

failed to achieve their target with lifestyle interventions alone. Secondly, metformin also has a positive effect on promoting endogenous intact GLP-1 levels,<sup>32</sup> presumably by increasing its synthesis but not inhibiting degradation.<sup>33,34</sup> Subjects taking vildagliptin with metformin caused about two times elevations in fasting plasma GLP-1 than in taking vildagliptin alone.<sup>35,36</sup> The following section presents some clinical evidence supporting vildagliptin as an add-on therapy to metformin in patients inadequately controlled with metformin monotherapy.

## Vildagliptin versus placebo as an add-on therapy to metformin

A 24-week study was performed in 544 patients who failed to achieve glucose control (HbA<sub>1c</sub> 7.5%–11%) with metformin ( $\geq 1500$  mg/day) alone. The patients were randomized to receive an addition of vildagliptin 50 mg/day ( $n = 177$ ), or an addition of vildagliptin 100 mg/day ( $n = 185$ ), or metformin/placebo ( $n = 182$ ). Compared with the metformin/placebo arm, a change in HbA<sub>1c</sub> from baseline to the study endpoint was −0.7% and −1.1% in patients receiving 50 mg or 100 mg of vildagliptin daily, respectively; likewise, the between-treatment difference (vildagliptin – placebo) in fasting plasma glucose was −0.8 mmol/L and −1.7 mmol/L in the vildagliptin 50 mg or 100 mg groups, respectively. Body weight did not change significantly from baseline after 24 weeks of treatment with vildagliptin 50 mg/day (−0.4 kg) or vildagliptin 100 mg/day (+0.2 kg), while in patients receiving metformin/placebo, body weight decreased by −1.0 kg ( $P < 0.001$ ). There were no significant differences between the three groups in terms of AEs, except for the experience of gastrointestinal AEs. Gastrointestinal AEs were reported by 9.6%, 14.8%, and 18.2% of patients receiving 50 mg vildagliptin daily, 100 mg vildagliptin daily, or placebo, respectively ( $P = 0.022$  versus placebo). One patient in each treatment group experienced one mild hypoglycemic event.<sup>37</sup>

In another randomized control trial, T2DM patients inadequately controlled with metformin 1500 mg/day ( $7\% \leq \text{HbA}_{1c} \leq 7\% \text{ to } 11\%$ , mean 8.14% to 8.16%) were assigned to the 1500 mg of metformin and 50 mg of vildagliptin bid group ( $n = 132$ ), and the metformin 2500 mg group ( $n = 125$ ). After 24 weeks of treatment, HbA<sub>1c</sub> decreased by 1.25% in the vildagliptin/metformin group and 0.9% in the metformin group ( $P < 0.0001$ ). AEs and gastrointestinal AEs were significantly less in the vildagliptin/metformin group (3.8%, 3.0%) than those in metformin arm (10.7%, 9.2%).<sup>38</sup>

### Vildagliptin versus SUs as an add-on therapy to metformin

A total of 3118 T2DM patients who failed to achieve their HbA<sub>1c</sub> target (HbA<sub>1c</sub> 6.5% to 8.5%, mean 7.3%) after metformin monotherapy were randomized into either metformin/vildagliptin (*n* = 1562) or metformin/glimepiride treatment groups (*n* = 1556). The dosage of vildagliptin was 50 mg bid, while up to 6 mg/day of glimepiride was prescribed in the control arm. After 2 years of treatment, the adjusted mean change in HbA<sub>1c</sub> was similar between the two groups: -0.1% (0.0%) and -0.1% (0.0%), respectively. Although the initial response rate was similar between the two groups, more patients with vildagliptin reached their target HbA<sub>1c</sub> without hypoglycemia (36.0% versus 28.8%, *P* = 0.004). Hypoglycemic events that occurred in the metformin/glimepiride group were 14-fold as high as those in metformin/vildagliptin group (838 versus 59). Body weight change was -0.3 kg in the vildagliptin group versus 1.2 kg in glimepiride group (*P* < 0.001). Both treatments were well tolerated and displayed similar safety profiles.<sup>39</sup>

