Alogliptin benzoate for management of type 2 diabetes

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Abstract: Dipeptidyl peptidase-4 (DPP-4) inhibitors, a new class of oral hypoglycemic agents, augment glucose-dependent insulin secretion and suppress glucagon levels through enhancement of the action of endogenous incretin by inhibiting DPP-4, an incretin-degrading enzyme. DPP-4 inhibitors are generally well tolerated because of their low risk of hypoglycemia and other adverse events. Moreover, with their potential to improve beta cell function, a core defect of type 2 diabetes, DPP-4 inhibitors are becoming a major component of treatment of type 2 diabetes. Alogliptin benzoate is a newly developed, highly selective DPP-4 inhibitor which has been approved in many countries throughout the world. Once-daily administration of alogliptin as either monotherapy or combination therapy with other oral antidiabetic drugs or insulin has a potent glucose-lowering effect which is similar to that of other DPP-4 inhibitors, with a low risk of hypoglycemia and weight gain. The cardiovascular safety of this drug has been confirmed in a recent randomized controlled trial. This review summarizes the efficacy and safety of alogliptin, and discusses the role of DPP-4 inhibitors in the treatment of type 2 diabetes.

Keywords: dipeptidyl peptidase-4 inhibitor, type 2 diabetes, efficacy, safety, alogliptin

Introduction
Dipeptidyl peptidase-4 (DPP-4) inhibitors, a new class of oral hypoglycemic agents, augment glucose-dependent insulin secretion through enhancement of the action of endogenous incretin (ie, glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide) by inhibiting DPP-4, a degrading enzyme of incretin. DPP-4 inhibitors also suppress glucagon secretion via elevation of glucagon-like peptide-1. They are generally well tolerated because of their low risk of hypoglycemia and other adverse events.\(^1\)

Alogliptin benzoate is a newly developed DPP-4 inhibitor developed by Takeda Inc (Osaka, Japan) that was approved for clinical use in the treatment of type 2 diabetes (T2DM) in Japan in April 2010 with the trade name Nesina\(^\circledast\). Alogliptin was also approved by the US Food and Drug Administration and the European Medicines Agency in January 2013 and September 2013, respectively (with the trade name Vipidia\(^\circledast\) in Europe) and, as of September 2014, is available in 39 countries. In Japan, sitagliptin was the first approved DPP-4 inhibitor in December 2009, and first approved by the US Food and Drug Administration in 2006. Currently, seven DPP-4 inhibitors, ie, sitagliptin, vildagliptin, alogliptin, linagliptin, teneligliptin, anagliptin, and saxagliptin, have been approved in Japan.

Alogliptin was developed by structure-based design and proved to have high selectivity for DPP-4.\(^2\) The efficacy and safety of alogliptin has been confirmed to be similar
to that of other DPP-4 inhibitors in recent clinical trials.3 This updated review of a previous publication4 focuses on the clinical efficacy and safety of alogliptin for the treatment of T2DM. The pharmacokinetics and pharmacodynamics of alogliptin have also been reviewed elsewhere.5,6

Methods
This review is based upon a MEDLINE search and personal experience with alogliptin. A MEDLINE search (1966 to December 2014) for published clinical trials and pertinent review articles published in English was conducted with the keywords “alogliptin”, “incretin”, and “DPP-4 inhibitor”. References of identified articles were searched for additional relevant sources. Relevant articles were also obtained from the author’s personal list of references.

Chemistry
The chemical structure of alogliptin is shown in Figure 1. Alogliptin shows high selectivity for DPP-4 (>10,000-fold over other DPP isozymes such as DPP-2, DPP-8, and DPP-9.2,7 High selectivity of alogliptin for DPP-4 has also been confirmed in a DPP-8/9-expressing cell model.8 A recent study using X-ray crystallography revealed that alogliptin interacts with the S1 and/or S2 subsites in addition to the S1 and S2 subsites of DPP-4, where vildagliptin interacts, suggesting that alogliptin offers more potent DPP-4 inhibition compared with vildagliptin.9

Pharmacokinetics
Alogliptin is rapidly absorbed after oral administration, with a median time taken to reach peak plasma concentration of 2 hours and a mean half-life of 12–21 hours across various doses (6.25–800 mg). Food does not affect the absorption of alogliptin.10–12

To date, no drug interaction with alogliptin has been reported, although among the DPP-4 inhibitors, the level of saxagliptin may be affected by inhibitors or inducers of the cytochrome P450 3A4/5 isozyme (eg, ketoconazole, diltiazem, and rifampicin).

The pharmacokinetics of alogliptin have also been evaluated in subjects with renal and hepatic impairment. Following administration of a single 50 mg dose of alogliptin, 1.7-fold, 2.1-fold, 3.2-fold, and 3.8-fold increases in alogliptin exposure in subjects with mild, moderate, severe renal insufficiency, and end-stage renal disease, respectively, were observed compared with levels in healthy volunteers.6,13 Thus, dose adjustment of alogliptin, as well as sitagliptin and saxagliptin, is recommended for patients with renal dysfunction (Table 1).

