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REVIEW ARTICLE

Benefit-Risk Assessment of Alogliptin for the Treatment of Type 2 Diabetes Mellitus

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Abstract

The dipeptidyl peptidase-4 inhibitor (DPP-4i) alogliptin is an oral, antidiabetic treatment that is approved in many countries to treat patients with type 2 diabetes mellitus (T2DM), including the USA, Europe, and Japan. Alogliptin is efficacious both as monotherapy and as add-on/combination therapy with other commonly prescribed T2DM treatments, such as metformin and pioglitazone. Overall, alogliptin is well-tolerated in patients with T2DM, including older patients, those with renal and/or hepatic impairment, and those at high risk of cardiovascular events. There is a low risk of hypoglycemia, weight gain, acute pancreatitis, and gastrointestinal adverse events with alogliptin treatment, as demonstrated in long-term trials (lasting up to 4.5 years) and in a real-world setting. Additionally, alogliptin has a generally favorable or similar safety profile in comparison to other antidiabetic agents (metformin, thiazolidinediones, sulfonylureas, glucagon-like peptide-1 receptor agonists, sodium-glucose cotransporter 2 inhibitors, α-glucosidase inhibitors, and insulin). However, further evaluation would be required to determine the mechanism and effect of alogliptin on heart failure, bullous pemphigoid, and inflammatory bowel disease. Of note, due to the ethnic diversity in the epidemiology of T2DM, alogliptin has been shown to be more efficacious in Asian patients than in non-Asian patients with T2DM, but with a similar tolerability profile. These data indicate that DPP-4is, including alogliptin, are important treatment options, especially for Asian patients with T2DM, for whom they have potential as a first-line therapy. This benefit-risk assessment aims to place alogliptin within the current armamentarium of T2DM and aid physicians when choosing optimal diabetes treatment for their patients.

1 Introduction

Alogliptin is an oral, dipeptidyl peptidase-4 inhibitor (DPP-4i), which has been extensively studied in phase II/III studies in patients with type 2 diabetes mellitus (T2DM) [1–19]. In clinical [1–22] and real-world settings [23–25], alogliptin has been generally well-tolerated and has demonstrated a reduction in hemoglobin A1c (HbA1c) when administered alone or as add-on/combination therapy with other antidiabetic agents [1–22, 24, 25].

Alogliptin was first approved to treat T2DM in 2010 in Japan, and subsequently in the USA and EU in 2013 [26–28]. The recommended dose of alogliptin as monotherapy is 25 mg in the USA and Japan; it is not approved as monotherapy but as a 25-mg add-on therapy in the EU [26–28]. Fixed-dose combinations (FDCs) of alogliptin + metformin and alogliptin + pioglitazone are also approved in Japan, the USA, and the EU [29–34]. The alogliptin + metformin FDC treatment is available as twice-daily (BID) 12.5 mg alogliptin with 500- or 1000-mg metformin tablets (USA), as BID 12.5 mg alogliptin with 850- or 1000-mg metformin tablets (EU), and as once-daily 25 mg alogliptin with 500 mg metformin (Japan) [29, 30, 32]. Alogliptin + pioglitazone FDC therapy is available as 12.5 or 25 mg alogliptin with 15-, 30-, or 45-mg pioglitazone doses [31, 33, 34].

Alogliptin is primarily excreted unchanged via renal clearance [35]. As such, reports suggest that exposure to alogliptin increases with decreasing glomerular filtration rate (GFR) [36, 37]. Thus, to maintain similar systemic

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Key Points

Alogliptin is an efficacious, oral, dipeptidyl peptidase-4 inhibitor (DPP-4i) for the treatment of type 2 diabetes mellitus (T2DM), which may be used alone or as add-on/combination therapy.

Alogliptin is generally safe, with a low risk of hypoglycemia, weight gain, acute pancreatitis, and gastrointestinal adverse events; however, caution is required when treating patients with renal and/or hepatic impairment.