### Vildagliptin versus TZDs as an add-on therapy to metformin

A 52-week, randomized, active-controlled study compared vildagliptin (50 mg bid, *n* = 295) with pioglitazone (30 mg qd, *n* = 281) in patients inadequately controlled (HbA<sub>1c</sub> 7.5% to 11%) with a stable dose of metformin (≥1500 mg). Vildagliptin was found to be noninferior to pioglitazone in lowering HbA<sub>1c</sub> throughout the trial period. In addition, vildagliptin did not significantly increase body weight (+0.2 kg), whereas pioglitazone induced a weight gain of 2.6 kg. Hypoglycemia occurred rarely in both groups. There were no significant differences in the overall AE rates between the two groups; however, serious AEs occurred more frequently in the pioglitazone group.<sup>40,41</sup>

Another 12-week randomized open-label study compared vildagliptin (100 mg, *n* = 1653) with TZD (agent and dose at the investigators' discretion, *n* = 825) as an add-on therapy in patients inadequately controlled (HbA<sub>1c</sub> 7% to 10%) on a stable dose of metformin (≥1000 mg/day). The mean change in HbA<sub>1c</sub> from baseline to the study endpoint was -0.68% in the vildagliptin group and -0.57% in the TZD group, meeting the noninferiority criteria. Body weight increased in the TZD group (0.33 kg) and decreased in the vildagliptin group (-0.58 kg, *P* < 0.001). Adverse events occurred in similar proportions of patients in both groups (vildagliptin 39.5% and TZD 36.3%), and hypoglycemia was rare.<sup>42</sup>

### Vildagliptin as an add-on therapy to SU

A 24-week, multicenter, randomized, double-blinded, placebo-controlled study assessed the effect of vildagliptin (50 mg qd or bid) versus placebo added to glimepiride (4 mg qd) in 515 T2DM patients. Compared with placebo, a change in HbA<sub>1c</sub> from baseline to the study's endpoint was -0.6% in patients receiving vildagliptin 50 mg/day, and -0.7% in those receiving vildagliptin 100 mg/day. Greater efficacy was seen in patients ≥ 65 years of age (-0.7% for 50 mg/day, -0.8% for 100 mg/day), and in patients with HbA<sub>1c</sub> levels > 9.0% (-1.0% for 50 mg/day, -0.9% for 100 mg/day). The incidences of AEs (67.1%, 66.3%, and 64.2%) and serious AEs (2.9%, 2.4%, and 5.1%) were similar in the three groups. The incidence was low but slightly higher in the vildagliptin 100 mg group (3.6%) than in both the vildagliptin 50 mg group (1.2%) and the control arm (0.6%). The results showed that in T2DM patients inadequately controlled with SU monotherapy, the addition of vildagliptin to glimepiride improves glycemic control and is well tolerated. The addition of vildagliptin 50 mg/day to a SU may be a particularly attractive therapy in elderly patients.<sup>43</sup>

### Vildagliptin as an add-on therapy to other antidiabetic drugs

Vildagliptin had been added to other antidiabetic drugs, such as pioglitazone,<sup>44</sup> and insulin in patients inadequately controlled with monotherapy.<sup>45-47</sup> The reduction in HbA<sub>1c</sub> varied from 0.5% to 1.0% with different dosages of vildagliptin. Vildagliptin posed a low risk of hypoglycemia when combined with pioglitazone or insulin,<sup>44,46,47</sup> and the weight gain was more apparent in the vildagliptin/insulin group.<sup>46</sup>

## Long-term benefit of vildagliptin

Vildagliptin showed long-term benefit for type 2 diabetes by preserving β-cell function and normalizing the lipid profile.