A single 25 mg dose of alogliptin was administered to eight patients with moderate hepatic impairment based on the Child-Pugh Scale, and there was no significant increase in serum concentration of alogliptin when compared with that in healthy volunteers. Thus, dose adjustment of alogliptin is not needed in patients with hepatic impairment.6,13

Pharmacodynamics
Mean plasma DPP-4 inhibition after a single dose of alogliptin (25–800 mg) ranged from 74% to 94% at 24 hours and 48% to 83% at 72 hours. After 14 days of dosing (25–400 mg/day), mean peak DPP-4 inhibition ranged from 94% to 99%, with mean inhibition at 24 hours after dosing of 82%–97%, supporting once-daily administration.10,11 A recent qualitative model of DPP-4 inhibition showed that with once-daily administration of alogliptin 25 mg, the usual recommended dosage of alogliptin, the percentage of time when DPP-4 inhibition was >80% was 88%, the percentage of DPP-4 inhibition at trough was 80%, and the percentage of weighted average DPP-4 inhibition over 24 hours was 88%, which is comparable with the results with once-daily administration of sitagliptin 100 mg.14

Table 1 Dosage modification of alogliptin for patients with renal impairment in Japan

<table>
<thead>
<tr>
<th>Level of Renal Impairment</th>
<th>Dosage Modification</th>
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<tbody>
<tr>
<td>Mild (CCr &gt;50 mL/min)</td>
<td>No dosage adjustment required (25 mg once daily)</td>
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<tr>
<td>Moderate (CCr 30 to &lt;50 mL/min)</td>
<td>Decrease dose to 12.5 mg once daily</td>
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<tr>
<td>Severe (CCr &lt;30 mL/min)</td>
<td>Decrease dose to 6.25 mg once daily*</td>
</tr>
</tbody>
</table>

Note: *Can be administered without regard to timing of hemodialysis.
Abbreviation: CCr, creatinine clearance.
Clinical efficacy

Glucose-lowering effect

The glucose-lowering effect of alogliptin has been evaluated in double-blind, placebo-controlled Phase II and III trials and also in recent Phase IV trials. The results of major clinical trials assessing the clinical efficacy of alogliptin compared with placebo or active comparators are summarized in Table 2.

Monotherapy

To evaluate the efficacy of alogliptin as monotherapy, 329 drug-naïve patients with poorly controlled T2DM (mean HbA1c 7.9%) were randomized to once-daily treatment with alogliptin 12.5 mg, alogliptin 25 mg, or placebo for 26 weeks.15 At week 26, the reduction in HbA1c from baseline was −0.56% and −0.59% in the alogliptin 12.5 mg and 25 mg groups, respectively, compared with 0.02% in the placebo group (P<0.001). Another dose-ranging study examined the efficacy of alogliptin (6.25–50 mg) in 480 drug-naïve Japanese patients with T2DM.16 HbA1c at week 12 was dose-dependently reduced by alogliptin, and the reduction in HbA1c from baseline was −0.68% and −0.77% in the alogliptin 12.5 mg and 25 mg groups, respectively, compared with 0.05% in the placebo group (P<0.0001).

Combination with other antidiabetic medications

Sulfonylureas

The efficacy of alogliptin in combination with sulfonylureas has also been evaluated.17 In one study, 500 patients with T2DM inadequately controlled by sulfonylurea monotherapy (mean HbA1c 8.1%) were randomized to treatment with glyburide plus alogliptin 12.5 mg or 25 mg or placebo for 26 weeks. At week 26, the reduction in HbA1c was −0.38% and −0.52% with alogliptin 12.5 mg and 25 mg, respectively, compared with 0.01% for placebo (P<0.001). In another study, 312 Japanese patients with T2DM inadequately controlled by sulfonylurea monotherapy (mean HbA1c 8.5%) were randomized to alogliptin 12.5 mg or 25 mg or placebo in addition to glimepiride 1–4 mg for 12 weeks.18 The HbA1c reduction at week 12 was −0.59% and −0.65% with alogliptin 12.5 mg and 25 mg, respectively, compared with 0.35% for placebo (P<0.0001).

Metformin

The efficacy of alogliptin in combination with metformin was evaluated in a study that included 527 patients with T2DM inadequately controlled on metformin monotherapy (mean HbA1c 8%).19 The patients were randomized to add-on treatment with alogliptin 12.5 mg or 25 mg or placebo for 26 weeks. At week 26, the reduction in HbA1c with either dose of alogliptin was −0.6% (P<0.001 versus placebo). In another Japanese study, a total of 288 patients with T2DM inadequately controlled with metformin 500 or 750 mg/day (mean HbA1c 8.0%) were randomized to receive alogliptin 12.5 mg or 25 mg or placebo in addition to metformin for 12 weeks.20 At week 12, the reduction in HbA1c was −0.55% and −0.64% with alogliptin 12.5 mg and 25 mg, respectively, compared with 0.22% for placebo (P<0.0001).