Alogliptin and other DPP-4is are prominent treatment options, especially in Asia, as they have demonstrated higher efficacy in Asian compared with non-Asian T2DM patients, without compromising safety.

exposure, dose adjustments for alogliptin are not required for patients with mild renal impairment (creatinine clearance [CrCl] ≥ 60 to < 90 mL/min [US definition] or ≥ 50 to ≤ 80 mL/min [EU definition]). However, in patients with moderate renal impairment (CrCl ≥ 30 to < 60 mL/min [US] or ≥ 30 to ≤ 50 mL/min [EU]) [27, 28], the recommended daily dose is 12.5 mg, and in patients with severe chronic kidney disease (CKD) (CrCl ≥ 15 to < 30 mL/min) [27] or end-stage renal disease (ESRD) (CrCl < 15 mL/min), it is 6.25 mg. In patients with CKD receiving hemodialysis (HD-CKD), a 3-h dialysis session removed roughly 7% of alogliptin; hence, alogliptin can be administered regardless of the timing of the session [27].

Although metformin monotherapy is the preferred first-line treatment for patients with T2DM in the USA and Europe (based on its efficacy, favorable tolerability profile, low cost, and weight neutrality) [38–40], alternative options are required for patients with metformin contraindications, intolerance, or those who cannot achieve glycemic control with metformin alone (Table 1) [38, 39, 41]. In fact, in Asia, metformin is not always the recommended first-line treatment, because of the different pathophysiology of (i.e., β-cell dysfunction with less adiposity and greater insulin sensitivity), and genetic susceptibility for, T2DM in Asian patients compared with Western patients [42–44]. In Japan, despite higher drug acquisition costs compared with metformin, DPP-4is are an option for first-line use [45] (a setting in which they are already the most widely prescribed antidiabetic drug class [46]), unlike in the USA and Europe, where they are recommended as add-on medications [38, 39, 47]. In this regard, DPP-4is have demonstrated greater glucose-lowering efficacy in Asian versus non-Asian patients with T2DM [48]. Notably, the Japanese Diabetes Society recommends antidiabetic agents on a patient-centric basis [45]. There are eight DPP-4is approved worldwide for T2DM: alogliptin, sitagliptin, vildagliptin, linagliptin, teneligliptin, anagliptin, saxagliptin, and gemigliptin [49]. The long-acting agents omarigliptin and trelagliptin are only approved in Japan, while evogliptin and gemigliptin are approved in some countries, not including the USA and EU [49]. The

Table 1 Summary of recommended antidiabetic agents for the treatment of type 2 diabetes mellitus [38, 39, 41]

Treatment (route of administration)	Primary physiological action(s)	Hypoglycemia risk	Weight gain	Most frequent side effects	Cost
Metformin (oral)	↓ Hepatic glucose production	Low	Neutral/Loss	Gastrointestinal	Low
TZD (oral)	↑ Insulin sensitivity	Low	Gain	Weight gain	Low
SU (oral)	↑ Insulin secretion	Moderate	Gain	Hypoglycemia	Low
DPP-4i (oral)	↑ Glucose-dependent insulin secretion ↓ Glucose-dependent glucagon secretion	Low	Neutral	Rare	High
GLP-1 receptor agonist (injection)	↑ Glucose-dependent insulin secretion ↓ Glucose-dependent glucagon secretion	Low	Loss	Gastrointestinal	High
SGLT2i (oral)	Blocks glucose reabsorption by kidneys, increasing glucosuria	Low	Loss	Genitourinary infections	High
α-GI (oral)	Slows intestinal carbohydrate digestion/absorption	Low	Neutral	Modest HbA1c efficacy, gastrointestinal	Moderate
Insulin (injection)	↑ Glucose disposal ↓ Hepatic glucose production	High	Gain	Hypoglycemia, weight gain	Variable[a]

α-GI α-glucosidase inhibitor, *DPP-4i* dipeptidyl peptidase-4 inhibitor, *GLP-1* glucagon-like peptide-1, *HbA1c* hemoglobin A1c, *SGLT2i* sodium-glucose cotransporter 2 inhibitor, *SU* sulfonylurea, *TZD* thiazolidinedione, ↑ increased, ↓ decreased

[a]Cost is dependent on type/brand (analogs > human insulins) and dosage

FDC of alogliptin + metformin has been available in Japan since 2016 [33].

This review will focus on alogliptin. We aim to evaluate the benefits and risks associated with alogliptin and to put alogliptin treatment into perspective within the armamentarium of current therapies for patients with T2DM. Key studies for alogliptin were identified by searching PubMed using the terms 'alogliptin' and 'diabetes' (search date: 21 March 2019). The publications identified in the search were reviewed manually for their relevance for inclusion in this article.