### Effect of vildagliptin on β-cell function

In animal studies, vildagliptin was observed to preserve β-cell function by increasing β-cell mass,<sup>48</sup> stimulating β-cell replication,<sup>49</sup> or reducing apoptosis.<sup>50</sup> The β-cell mass increase may partly be attributed to the developmental regulation and suppression of oxidation and endoplasmic reticulum stress.<sup>51</sup>

Studies of vildagliptin in patients with type 2 diabetes demonstrated improvements in meal-test derived markers of β-cell function.<sup>21,25,28,37,44,52-54</sup> The homeostatic model assessment-β was increased while the proinsulin to insulin

ratio was decreased by vildagliptin.<sup>53</sup> Insulin secretion [defined as the ratio of the incremental area under the curve ( $\Delta$ AUC) for C-peptide to the  $\Delta$ AUC for glucose during standard meal tests] increased by >30% from 12 weeks throughout 1 year of treatment.<sup>54</sup> Some trials calculated the insulin secretory rate (ISR) by deconvolution of C-peptide levels, and used the  $\Delta$ AUC for ISR/ $\Delta$ AUC for glucose (ISR/G) as a  $\beta$ -cell function index. This index was consistently found to be increased in patients receiving vildagliptin in monotherapy,<sup>53</sup> or as an add-on to glimepiride,<sup>43</sup> a thiazolidinedione,<sup>44</sup> or metformin.<sup>55</sup> Further, given a single dose of vildagliptin before the evening meal, insulin secretion relative to glucose (ISR/G) increased significantly overnight.<sup>52</sup> There is evidence that has shown that vildagliptin increased  $\beta$ -cell function (assessed as ISR/G) in different populations, including those with IFG,<sup>57</sup> impaired glucose tolerance,<sup>56</sup> or T2DM, and mild hyperglycemia.<sup>20</sup> Clinical trials have also demonstrated that the insulin demand was brought down by adding vildagliptin, which achieved a negative caloric balance.<sup>45,46</sup>

### Effect of vildagliptin on plasma lipids

The lipid profile is an important determinant of cardiovascular risk in type 2 diabetes.<sup>58,59</sup> It is conceivable that glucose-lowering agents have a positive impact on the lipid profile due to the close relationship between glucose and lipid metabolism. A meta-analysis including five trials showed that vildagliptin significantly reduced the total cholesterol level (the difference in means,  $-0.42$  mmol/L, 95% CI  $-0.59$  to  $-0.25$  mmol/L,  $P < 0.001$ ),<sup>60</sup> but the results of other lipid parameters are inconsistent across trials (see Table 1).<sup>19,28,29,41,61</sup>

Some researchers have addressed the underlying mechanism of the change in lipid profiles after vildagliptin therapy. In animal studies, both GLP-1 and GIP inhibit lipolysis, indicating that the effect of vildagliptin is incretin hormone-mediated. In humans, vildagliptin was found to reduce fasting lipolysis, and increase postprandial lipolysis in adipose tissue as well as postprandial fat oxidation in muscle. These results indicated that the fat accumulated in adipocytes during fasting, and became mobilized and burned in muscle after meals.<sup>62</sup> Further, decreasing fasting lipolysis over 6 weeks is predicted to decrease stored triglycerides in nonfat tissues.<sup>63</sup> In summary, in addition to preserving  $\beta$ -cell function, vildagliptin improves insulin resistance by reducing glucose-toxicity, decreasing fasting lipolysis in fat cells, and reducing stored triglycerides in muscle, the liver, and pancreas.

**Table 1** Comparison of effect of vildagliptin with other antidiabetic agents on blood lipids

Study	Drug	Patient N (drug)	Comparator	Patient N (comparator)	Total cholesterol (drug/comparator)	HDL (drug/comparator)	Triglycerides (drug/comparator)
Dejager et al <sup>19</sup>	Vildagliptin	472	Placebo	160	-0.115	0.037	-0.092
Schweizer et al <sup>29</sup>	Vildagliptin	526	Metformin	254	-0.150	-0.100	0.13
Bolli et al <sup>41</sup>	Vildagliptin	295	Proglitazone	281	-0.165	0.015	-0.020
Rosenstock et al <sup>61</sup>	Vildagliptin	292	Placebo	161	-0.593	0.125	-0.276
Rosenstock et al <sup>61</sup>	Vildagliptin	154	Proglitazone	161	-0.307	0.085	-0.145