Two more studies have been published recently. One trial was designed to evaluate the efficacy of initial therapy with alogliptin plus metformin.21 A total of 784 drug-naïve patients (mean HbA1c 8.45%) were randomized to receive placebo, alogliptin 12.5 mg twice daily or 25 mg once daily, metformin 500 mg or 1,000 mg twice daily, or a combination of alogliptin 12.5 mg plus metformin 500 mg or 1,000 mg twice daily. The reduction in HbA1c at week 26 was −1.22% and −1.55% with the combination of alogliptin 12.5 mg plus metformin 500 mg or 1,000 mg twice daily, respectively, compared with −0.52% and −1.11% with alogliptin 25 mg once daily and metformin 1,000 mg twice daily, respectively (P<0.001). The number of patients who achieved HbA1c <7% was greater for combination therapy compared with monotherapy (47.1%–59.5% versus 20.2%–34.3%). The second study was designed to compare the long-term efficacy and safety of alogliptin plus metformin with that of glipizide plus metformin.22 A total of 2,639 patients with a mean age 55.4 years, a mean duration of diabetes of 5.5 years, and a mean HbA1c of 7.6% were randomized to receive alogliptin 12.5 mg or 25 mg once daily or glipizide 5–20 mg once daily in addition to metformin for 104 weeks. The HbA1c reduction at week 104 was significantly greater with alogliptin 25 mg than with glipizide (−0.72% versus −0.59%, P=0.010), with less hypoglycemia (1.4% versus 23.2%) and weight gain (−0.89 versus 0.95 kg, P<0.001).

Thiazolidinediones

The efficacy of alogliptin in combination with a thiazolidinedione (TZD) was also evaluated. A total of 493 patients with T2DM inadequately controlled on a TZD (mean HbA1c 8.0%) were randomized to treatment with pioglitazone plus alogliptin 12.5 mg, alogliptin 25 mg, or placebo for 26 weeks.23 At week 26, the reduction in HbA1c was −0.66% with alogliptin 12.5 mg and −0.80% with alogliptin 25 mg, compared with −0.19% for placebo (P<0.001). In another Japanese study,24 339 patients with T2DM inadequately controlled on pioglitazone (mean HbA1c 7.9%) were randomized
Table 2 Selected efficacy outcomes from clinical trials of alogliptin

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients (n)</th>
<th>Background treatment (mg)</th>
<th>Treatment group (intervention, mg)</th>
<th>Treatment period (weeks)</th>
<th>Baseline HbA1c (%)</th>
<th>HbA1c change (%)</th>
<th>Achievement of HbA1c ≤7.0% (%)</th>
<th>Body weight change (kg)</th>
<th>Hypoglycemia</th>
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<tr>
<td>DeFronzo et al15</td>
<td>329</td>
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<td>PBO</td>
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<td>PBO</td>
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<td>0.05</td>
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<td>-0.22</td>
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<td>SU</td>
<td>GLB + PBO</td>
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<td>PBO</td>
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<td>M ≥1,500 or MTD</td>
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<td>493</td>
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<tr>
<td>Kaku et al. [1]</td>
<td>339 patients with T2DM</td>
<td>16 weeks</td>
<td>Alogliptin 2.5 mg with metformin</td>
<td>-1.4%</td>
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<td>Van Raalte et al. [2]</td>
<td>71 patients</td>
<td>16 weeks</td>
<td>Alogliptin 2.5 mg with metformin</td>
<td>-1.3%</td>
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<tr>
<td>Rosenstock et al. [3]</td>
<td>390 patients</td>
<td>26 weeks</td>
<td>Alogliptin 2.5 mg with metformin</td>
<td>-1.1%</td>
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<tr>
<td>Kaku et al. [4]</td>
<td>179 patients</td>
<td>18 months</td>
<td>Alogliptin 2.5 mg with metformin</td>
<td>-0.8%</td>
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<td>Rosenstock et al. [5]</td>
<td>441 patients (aged 65–90 years)</td>
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<td>-0.7%</td>
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<td>White et al. [6]</td>
<td>5380 patients</td>
<td>6 months</td>
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</tr>
</tbody>
</table>

**Notes:**
- Achievement of HbA1c <6.9%.
- Calculated from the number of subjects.
- Least square mean differences relative to PBO.
- Estimated from the graph.
- Among patients who completed the study. The readers should refer to the text or original article for statistical significance.

**Abbreviations:** DPP-4, dipeptidyl peptidase-4; PBO, placebo; ALO, alogliptin; VOG, voglibose; PIO, pioglitazone; M, metformin; SU, sulfonylurea; GLB, glyburide; GLM, glimepiride; GLP, glucosidase; MTD, maximum tolerated dose; OAD, oral antidiabetic agent; GLP-1, glucagon-like peptide-1; NA, not available; HbA1c, glycated hemoglobin.

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**Insulin**

The efficacy of alogliptin when added to insulin therapy in patients with T2DM was assessed in two trials. In one study, 458 patients with T2DM were randomized to receive alogliptin 2.5 mg or placebo in addition to insulin monotherapy, with or without alogliptin 2.5 mg added to insulin therapy. The reduction in HbA1c was 0.9% with alogliptin 2.5 mg plus placebo (P <0.001 versus placebo).