2 Benefit Evaluation

T2DM is a chronic progressive metabolic disorder associated with, but not limited to, micro- and macrovascular complications and hepatic and renal impairment [50, 51]. The following section evaluates the benefit of alogliptin monotherapy and add-on/combination therapy based on clinical and real-world studies and studies assessing the health economic impact of treating diabetes.

2.1 Epidemiology and Natural History of T2DM

In 2016, an estimated 1.6 million deaths were attributable to diabetes [52]. The development of T2DM is associated with non-modifiable and/or modifiable risk factors [53, 54]. Key non-modifiable risk factors include genetic factors, metabolic disturbances, ethnicity, and older age, while modifiable factors include obesity, a sedentary lifestyle, an unhealthy diet, and smoking [53, 54]. Despite modifiable risk factors, the global prevalence of T2DM is expected to rise to 629 million by 2045 compared with an estimated 425 million in 2017. In Asia, T2DM is an increasing epidemic. Studies have demonstrated ethnic differences in the epidemiology and natural history of T2DM [42, 55]. For example, although Asians with diabetes generally have a lower body mass index (BMI) [55], they have higher insulin sensitivity and lower insulin response compared with non-Asians [42]. Analyses also suggest that decreased insulin secretion is a common cause of T2DM [42, 55] in Asians and, moreover, diabetes occurs at a much lower mean BMI than in non-Asians [55]. Consequently, the choice of and response to treatment will differ between ethnicities; for example, insulin secretagogues, such as sulfonylureas (SUs), are more commonly prescribed in Asians than non-Asians [55].

2.2 Purpose and Outcome of Treatment

The aim of treatment is to help patients achieve glycemic control, a quality of life (QoL) similar to those without diabetes, and to minimize the risk of long-term complications [56]. Another objective of T2DM treatment is to reduce burden on the economy [56]. Optimal management of T2DM is complex [56]. Poorly controlled diabetes can lead to complications and negatively impact patient outcomes and QoL [50, 51]. Guidelines recommend diet and lifestyle changes, followed by administration of one or more oral antidiabetic agents or injectable treatment [57] if glycemic control is inadequate [56]. Several factors related to antidiabetes medication should be considered when making treatment decisions, including glycemic control (HbA1c levels), pleiotropic effects (e.g., blood pressure), patient preferences, existing comorbidities, adverse-effect profile, risk of hypoglycemia, and necessity for weight loss [38, 58].

2.3 Mechanism of Action, Pharmacokinetic, and Pharmacodynamic Profile

Alogliptin, a highly potent and selective, noncovalent inhibitor of DPP-4, was developed using Structure-based Drug Design System technology [59]. Notably, alogliptin is > 10,000-fold more selective for DPP-4 than DPP-2, -8, and -9 [59, 60]; this is particularly important as DPP-8 and -9 have been associated with the activation of pro-inflammatory caspase-1, which is, in turn, involved in pyroptosis [61]. By inhibiting DPP-4 activity, alogliptin slows the inactivation of incretin hormones, glucagon-like peptide-1 (GLP-1), and glucose-dependent insulinotropic polypeptide (GIP); GLP-1 and GIP increase insulin secretion and inhibit glucagon secretion when glucose levels are high [26, 27]. Thus, alogliptin improves glycemic control via a glucose-dependent mechanism [26, 27].

Alogliptin is rapidly absorbed and evenly distributed in the tissues [27, 35]. DPP-4i efficacy requires steady-state trough DPP-4 activity inhibition of approximately 80% [62], and alogliptin has been shown to suppress this by up to 99% after 14 days of once-daily administration at therapeutic doses [35]. The absolute bioavailability of alogliptin is high (100%) [27], is not significantly affected by food [63], and has not been associated with any clinically significant interactions with common antidiabetic drugs, such as metformin [63], pioglitazone [64] (a thiazolidinedione [TZD]), and glyburide (an SU) [64]. Alogliptin does not undergo extensive metabolism, and cytochrome P450 (CYP)-related metabolism is negligible; thus, no dose adjustments are required with concomitant use of CYP substrates or inhibitors [27]. Further, no clinically relevant interactions have been observed between alogliptin and p-glycoprotein inhibitors or substrates [26, 27]. For a comparison of the clinical pharmacology (pharmacokinetic and pharmacodynamic properties) of alogliptin with other DPP-4is, please refer to a recent review by Chen et al. (2015) [65].