**Abbreviations:** N, number; HDL, high-density lipoprotein.

## Effects of vildagliptin on surrogate markers of atherosclerosis

In an animal study, 17-week-old ApoE (-/-) mice fed an atherogenic diet were administered a DPP-4 inhibitor, vildagliptin analogue (PKF275-055 [PKF], 100 µg/kg/day), over a period of 4 weeks. Aortic atherosclerosis and oxidized low-density lipoprotein-induced foam cell formation were determined. PKF increased the plasma levels of active glucagon-like peptide-1 by 3.5-fold, increased the total glucose-dependent insulinotropic polypeptide levels by twofold, reduced body weight by 13%, and reduced plasma cholesterol levels by 30%. Compared with drinking water controls, PKF significantly suppressed total aortic atherosclerotic lesions, atheromatous plaques in the aortic root, and macrophage accumulation in the aortic wall by 30% to 40% ( $P < 0.001$ ). Foam cell formation was suppressed by 40%.<sup>64</sup>

In another animal study, 14 pigs were randomized to receive either a DPP-4 inhibitor (vildagliptin; 50 mg) or normal saline intravenously prior to a 90-minute left anterior descending artery occlusion, followed by a 120-minute reperfusion period. The hemodynamic, cardiac, electrophysiological, and arrhythmic parameters, as well as the infarct size were determined before and during interventional radiology. During interventional radiology, the DPP-4 inhibitor stabilized the cardiac electrophysiology by preventing the event-related potential shortening, decreasing the number of pre-ventricular contractions, increasing the ventricular fibrillation threshold, and decreasing the infarct size.<sup>65</sup>

In a 12-week animal study, male Wistar rats were fed with either a normal diet or a high-fat diet ( $n = 24$  in each group). Rats in each group were divided into three subgroups to receive the vehicle, metformin (30 mg/kg, bid), or vildagliptin (3 mg/kg, qd) for another 21 days. Heart rate variability, cardiac function, and cardiac mitochondrial function were determined and compared among these treatment groups. Rats exposed to a high-fat diet developed increased body weight, visceral fat, plasma insulin, cholesterol, oxidative stress, depressed heart rate variability, and cardiac mitochondrial dysfunction. It was found that vildagliptin was more effective in preventing cardiac sympathovagal imbalance and cardiac dysfunction, as well as cardiac mitochondrial dysfunction, than metformin in rats with insulin resistance induced by a high-fat diet.<sup>66</sup>

Matsui et al<sup>67</sup> investigated whether vildagliptin inhibits vascular damage in the thoracic aorta of Otsuka Long-Evans Tokushima Fatty rats (OLETF rats), an animal model of type 2 diabetes with obesity, by blocking the advanced

glycation end product–receptor for advanced glycation end product (AGE–RAGE) axis. OLETF and control Long-Evans Tokushima Otsuka (LETO) rats at 22 weeks old were given a vehicle or 3 mg/kg of vildagliptin for another 12 weeks. Vildagliptin treatment significantly inhibited levels of AGE, RAGE, mRNA, protein, an oxidative stress marker, 8-hydroxydeoxyguanosine, two membrane components of nicotinamide adenine dinucleotide phosphate oxidase, p22, and gp91phox mRNAs, as well as phospho-NF-κB p65. Vildagliptin also significantly reduced both mRNA and protein levels of monocyte chemoattractant protein-1, vascular cell adhesion molecule-1, and plasminogen activator inhibitor-1. All these data suggest that vildagliptin could play a protective role against vascular injury in diabetes partly by attenuating the deleterious effects of the AGE–RAGE–oxidative stress axis.