---

**Combination therapy of alogliptin and pioglitazone**

A total of 1,554 patients with T2DM inadequately controlled on metformin monotherapy was evaluated in another study. A total of 1,554 patients with T2DM inadequately controlled on metformin monotherapy (mean HbA1c, 8.4%) were randomized into four treatment arms: alogliptin 2.5 mg, alogliptin 2.5 mg plus pioglitazone 30 mg, combination therapy for 26 weeks. At week 26, combination therapy resulted in a greater reduction of HbA1c (1%) versus alogliptin 2.5 mg monotherapy (1.2%; P <0.001).

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**Alogliptin for type 2 diabetes**

Initial combination therapy of alogliptin and pioglitazone in drug-naive patients with T2DM was also evaluated. A total of 655 drug-naive patients with inadequately controlled diabetes (mean HbA1c, 8.8%) were randomized into four treatment arms: alogliptin 2.5 mg compared with placebo (P <0.01).
therapy for 12 weeks. The HbA1c reduction at week 12 was −0.96% for alogliptin compared with −0.29% for placebo (P<0.0001). The proportion of patients who achieved HbA1c <7% was greater with alogliptin than with placebo (23.3% versus 5.7%).

Lastly, the large-scale, randomized, controlled EXAMINE (Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care) study was conducted to assess the cardiovascular safety of alogliptin. In this study, treatment with alogliptin on top of other antidiabetic medications showed a significant reduction in HbA1c (−0.36%, P<0.001) compared with placebo during a median follow-up of 18 months.

Recently, Berhan et al conducted a meta-analysis of ten randomized controlled trials to assess the efficacy of alogliptin in T2DM. The pooled standardized mean difference for the reduction in HbA1c in patients treated with alogliptin 12.5 mg was −0.81% (95% confidence interval [CI] −1.11, −0.51) and that in patients treated with alogliptin 25 mg was −0.98% (95% CI −1.30, −0.66). The standardized mean difference of the reduction in fasting plasma glucose in patients treated with alogliptin 25 mg was −0.51 mmol/L (95% CI −0.68, −0.34).

Although there has been no head-to-head trial comparing the efficacy of alogliptin with that of other DPP-4 inhibitors, the improvement of HbA1c seen with alogliptin seems to be in the same range as that seen with other DPP-4 inhibitors, with the exception of vildagliptin 50 mg twice daily, which was reported to have a small advantage in glucose-lowering effect compared with other DPP-4 inhibitors.

**Predictors of HbA1c reduction by DPP-4 inhibitors**

Recent meta-analyses of randomized controlled trials have shown that the efficacy of DPP-4 inhibitors is mainly related to baseline HbA1c level, as is seen with other antidiabetic medications. Esposito et al examined the clinical characteristics that predict the HbA1c response to DPP-4 inhibitors in their meta-regression analysis of 78 randomized controlled trials with 20,053 patients, and found a greater absolute reduction of baseline HbA1c in patients with higher baseline HbA1c and lower fasting glucose levels.

Recent meta-analyses have also suggested the efficacy of incretin therapy differs between ethnic groups. It has been shown that the efficacy of HbA1c reduction by DPP-4 inhibitors or glucagon-like peptide-1 receptor agonists is greater in Asian populations than in non-Asian populations, suggesting that lower body mass index is associated with a better HbA1c response to incretin therapy.

The long-term glycemic durability of DPP-4 inhibitors in patients with T2DM has also been reported. A meta-analysis of 12 trials with 14,829 patients showed that the effect of DPP-4 inhibitors on HbA1c declined significantly by −0.2% during the second year of treatment, while a greater HbA1c reduction at 2 years was reported for alogliptin compared with glipizide in the above-mentioned trial.

**Efficacy in the elderly**

The efficacy of alogliptin in the elderly was evaluated in a randomized, double-blind, active-controlled study. In this study, 441 elderly type 2 diabetic patients of mean age 70 (range 65–90) years and with mild hyperglycemia on diet/exercise therapy alone or combined with oral antidiabetic monotherapy (mean HbA1c 7.5%) were randomized to alogliptin 25 mg or glipizide 5–10 mg for 52 weeks. The reduction in HbA1c at the end of study was −0.42% with alogliptin and −0.33% with glipizide, demonstrating no inferiority of alogliptin to glipizide. A post hoc analysis using this cohort showed that the proportion of patients achieving HbA1c ≤7.0% without hypoglycemia or weight gain was significantly higher with alogliptin than with glipizide (24% versus 13%, P<0.03). It has also been shown that patients with baseline HbA1c ≤8.0% receiving alogliptin are also more likely to achieve HbA1c ≤7.0% without hypoglycemia or weight gain than those receiving glipizide (29% versus 13%, P<0.03).

A pooled analysis of Phase II and III studies to assess the efficacy of alogliptin in elderly patients with T2DM has also been reported. Analysis of six randomized controlled trials of alogliptin showed a similar improvement in HbA1c in elderly patients (mean age 70 years) compared with younger patients (mean age 52 years).

**Efficacy in hemodialysis patients**

Since alogliptin is excreted by the kidney, the dose of alogliptin should be reduced in patients with moderate to severe renal impairment, as shown in Table 1. In a single-arm study, treatment with alogliptin 6.25 mg reduced HbA1c and glycated albumin levels from 7.1%±0.2% to 5.8%±1.6% and from 22.5%±0.7% to 19.6%±0.6%, respectively, after 24 months in 16 hemodialysis patients with T2DM.