2.4 Evidence of Benefit

2.4.1 Clinical Trials

Alogliptin has demonstrated improvements in glycemic control, as indicated by changes in HbA1c in treatment-naïve and previously treated patients in global and Asian phase II/III placebo-controlled and active-controlled studies, as (1) monotherapy [1, 12]; (2) dual therapy (add-on/combination) with metformin, SUs, TZDs, α-glucosidase inhibitors (α-GIs), and insulin [2–5, 13–19, 66–70]; and (3) triple (add-on) therapy to insulin with or without metformin, and add-on to metformin with a TZD (Online Resource, Table S1, see the electronic supplementary material [ESM]) [6–10, 15]. Below, we evaluate the effect of alogliptin on glycemic control (change in HbA1c) compared with placebo, focusing on data from phase III studies that have a primary efficacy endpoint of change in HbA1c from baseline to at least week 12, with most evaluating at week 26.

Alogliptin monotherapy (12.5 mg and 25 mg) resulted in significant glycemic control compared with placebo at week 26 in treatment-naïve patients with [1] uncontrolled T2DM on diet and exercise therapy alone (Online Resource, Table S1; both alogliptin doses $p < 0.001$). In the same study, 44% of patients achieved HbA1c levels ≤ 7.0% (guideline recommended target) [38, 39, 45] and a significant reduction in fasting plasma glucose at 26 weeks in the alogliptin group compared with placebo (both alogliptin doses; $p < 0.001$). Five other phase III, placebo-controlled, 26-week studies in patients with T2DM examined the effect of alogliptin dual therapy (with metformin or an SU) [13, 14] or triple therapy (with pioglitazone ± metformin or an SU, or with insulin ± metformin) [6, 7, 9] on glycemic control. In all five studies, 12.5-mg and 25-mg alogliptin doses as add-on treatment demonstrated significant reductions in HbA1c compared with placebo (Online Resource, Table S1; $p < 0.001$).

The results of a meta-analysis of phase II/III and III studies revealed significantly greater reductions in HbA1c in Asian patients compared with non-Asian patients who received alogliptin ($p = 0.02$), with similar safety ($p = 0.71$) [71]. These data are further supported by studies investigating alogliptin monotherapy [12], dual therapy (to metformin, pioglitazone, α-GI, or insulin) [3–5, 16, 19], and triple therapy (to pioglitazone ± metformin) in Asia [10], all of which reported a significant reduction in HbA1c levels with alogliptin versus placebo (Online Resource, Table S1; $p < 0.001$).

2.4.2 Real-World Evidence

The efficacy of alogliptin has also been demonstrated in a real-world setting, primarily in Japan, via retrospective and observational studies. Results from the ATTAK-J study conducted in Japanese patients with T2DM revealed a 0.54% ± 1.22% reduction in HbA1c following 1 year of treatment with alogliptin [25]. In the same study, a significantly higher proportion of patients achieved HbA1c levels < 7.0% after 3 months of alogliptin treatment compared with baseline ($p < 0.001$) [25]. Further analysis revealed that increased adherence to diet therapy led to a further reduction in HbA1c at 12 months, despite the removal of SU treatment [25]. In support of these data, a significant reduction in HbA1c (vs. baseline; $p = 0.0005$) was found in a subgroup of patients from a long-term, 3.5-year retrospective study of Japanese patients with T2DM receiving alogliptin and SU who either did not change their antidiabetic drugs or did not reduce the dose or strength of their SU, thus demonstrating the effective long-term durability of alogliptin [24].

Prescription patterns of T2DM treatments are changing as more patients are prescribed newer second-line oral treatments, such as DPP-4is, sodium-glucose cotransporter 2 inhibitors (SGLT2is), and α-GIs [47, 72–76]. A large-scale ($n = 20{,}000$), 3-year, prospective, observational, real-world study (Japan-Based clinical ReseArch Network for Diabetes Registry [J-BRAND Registry]), designed to examine the safety and efficacy of alogliptin compared with non-DPP-4i oral hypoglycemic agents in Japanese patients with T2DM, is ongoing [23]. The J-BRAND Registry study will help determine the long-term appropriate use of alogliptin when used alone or in combination with other antidiabetic agents.