## Safety

The most frequent AEs of vildagliptin were gastrointestinal AEs, hypoglycemia, headache, nasopharyngitis, influenza, cough, edema, and dizziness. Although the absolute occurrence was low, the incidence of AEs while taking vildagliptin varied in different trials when compared with placebo.<sup>20,21,68–70</sup> However, the incidence of gastrointestinal AEs, as well as the total AEs were significantly lower with vildagliptin compared with metformin,<sup>55,71</sup> and α-glycosidase inhibitors.<sup>27,72</sup> Dizziness and upper respiratory infections were more common in the vildagliptin group compared with TZDs.<sup>28,61</sup> A meta-analysis summarized the AEs of vildagliptin.<sup>73</sup> In that analysis, vildagliptin was not related to an increase in overall risk for any AEs when compared with placebo (relative risk (RR), 0.97; 95% CI 0.94 to 0.99); the incidence of hypoglycemia was low with vildagliptin, and the risk was similar to the comparators (RR 0.85, 95% CI 0.49 to 1.47). The use of vildagliptin did not pose any additional risks of infection for nasopharyngitis (RR 1.03, 95% CI 0.94 to 1.13) or for upper respiratory tract infections (RR 1.07, 95% CI 0.90 to 1.27).

## Risk of hypoglycemia

There is emerging concern about the increased risk of brain dysfunction in patients with repeated episodes of hypoglycemia, which may also lead to dysrhythmias, dizziness, confusion, or infection, which can be especially dangerous in the elderly.<sup>74</sup> Further, the frequency of both minor and major hypoglycemia was threefold higher in intensively managed patients than the frequency associated with conventional therapy in the ACCORD trial,<sup>75</sup> indicating a tight control target

is more likely to cause hypoglycemia events. Accordingly, in at-risk individuals, drug selection should favor agents that do not precipitate such events and, in general, blood glucose targets may need to be moderated.<sup>9</sup>

Clinical evidence has shown that vildagliptin caused fewer hypoglycemic events than insulin secretagogues, no matter of whether it was used as a monotherapy or combined with other agents. Twenty-nine studies with almost 15,000 participants showed that the risk of hypoglycemia occurs at the placebo level for all gliptins in the absence of insulin or SU cotherapy.<sup>88</sup> Moreover, ten trials with over 4700 participants indicated that as part of a combination therapy with an SU or insulin, the risk of hypoglycemia is elevated with sitagliptin and or linagliptin, but vildagliptin and saxagliptin appear to be safer agents to use in this context.<sup>76</sup> Of course, further studies are needed to clarify these differing hypoglycemia potentials.

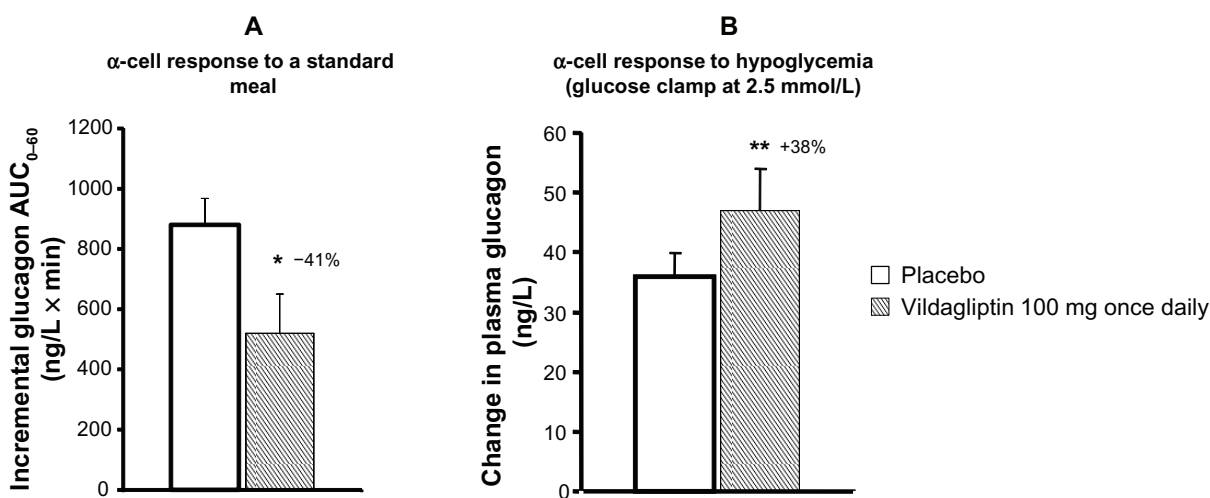
The distinctive pharmacological characteristics of vildagliptin could explain its advantage. The mechanism of action of vildagliptin is quite different from that of SUs, which work by closing adenosine triphosphate-sensitive potassium channels on  $\beta$ -cells and stimulates insulin release.<sup>77</sup> SUs increase insulin secretion independent of plasma glucose levels over time,<sup>78</sup> decrease the sensitivity of the  $\alpha$ - and  $\beta$ -cells to glucose,<sup>79</sup> and exacerbate islet dysfunction after long-term use.<sup>80</sup> On the contrary, active endogenous GLP-1 and GIP concentrations are increased two- to threefold by vildagliptin, lowering blood sugar in a glucose-dependent way after a meal, which is anticipated to have a low risk of hypoglycemia. Furthermore, vildagliptin not only suppresses