**Effect on beta cell function**

Alogliptin has been shown to improve beta cell function and increase beta cell mass in rodents. In humans, it
was reported that there was no or only modest improvement of beta cell function assessed by proinsulin to insulin ratio or homeostasis model assessment (HOMA)-β by alogliptin monotherapy or combination therapy with metformin or a sulfonylurea. In the other hand, significant improvement of beta cell function was reported when patients were treated with alogliptin combined with pioglitazone. It has been reported that treatment with a combination of alogliptin 25 mg and pioglitazone 30 mg for 16 weeks significantly improved beta cell glucose sensitivity and fasting secretory tone compared with placebo, while alogliptin 25 mg monotherapy did not change beta cell function parameters. A recent study has shown that treatment with alogliptin improved the function and proliferation of adult human beta cells engrafted in diabetic immunodeficient mice; however, the effect of DPP-4 inhibitors on beta cell mass in humans remains unclear.

Effect on lipids
Eliasson et al reported a change in postprandial lipids during treatment with alogliptin. Seventy-one patients with inadequately controlled T2DM were randomized to treatment with alogliptin 25 mg, alogliptin 25 mg plus pioglitazone 30 mg, or placebo for 16 weeks. At 16 weeks, a significant reduction in postprandial triacylglycerol and triacylglycerol-rich lipoproteins was observed with alogliptin monotherapy and alogliptin plus pioglitazone combination therapy compared with placebo. A meta-analysis of 17 studies also showed a significant reduction in total cholesterol (−0.18 mmol/L [−7 mg/dL]) and triacylglycerol (−0.15 mmol/L [−13 mg/dL]) on treatment with a DPP-4 inhibitor, although the reduction was small. A separate analysis of the effect of individual DPP-4 inhibitors showed a significant reduction in total cholesterol with alogliptin and vildagliptin, but not with sitagliptin. However, in the EXAMINE study, no significant difference in lipoprotein levels was found between the alogliptin and placebo groups.

Effect on atherosclerosis and cardiovascular events
In animal studies, it was reported that alogliptin suppressed the progression of atherosclerosis in diabetic mice through downregulation of proinflammatory cytokines. It was also reported that alogliptin reduced the volume of the infarct lesion and neurological deficit after the induction of temporary focal ischemia in nondiabetic male C57BL/6J mice, suggesting that the neuroprotective effect of alogliptin is independent of its glucose-lowering effect.

The effect of DPP-4 inhibitors on atherosclerosis in humans is unclear. In a preliminary study of ten healthy volunteers, treatment with alogliptin 25 mg for 1 week significantly suppressed the postprandial elevation in serum triacylglycerol and improved postprandial endothelial dysfunction, as assessed by brachial artery flow-mediated dilation.

Effect on kidney function
Although a protective effect of DPP-4 inhibitors against renal injury has been reported in rodent studies, the presence of such an effect remains to be established in humans. It has been reported that switching from sitagliptin to alogliptin, combined with an angiotensin II type 1 receptor blocker, resulted in a significant reduction in the urinary albumin to creatinine ratio in 12 patients with T2DM and albuminuria. This improvement in albuminuria was accompanied by an elevated plasma level of stromal cell-derived factor-1 alpha and a decrease in urinary 8-hydroxy-2′-deoxyguanosine, an oxidative stress marker, suggesting that alogliptin ameliorated albuminuria by reducing oxidative stress. Sakata et al reported that treatment with alogliptin for 12 weeks significantly reduced the urinary albumin to creatinine ratio, as well as HbA1c and the circulating soluble form of the receptor for advanced glycation end products, in 61 patients with T2DM.

In the EXAMINE trial, no difference in change in estimated glomerular filtration rate was reported between alogliptin and placebo. On the other hand, fewer patients showed worsened urinary albumin to creatinine ratio with saxagliptin versus placebo in the SAVOR (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus)-TIMI (Thrombolysis in Myocardial Infarction) 53 trial, although it remains unclear whether this effect of a DPP-4 inhibitor is independent of its glucose-lowering effect.

The effect of DPP-4 inhibitors on other types of microangiopathy such as retinopathy and neuropathy in humans remains largely unknown.

Safety
In general, the incidence of adverse events with DPP-4 inhibitors is reported to be low, and these agents are well tolerated.

Hypoglycemia
The risk of hypoglycemia is low on treatment with alogliptin. The incidence of hypoglycemia with alogliptin was reported to be as low as that with placebo or metformin monotherapy.
and lower than that with sulfonylureas.\textsuperscript{15,17,19,41} Adding alogliptin to insulin therapy resulted in improvement of HbA\(_{1c}\) without increasing hypoglycemia compared with insulin therapy alone.\textsuperscript{28,29} However, use of a DPP-4 inhibitor as combination therapy with a sulfonylurea can increase the risk of hypoglycemia.\textsuperscript{1} Therefore, caution is needed when a DPP-4 inhibitor is added to a sulfonylurea, especially in patients at risk of hypoglycemia, such as the elderly, patients with renal impairment, patients treated with a high dose of sulfonylureas, and patients with autonomic neuropathy.