2.4.3 Tolerability

Data from long-term studies that have evaluated the safety/tolerability of alogliptin will now be discussed. Treatment-emergent adverse events (TEAEs) and adverse events of special interest (AESIs) will be examined in detail in Sect. 3.

Overall, alogliptin is well-tolerated, as demonstrated in long-term studies (≥ 52 weeks), both in a clinical trial and in real-world settings [17, 77]. When compared with glipizide (an SU) or standard of care (SoC) [17, 77], there were no differences observed in the incidence of adverse events (AEs) between alogliptin- and comparator-treated patients [17, 77]; most AEs were mild in severity [17, 77]. A 1-year retrospective analysis (ATTAK-J) also revealed low rates of AEs [25] in patients with T2DM receiving alogliptin (2.5%; $n = 314$).

These findings are further supported by a meta-analysis examining the efficacy and safety of alogliptin as monotherapy or combination therapy [78, 79]. Here, the number of patients who discontinued due to AEs was not significantly different in patients treated with alogliptin versus placebo or other antidiabetic control treatments (odds ratio [OR] 0.83; 95% confidence interval [CI] 0.61–1.58 for alogliptin 12.5 mg; OR 0.98; 95% CI 0.44–1.58 for alogliptin 25 mg) [78]. Additionally, a systematic review and meta-analysis examining DPP-4i safety reported that treatment

was generally well-tolerated [80]. The study highlighted the need for future studies evaluating the effects of DPP-4is on heart failure (HF) and acute pancreatitis [80], as discussed in Sect. 3.

2.4.4 Convenience and Preference

In chronic conditions, such as T2DM, adherence to treatment is often poor, with an average of approximately 50% in developed countries [81]. Decreased adherence leads to poor clinical outcomes and QoL, and negatively impacts healthcare costs [57]. To improve treatment adherence, guidelines recommend considering patient preferences when determining optimal T2DM management [38, 45].

One initiative to improve adherence is to understand patient preferences for an antidiabetic treatment [38, 39, 45]. In a recent US survey conducted in patients with diabetes (type 1 or 2), the most influential attributes to patient preference were treatment regimen (e.g., mode and frequency of administration), risk of diarrhea, weight change, risk of hypoglycemia, and treatment efficacy [82]. In the same survey, patients demonstrated a preference for DPP-4is over GLP-1 receptor agonists, SGLT2is, SUs, and TZDs due to their favorable regimen and risk profile [82]. For example, similar to DPP-4is, GLP-1 receptor agonists also target the incretin system [38, 39, 83]; however, GLP-1 receptor agonists are injectable, while DPP-4is have oral formulations [83]. In a US- and European-based survey, patients significantly preferred, and were significantly more likely to prefer, a DPP-4i oral formulation to a GLP-1 injectable formulation (both $p < 0.001$) [83]. Additionally, the frequency of administration is an important regimen-related factor that has been linked to both adherence and patient QoL [84]. For instance, a once-daily regimen of DPP-4i significantly improved Diabetes Therapy-Related Quality of Life 17 questionnaire scores from baseline to week 12 when compared with the thrice-daily regimen of an α-GI, voglibose ($p = 0.034$) [84]. Furthermore, FDC regimens, similar to alogliptin/metformin and alogliptin/pioglitazone formulations, have been shown to improve adherence compared with two-pill regimens [85]. FDCs could therefore benefit the patient, result in cost-savings to the healthcare system, and save manufacturing and distribution costs [85].

2.4.5 Health Economic Impact

T2DM is associated with significant healthcare costs, placing a considerable burden on the economy [86]. According to the International Diabetes Federation, the global healthcare costs of diabetes treatment and related complications in 2017 were estimated to be US$850 billion in patients aged 18–99 years; this expenditure is expected to reach US$958 billion by 2045 [86]. Interventions to prevent or control diabetes, as recommended by guidelines such as those of the American Diabetes Association (e.g., intensive glycemic control and lifestyle changes) [38], have proven to be cost-effective [87].