inappropriate glucagon secretion in response to glucose or mixed meals, but also enhances  $\alpha$ -cell responsiveness to the stimulatory effect of hypoglycemia.<sup>25</sup> When hypoglycemia occurs, glucagon levels were significantly higher in the vildagliptin group than in the placebo group (see Figure 1),<sup>25</sup> possibly due to the attenuation or abstentions of inhibition of glucagon secretion by GLP-1, and maximized stimulation of glucagon secretion by GIP.<sup>81</sup> Vildagliptin also extends the surge in GLP-1 and GIP after meals to intermeal and overnight periods,<sup>52,82</sup> which may protect the body from hypoglycemia (see Figure 2). Taken together, the bifunctional effect on glucagon by vildagliptin can well explain the low risk of hypoglycemia caused by vildagliptin when glycemic control is achieved.

## Effect of vildagliptin on body weight

In overweight or obese patients with type 2 diabetes, successful weight loss can improve glycemic control and reduce concomitant cardiovascular risk factors, such as hypertension and dyslipidemia.<sup>83</sup> The effect of antidiabetic drugs on weight is considered to be an important issue in the selection of therapy. GLP-1 receptor agonists and metformin were associated with weight loss, whereas insulin, insulin secretagogues (eg, SUs and TZDs) were all associated with weight gain.<sup>14</sup>

Clinical trials have demonstrated that vildagliptin has a neutral effect on weight, which is partly explained by its low risk for hypoglycemia. Hypoglycemia is more common in patients treated with weight-gain insulin or SUs. In addition, the experience of hypoglycemia was often followed by “defensive eating,” leading to an excess of caloric intake.<sup>12</sup>