**Effect on body weight**

The effect of DPP-4 inhibitors on body weight is generally reported to be neutral.\textsuperscript{1} Treatment with alogliptin has shown less weight gain compared with sulfonylureas.\textsuperscript{22,41} It was reported that alogliptin neither prevented nor exacerbated weight gain when it was combined with pioglitazone.\textsuperscript{23–26,49}

**Cardiovascular safety**

Recently, regulatory agencies have created cardiovascular safety guidelines for the development of therapies for diabetes. A pooled analysis of alogliptin trials including 4,168 patients showed no sign of increased cardiovascular risk with alogliptin in patients with T2DM (hazard ratio, 0.635, 95% CI 0.0–1.41).\textsuperscript{56}

The results of the EXAMINE study assessing the long-term cardiovascular safety of alogliptin were published in September 2013.\textsuperscript{30} In this study, 5,380 patients with T2DM and recent acute coronary syndrome were randomized to receive alogliptin or placebo in addition to existing antihyperglycemic therapy. During a median follow-up period of 1.8 years, the rate of major adverse cardiovascular events, a composite of death from cardiovascular causes, nonfatal myocardial infarction, and nonfatal stroke, was not increased with alogliptin compared with placebo (11.3% versus 11.8%, hazard ratio 0.96; upper boundary of one-sided repeated CI, 1.16; \(P<0.001\) for noninferiority).

Another cardiovascular outcome trial of a DPP-4 inhibitor was published at the same time. The SAVOR-TIMI 53 trial\textsuperscript{64} was designed to evaluate the safety and efficacy of saxagliptin with respect to cardiovascular outcomes in patients with T2DM and at risk of a cardiovascular event. A total of 16,492 patients were randomized to receive saxagliptin or placebo and followed for a median of 2.1 years. There was no significant difference in incidence of a primary endpoint event, a composite of cardiovascular death, myocardial infarction, and ischemic stroke, between the groups (hazard ratio 1.00, 95% CI 0.89–1.12; \(P=0.99\) for superiority; \(P<0.001\) for noninferiority).

The results of these two randomized controlled trials confirmed the cardiovascular safety of DPP-4 inhibitors. However, in the SAVOR-TIMI 53 trial, more patients in the saxagliptin group than in the placebo group were hospitalized for heart failure (3.5% versus 2.8%; hazard ratio 1.27, 95% CI 1.07–1.51, \(P=0.007\)).\textsuperscript{64} Meta-analyses of trials using different DPP-4 inhibitors including alogliptin also suggested an increased risk of heart failure with DPP-4 inhibitor treatment,\textsuperscript{67,68} although in the EXAMINE study the incidence of heart failure was not significantly increased in the alogliptin group (hazard ratio 1.19, 95% CI 0.89–1.58, \(P=0.24\)).\textsuperscript{30} Further investigation is needed to clarify whether DPP-4 inhibitors are associated with a risk of heart failure.

**Other adverse events**

Angioedema has been reported as an adverse event of DPP-4 inhibitors, especially when combined with an angiotensin-converting enzyme inhibitor.\textsuperscript{69} We have had a patient who developed facial angioedema after the introduction of vildagliptin, which improved after switching from vildagliptin to alogliptin.\textsuperscript{70} The incidence of angioedema due to DPP-4 inhibitors is generally low, and no difference in its incidence was reported between the alogliptin and placebo groups in the EXAMINE trial.\textsuperscript{30}

To date, no meta-analyses of clinical trials or large-scale, randomized controlled trials of DPP-4 inhibitors suggest any increase in specific adverse events, such as nasopharyngitis, upper respiratory tract infection, skin reaction, hepatotoxicity, or pancreatitis, with the exception of heart failure as described above.\textsuperscript{1,30,64,71,72} Concern has been raised regarding the risk of pancreatitis or pancreatic cancer associated with incretin therapy;\textsuperscript{73,74} however, no increase in the incidence of acute pancreatitis has been reported in patients treated with incretin therapy in recent health insurance claims database and case-control studies.\textsuperscript{75,76} or in randomized controlled trials.\textsuperscript{30,64} Although case reports of liver injury in patients treated with alogliptin have raised the question of possible hepatotoxicity with this agent, no evidence of liver injury was reported in the EXAMINE trial.\textsuperscript{30,77} Completion of pooled analysis of ongoing long-term, large-scale clinical trials is needed to determine the longer-term safety profile, such as the incidence of cancer (Table 3).

Table 3 Issues concerning dipeptidyl peptidase-4 inhibitors in need of further clarification

<table>
<thead>
<tr>
<th>Type of Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatotoxicity</td>
</tr>
<tr>
<td>Heart failure</td>
</tr>
<tr>
<td>Pancreatitis</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
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</table>
Role of DPP-4 inhibitors in treatment of T2DM

It is now well appreciated that not only type 1 diabetes but also T2DM is characterized by a deficit of beta cells. Beta cell dysfunction is a strong predictor of future development of T2DM, suggesting that beta cell dysfunction is a core pathogenetic feature of the disease. Further, beta cell function in patients with T2DM progressively declines with duration of disease and is negatively associated with glycemic control. Thus, preservation or recovery of beta cell function is an important treatment strategy in T2DM.