An analysis of 29 randomized controlled trials (RCTs) by Pedrazzoli et al. suggested that alogliptin as a monotherapy and add-on/combination therapy was more cost-effective than other DPP-4is, such as sitagliptin, saxagliptin, and linagliptin [88]. The total savings with alogliptin in Europe, particularly in combination with metformin, were up to €158 per patient-year [PY] based on a higher proportion of patients achieving a target HbA1c of < 7%, reduced need for alogliptin treatment escalation, better lipid profile, proven cardiovascular (CV) safety, lower hypoglycemia incidence, and increased adherence to treatment [88]. Notably, alogliptin is available as FDCs; thus, pill burden and pharmacy dispensing fees may allow for adherence improvement and further cost savings, respectively [89]. Studies have reported that alogliptin in combination with metformin is an alternative, cost-effective treatment compared with SUs in patients with T2DM [90, 91]. In a UK study, long-term alogliptin + metformin combination treatment achieved greater estimated lifetime quality-adjusted life-year (QALY) gains compared with SU + metformin; the associated incremental cost-effectiveness ratios (ICERs) were £10,959/QALY (12.5 mg alogliptin) and £7217/QALY (25 mg alogliptin) [90]. Results from a US study showed that DPP-4i + metformin therapy had an ICER of US$19,420 per life-year gained compared with SU + metformin [91]; incremental costs and life-years gained were US$11,849 and 0.61 years, respectively [91]. Similarly, in a pharmacoeconomic analysis of DPP-4is (sitagliptin, vildagliptin, and alogliptin) in Japan, 25 mg alogliptin was the second most cost-effective treatment (ICER of ¥102,062 per patient) after 100 mg vildagliptin [92]. Further studies comparing the cost-effectiveness of alogliptin in combination with other treatments available for T2DM are required, as are health economic analyses of alogliptin versus other antidiabetic therapies (e.g., metformin) in first-line use (especially in Asian patients).

2.4.6 Alternative Therapies

Below we compare (head-to-head, direct comparisons) alogliptin with other antidiabetic treatments recommended for patients with T2DM.

Phase III international studies and studies in Asian patients have compared the efficacy (change in HbA1c) of alogliptin as dual and triple therapy (in combination with metformin, pioglitazone, an SU, or metformin + pioglitazone) with component monotherapies or an active comparator (Online Resource, Table S1, see the ESM) [5, 9, 15, 17, 18]. In each study, alogliptin in combination was significantly more efficacious in decreasing HbA1c levels versus

placebo or component monotherapy (p values from <0.05 to <0.0001; Online Resource, Table S1) [5, 9, 15, 17, 18]. However, when used as monotherapies, alogliptin and metformin yielded similar results to each other after 26 weeks of treatment [5, 18].

Alogliptin as add-on therapy with metformin has demonstrated sustained efficacy in a phase III, international, multicenter, 2-year study in patients with inadequate glycemic control who received metformin in combination with either alogliptin or an SU (Online Resource, Table S1) [17]. Patients receiving alogliptin (12.5 mg and 25 mg) demonstrated significantly superior HbA1c control and were more likely to achieve an HbA1c target of $\leq 7.0\%$ compared with the SU, glipizide (both $p<0.001$; Online Resource, Table S1) [17]. In the same study, a significantly higher proportion of patients receiving alogliptin 12.5 mg or 25 mg achieved HbA1c $\leq 7.0\%$ without hypoglycemia or weight gain compared with glipizide (glipizide 10.7% vs. alogliptin 12.5 mg 24.2% and alogliptin 25 mg 26.9%; $p<0.001$ for both comparisons) [17]. These data support alogliptin as a long-term efficacious and viable treatment option for patients with T2DM.

3 Risk Evaluation

Safety evaluations and primarily adverse reaction profiles are some of the major considerations physicians face when making treatment decisions for patients with T2DM [58]. The following section will focus on TEAEs and AESIs based on standardized Medical Dictionary for Regulatory Activities (MedDRA) queries for alogliptin monotherapy and as add-on/combination therapy compared directly with placebo or active comparators.