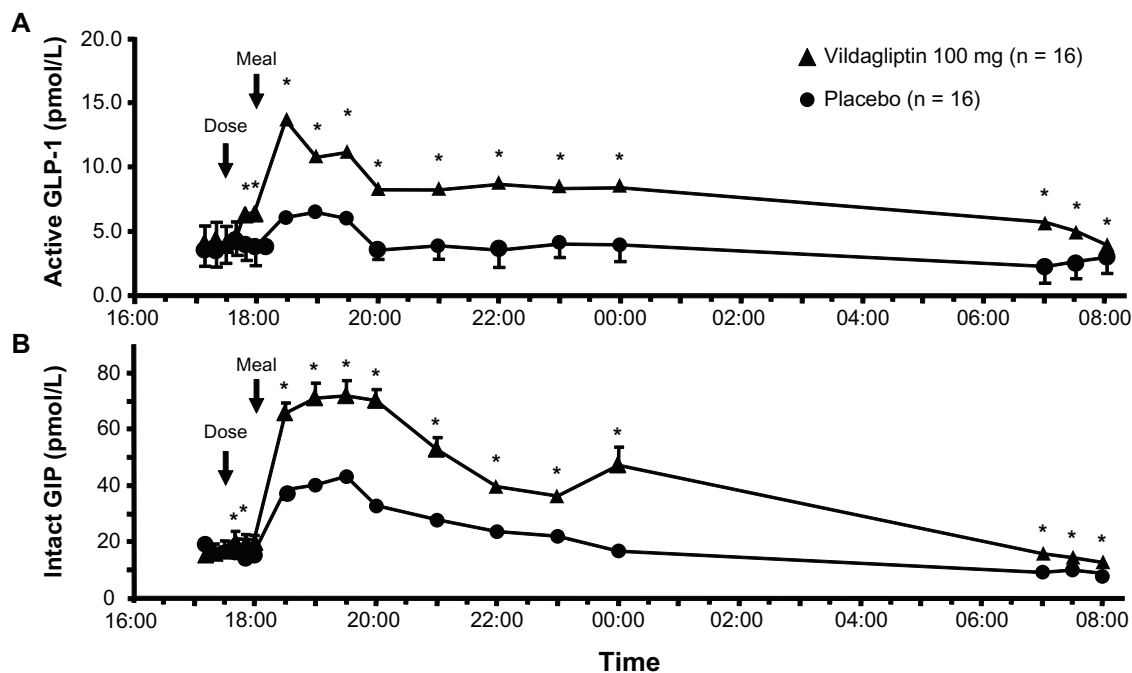


**Figure 1** Effect of vildagliptin on  $\alpha$ -cell function in hyperglycemia (A) and hypoglycemia (B).

**Notes:** \* $P = 0.019$ ; \*\* $P = 0.039$ .

Adapted with permission from Ahrén B, Landin-Olsson M, Jansson PA, Svensson M, Holmes D, Schweizer A. Inhibition of dipeptidyl peptidase-4 reduces glycemia, sustains insulin levels, and reduces glucagon levels in type 2 diabetes. *J Clin Endocrinol Metab.* 2004;89(5):2078–2084.24 ©2009, The Endocrine Society.

**Abbreviation:** AUC, area under the curve.



**Figure 2** Instant effect of vildagliptin 100 mg/day versus placebo on glucose fluctuations.

**Note:** \* $P < 0.05$  or better than placebo. Plasma GLP-1(A), GIP(B) during the meal tolerance test after ingestion of vildagliptin and placebo. Data are the mean  $\pm$  SE. Adapted with permission from Balas B, Baig MR, Watson C, et al. The dipeptidyl peptidase IV inhibitor vildagliptin suppresses endogenous glucose production and enhances islet function after single-dose administration in type 2 diabetic patients. *J Clin Endocrinol Metab.* 2007;92(4):1249–1255.<sup>52</sup> © 2007, The Endocrine Society.

**Abbreviations:** GLP-1, glucagon-like peptide-1; GIP, gastric inhibitory polypeptide.

Vildagliptin can prevent defensive eating by decreasing the risk of hypoglycemia.

It has also been found that vildagliptin significantly lowered chylomicron lipid and apolipoprotein levels, suggesting that it may inhibit intestinal fat extraction.<sup>63</sup> Another trial demonstrated that vildagliptin can increase norepinephrine levels and promote lipolysis through sympathetic stimulation, in conjunction with the postprandial fatty acid mobilization and oxidation.<sup>62</sup> These new potential roles of vildagliptin may also contribute to its weight-neutral effect.