Despite recent advances in the treatment of T2DM, several issues remain to be resolved (Table 4), all of which are related to nonphysiological, inappropriate insulin supplementation by treatment, such as with sulfonylureas or insulin. In contrast, DPP-4 inhibitors have benefits with respect to all these issues (Table 4). Further, DPP-4 inhibitors improve the dynamics of glucagon, whereas raised plasma glucagon levels and a paradoxical increase in postprandial glucagon are another major defect in diabetes. Therefore, one of the most important characteristics of DPP-4 inhibitors is recovery of endogenous insulin (and glucagon) secretion in a more physiological fashion compared with previous antidiabetic medications.

A proposed concept with regard to a treatment strategy for T2DM in relation to beta cell function is shown in Figure 2. T2DM is a progressive disease, and usually medication needs to be uptitrated with time. Currently, the most effective way to preserve or restore beta cell function is to reduce beta cell workload. Since metformin reduces insulin demand and beta cell workload through lowering hepatic glucose production, the use of metformin in addition to lifestyle modification should be considered at as early a stage of disease as possible, unless contraindicated. In Japan, alpha-glucosidase inhibitors are approved for clinical use in patients with impaired glucose tolerance and metabolic syndrome, in addition to T2DM. Since DPP-4 inhibitors are expected to improve beta cell function in addition to their glucose-lowering effect, the use of DPP-4 inhibitors can also be considered for a broad range of disease stages. In contrast, the use of insulin secretagogues, sulfonylureas, may not be considered as initial therapy but rather for use at a lower dose to support the insulinotropic effect of incretin therapy. Since to date no drug can cure diabetes, combination therapy should be considered in most cases. Triple combination therapy with metformin, pioglitazone, and alogliptin has been shown to be effective in reducing HbA1c, and improving beta cell function. Medications not approved in Japan are not included in the figure. Copyright © 2015. The Author. Reproduced from Saisho Y. Beta cell dysfunction: its critical role in prevention and management of type 2 diabetes. World J Diabetes. 2015;6(1):109–124.

Table 4 Remaining issues in the treatment of type 2 diabetes and potential of DPP-4 inhibitors

<table>
<thead>
<tr>
<th>Remaining issues</th>
<th>Potential of DPP-4 inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoglycemia</td>
<td>Low risk of hypoglycemia</td>
</tr>
<tr>
<td>Weight gain</td>
<td>Neutral effect on body weight</td>
</tr>
<tr>
<td>Postprandial hyperglycemia</td>
<td>Reduce glycemic variability</td>
</tr>
<tr>
<td>Concern about increased risk of malignancy and/or atherosclerosis due to systemic (peripheral) hyperinsulinemia (especially with insulin therapy)</td>
<td>Restore endogenous insulin secretion in a more physiological manner</td>
</tr>
<tr>
<td>Progressive decline in beta cell function</td>
<td>Improve beta cell function</td>
</tr>
</tbody>
</table>

Abbreviation: DPP-4, dipeptidyl peptidase-4.
Table 5 Summary of characteristics of antidiabetic medications when combined with metformin

<table>
<thead>
<tr>
<th></th>
<th>DPP-4 inhibitors</th>
<th>TZD</th>
<th>Sulfonylureas</th>
<th>AGIs</th>
<th>Glinides</th>
<th>SGLT2 inhibitors</th>
<th>GLP-1 receptor agonists</th>
<th>Insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy of HbA1c reduction</strong></td>
<td>Moderate</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Modest to moderate</td>
<td>Modest to moderate</td>
<td>Moderate</td>
<td>High</td>
<td>High (Highest)</td>
</tr>
<tr>
<td><strong>Risk of hypoglycemia</strong></td>
<td>Low</td>
<td>Low</td>
<td>High</td>
<td>Low</td>
<td>Moderate to high</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td><strong>Other side effects</strong></td>
<td>Edema, heart failure, bone fracture, bladder cancer?</td>
<td>Abdominal bloating, flatulence, constipation, diarrhea</td>
<td></td>
<td></td>
<td>Genitourinary infection, polyuria, volume depletion</td>
<td></td>
<td>Nausea/vomiting, constipation, diarrhea</td>
<td></td>
</tr>
<tr>
<td><strong>Inhibitory effect of weight gain</strong></td>
<td>±</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>± to −</td>
<td>+</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td><strong>Preservation effect on beta cell function</strong></td>
<td>+</td>
<td>+</td>
<td>− to ±</td>
<td>± to +</td>
<td>±</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Other additional effects</strong></td>
<td>Improvement of postprandial hyperglycemia, suppression of glucagon secretion, extra-pancreatic effects of incretin</td>
<td>Improvement of lipid profile, antiatherosclerotic effect, CV protective effects</td>
<td>Microvascular complications ↓ (UKPDS)</td>
<td>Improvement of postprandial hyperglycemia, CV protective effect</td>
<td>Improvement of postprandial hyperglycemia</td>
<td>Improvement of blood pressure and lipid profile</td>
<td>Improvement of blood pressure and lipid profile, suppression of glucagon secretion, extra-pancreatic effects of GLP-1</td>
<td>Microvascular complications ↓ (UKPDS)</td>
</tr>
<tr>
<td><strong>Cost</strong></td>
<td>$</td>
<td>$ to $</td>
<td>$</td>
<td>$</td>
<td>$</td>
<td>$</td>
<td>$ to $</td>
<td>$ to $</td>
</tr>
</tbody>
</table>