Alogliptin was generally well-tolerated in clinical studies of up to 4.5 years in duration [2, 17, 93, 94]; mean exposure to alogliptin was 40 weeks in patients treated for >1 year [27]. The overall TEAE incidence rates were similar between alogliptin and placebo or the active comparator (286.1 vs. 283.3 events per 100 PYs, respectively; Fig. 1 [93]) in the 2016 pooled safety analysis of 20 double-blind RCTs by Munsaka et al., which included 16,933 patients with T2DM (alogliptin [monotherapy and combination or add-on therapy] $n=10{,}403$; comparator [placebo or active-control] $n=6530$; Fig. 1 [93]). In another pooled analysis of controlled phase II/III studies, the most commonly reported TEAEs occurring in $>3\%$ of patients receiving alogliptin 25 mg, which were numerically more frequent versus placebo, were nasopharyngitis, upper respiratory tract infection, headache, diarrhea, and urinary tract infection; nasopharyngitis was the only TEAE that occurred more frequently in patients receiving alogliptin 25 mg versus an active comparator (Table 2) [36]. TEAEs were primarily described as mild or moderate in severity in both pooled analyses [36, 93], with few severe TEAEs [36]. There were no severe TEAEs that occurred in $>1.0\%$ of patients in any group in the pooled analysis of controlled phase II/III studies [36]. The proportion of patients experiencing at least one serious adverse event (SAE) was also low and similar between treatment groups (from 3.2% in the placebo to 5.2% in the active comparator group) [36]. Cardiac disorders were the most commonly reported SAE, which were comparable between patients treated with alogliptin 25 mg (1.0%) and active comparators (1.2%), yet greater than in patients treated with placebo (0.4%) [36]. Most deaths were considered unrelated to the study drug; however, in one open-label alogliptin extension study, ten deaths (0.003%) were considered to have a possible relationship to the study drug [36, 94]. In a pooled analysis of 23 phase II–IV RCTs, the proportion of patients who discontinued because of a TEAE was lower in the alogliptin groups (6.1%) than the placebo group (7.1%), but similar to the active comparator group (6.1%) [95]. Data from a meta-analysis comparing Asian and non-Asian studies demonstrated no difference in the number of any AEs (11 studies; $p=0.71$) or SAEs (15 studies; $p=0.08$), as well as the number of hypoglycemic events (12 studies; $p=0.58$) and weight gain (eight studies; $p=0.47$) [71].

Based primarily on the pooled safety analysis by Munsaka et al., this section will focus on the following AEs and AESIs: hypoglycemia, weight gain, CV events, acute pancreatitis, skin-related AEs, gastrointestinal events, renal failure, and hepatotoxicity [93]. There is limited evidence to suggest safety differences between the drugs in the gliptin class [96]. Therefore, where data are available, we have compared (head-to-head, direct comparisons) the safety of alogliptin with placebo and alternative antidiabetic treatments for T2DM (Table 1). Although not considered here, there is some evidence for an increase in non-serious infections, especially low-grade upper respiratory tract infections, in patients treated with DPP-4is (including alogliptin) compared with users of other antidiabetic drugs during post-marketing evaluation [97].

3.1 Hypoglycemia

Hypoglycemia is a common and important complication of diabetes therapy, and is associated with diminished QoL, aggravated clinical outcomes, and, in severe cases, seizures, coma, and death [98]. It can also result in treatment discontinuations and increased healthcare costs [99]. Special populations, including older patients (aged ≥ 65 years), have a higher risk of developing hypoglycemia [11, 100]. Older patients, including those who are healthy, are at increased risk of developing hypoglycemia [100], and may require more careful HbA1c and body weight targets than their younger counterparts, as suggested by guidelines [38].