## Cardiovascular and cerebrovascular safety

Cardiovascular and cerebrovascular (CCV) events are comorbidities of T2DM, and the major cause of death in such settings.<sup>84,85</sup> To reduce CCV incidence is always the treatment target of type 2 diabetes. Unexpectedly, however, some antidiabetic agents are associated with increased risk of CV AEs.<sup>86,87</sup> Thus, the evaluation of CCV risk of therapy is very important. A systematic review pooled studies of patients treated with vildagliptin and analyzed its CCV safety.<sup>88</sup> A total of 25 Phase III studies of vildagliptin ( $n = 7509$ ), used either as monotherapy or as part of combination therapy (placebo or comparators,  $n = 6061$ ), with durations of 12 weeks to  $\geq 2$  years were included. Outcomes included the composite

endpoints of acute coronary syndrome, transient ischemic attack (with imaging evidence of infarction), stroke, and CCV death. Compared with all comparators, the RRs for the composite endpoint were  $< 1$  for both vildagliptin 50 mg qd (RR 0.88, 95% CI 0.37 to 2.11) and vildagliptin 50 mg bid (RR 0.84, 95% CI 0.62 to 1.14), which were also consistent across subgroups defined by age, gender, and CV risk status. As a conclusion, vildagliptin did not increase the risk of adjudicated CCV events relative to all comparators in the broad population of type 2 diabetics, including those at increased risk of CCV events.

## Safety of vildagliptin in patients with chronic kidney disease

In a 24-week study of 515 patients with T2DM and moderate or severe renal impairment (RI), vildagliptin was added to ongoing antidiabetic therapy. After 24 weeks, the between-treatment difference in the adjusted mean change in HbA<sub>1c</sub> was  $-0.5\% \pm 0.1\%$  ( $P < 0.0001$ ) in moderate RI (baseline HbA<sub>1c</sub> = 7.9%), and  $-0.6\% \pm 0.1\%$  ( $P < 0.0001$ ) in severe RI (baseline HbA<sub>1c</sub> = 7.7%). In patients with moderate RI, similar proportions of those receiving vildagliptin or placebo experienced any AE (68% versus 73%, respectively), any serious AE (9% versus 9%, respectively), any AE leading to discontinuation (3% versus 5%, respectively), or



death (1% versus 1%, respectively). This was also true for patients with severe RI: AEs (73% versus 74%, respectively), serious AEs (19% versus 21%, respectively), AEs leading to discontinuation (9% versus 6%, respectively), and death (2% versus 4%, respectively). Vildagliptin added to ongoing antidiabetic therapy had a safety profile similar to placebo. Furthermore, relative to placebo, vildagliptin elicited a satisfactory and clinically significant decrease in HbA<sub>1c</sub> in patients with moderate or severe RI.<sup>89</sup>

## Patients' acceptability

Diabetes, including T2DM is usually a lifelong (chronic) disease. One study has shown that patients' poor adherence to therapy is a great obstacle in achieving their glycemic control target.<sup>90</sup> Therefore, the patients' acceptability of antidiabetic agents is as important as their efficacy and safety. Unlike some SUs, meglitinides (which should be given before a meal), and alpha-glucosidase inhibitors (which should be taken just prior to ingesting the first portion of each meal), vildagliptin can be ingested at any time of the day. Unlike insulin, which requires an injection, vildagliptin is an oral glucose-lowering agent. In addition, it has little drug interaction and it can be combined with other OADs. Vildagliptin is currently approved in the European Union for use in combination with metformin and TZD at 50 mg bid, with SU at 50 mg qd, or prepared in a fixed-dose and combined with metformin (50 mg/500 mg, 50 mg/850 mg, and 50 mg/1000 mg). All of these advantages of vildagliptin promote patients' adherence for long-term treatment.

## Conclusion

Vildagliptin is a potent DPP-4 inhibitor. When used alone or added to other OADs, it effectively improves glycemic control, preserves both the  $\alpha$ - and  $\beta$ -cell function, and reduces lipotoxicity and insulin resistance. This drug is well tolerated and is weight-neutral. It poses a low risk of AEs to patients, including hypoglycemia, as well as CCV events. Vildagliptin can be taken before or after a meal, and has little drug interaction; thus, it will be well accepted.

## Disclosure

The authors report no conflicts of interest in this work.

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