**Note:** ±, plus minus; +, plus; −, minus; ↓, reduced; $, low cost; $$, moderate cost; $$$, high cost; ?, unconfirmed.

**Abbreviations:** DPP-4, dipeptidyl peptidase-4; TZD, thiazolidinedione; AGI, alpha-glucosidase inhibitor; SGLT2, sodium-glucose cotransporter 2; GLP-1, glucagon-like peptide-1; CV, cardiovascular; UKPDS, UK Prospective Diabetes Study; HbA1c, glycated hemoglobin.
The glucose-lowering effect of TZDs has been shown to have greater durability compared with that of sulfonylureas or even metformin. Thus, combination therapy with a DPP-4 inhibitor and a TZD is also expected to have a glucose-lowering effect with high efficacy and durability and a low risk of hypoglycemia, and to effectively improve beta cell function. However, since TZDs are associated with weight gain, weight reduction should not be expected. In addition, a risk of bladder cancer and bone fractures are a concern with TZDs, although a recent large cohort study showed no increased risk of bladder cancer in patients treated with pioglitazone. Thus, it might be advisable to use TZDs such as pioglitazone at a lower dosage to reduce the risk of adverse effects.

Fixed-dose combination tablets of alogliptin and metformin (Kazano®) or pioglitazone (Liovel® or Oseni®) are now available in many countries. It has been reported that use of fixed-dose combination tablets improves patient adherence to treatment and treatment satisfaction, possibly resulting in improved glycemic control. Thus, fixed-dose combinations containing alogliptin will be an important option for the treatment of T2DM. A combination of a DPP-4 inhibitor and another non-insulin secretagogue such as an alpha-glucosidase inhibitor or sodium-glucose cotransporter 2 inhibitor has also been shown to be effective for improving HbA1c and glycemic variability, with a low risk of hypoglycemia and weight neutrality or modest weight loss, although gastrointestinal disturbance with alpha-glucosidase inhibitors often limits their use. The long-term efficacy and safety of the combination of a DPP-4 inhibitor and a sodium-glucose cotransporter 2 inhibitor remains to be established.

In contrast, sulfonylureas (insulin secretagogues) may not be considered as initial therapy, but rather for use at a lower dose to support the insulinotropic effect of incretin therapy, because of their risk of hypoglycemia and weight gain. Glinides, short-acting insulin secretagogues, correct postprandial hyperglycemia. Although the glucose-lowering effect of glinides is modest, the risk of hypoglycemia with glinides is lower than that with sulfonylureas. Therefore, combined use of a DPP-4 inhibitor and a glinide may be useful to manage postprandial hyperglycemia while minimizing the risk of hypoglycemia and weight gain.

Insulin shows the greatest efficacy in reducing HbA1c and has been shown to improve beta cell function. Thus, combination of a DPP-4 inhibitor and insulin should be considered for patients with various stages of T2DM, although the risk of hypoglycemia, weight gain, and fear or unwillingness to carry out injections may limit this combination. The efficacy of combination of a DPP-4 inhibitor and a glucagon-like peptide-1 agonist remains to be determined.

Since there is no drug to date that can cure diabetes, combination therapy should be considered in most cases. To date, on top of metformin, each combination of antidiabetic medication has its advantages and disadvantages (Table 5). The results of the ACCORD (Action to Control Cardiovascular Risk in Diabetes) study have warned us not to simply intensify medical treatment to reduce HbA1c to near-normal levels. Hospital admission rates for hypoglycemia now exceed those for hyperglycemia among older adults. The burden of medical treatment may rather result in reducing the patient’s quality-adjusted life years. Therefore, each combined drug should be selected for each individual patient with consideration of the patient’s preference. Although studies suggest that initial combination therapy reduces HbA1c more effectively than monotherapy in the short term, the longer-term efficacy remains unknown.

It has been reported that the glucose-lowering effect of DPP-4 inhibitors is more potent in Asians than in Caucasians. Moreover, recent studies suggest that there is a difference in the pathophysiological features of T2DM according to ethnicity. Thus, the above-mentioned treatment strategy may not be applicable to other ethnicities or countries, and may need to be modified in each situation.

Conclusion
Alogliptin, a highly selective DPP-4 inhibitor, has a glucose-lowering effect, the degree of which is similar to that of other DPP-4 inhibitors, with a low risk of hypoglycemia and weight gain. The safety of alogliptin, including cardiovascular adverse events, has been confirmed in a large-scale trial. Having a low risk of hypoglycemia, weight neutrality, and the potential to improve beta cell function, DPP-4 inhibitors are expected to become an important component of the treatment of T2DM. In Japan, currently more than half of patients with T2DM are treated with DPP-4 inhibitors. The cost-effectiveness of DPP-4 inhibitors needs to be assessed in future trials.

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Disclosure
The author reports no conflicts of interest in this work.
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