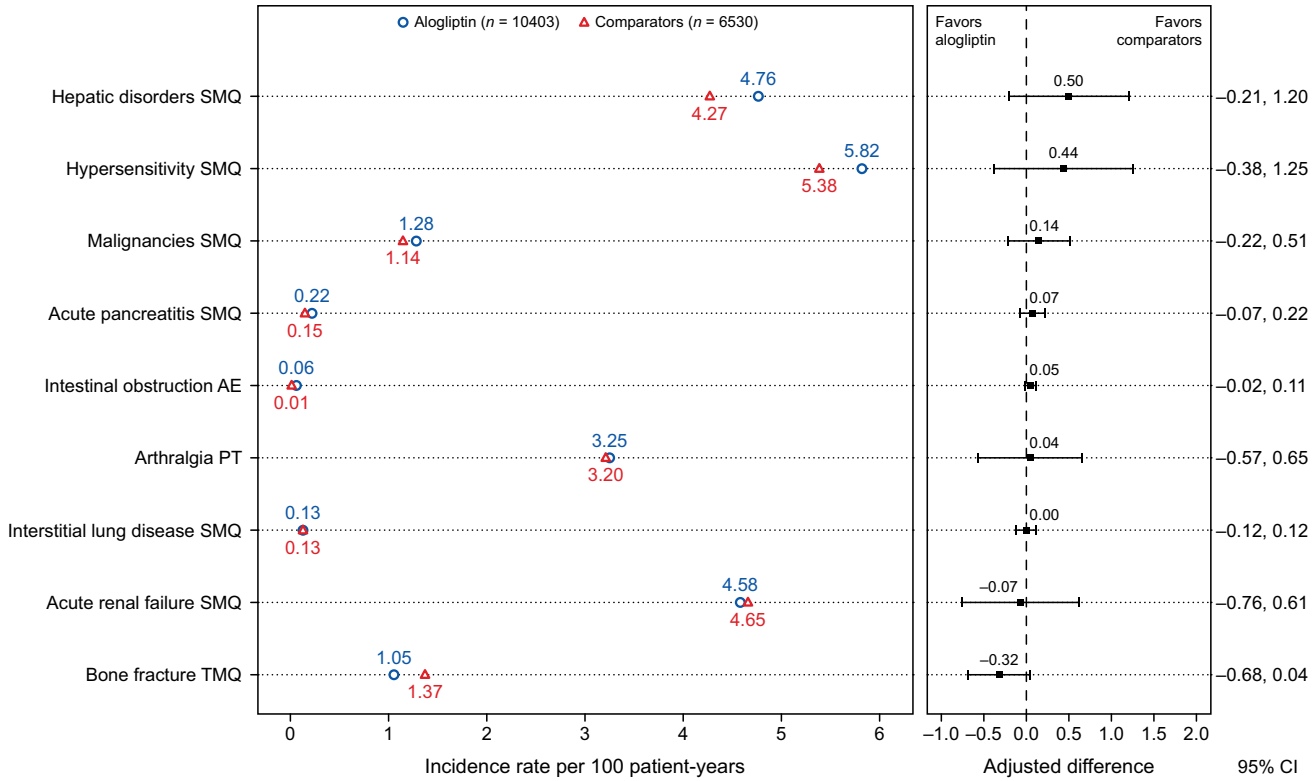

Fig. 1 Adverse events of special interest in a pooled analysis of 20 double-blind randomized controlled clinical studies [93]. *CI* confidence interval, *PT* preferred term, *SMQ* standardized Medical Dictionary for Regulatory Activities (MedDRA) queries, *TMQ* sponsor defined custom MedDRA query. Reprinted with permission from the Springer Nature Customer Service Centre GmbH: Springer Nature, Diabetologia [93], © Springer-Verlag Berlin Heidelberg 2016 (2016). Please note that this figure is NOT republished under the CC BY-NC license

Generally, in patients with T2DM, hypoglycemic events were infrequent or comparable to placebo and mild in severity in phase II/III studies of alogliptin monotherapy and add-on/combination therapy with metformin, SUs, metformin + SU, insulin, metformin + insulin, pioglitazone, pioglitazone + metformin, pioglitazone + metformin + SU, and an α-GI [1, 3, 7, 8, 12–14, 16, 17, 21, 67, 69, 70, 101]. Furthermore, incidences of any hypoglycemic event occurred in ≤ 8.3% of at-risk, older patients receiving alogliptin (12.5 and 25 mg as monotherapy or add-on/combination therapy) versus ≤ 10.5% in patients treated with placebo in a pooled analysis of phase II/III studies [11]. In the same analysis of older patients, the highest incidences of hypoglycemic severity occurred in the placebo group (10.5%) [11].

As depicted in Table 1, SU therapy has a higher risk of hypoglycemia compared with DPP-4is. While DPP-4is as an add-on therapy to SU treatment have been shown to increase the risk of hypoglycemia [102], this was contradicted in an international phase III study reported by Pratley et al., which demonstrated that 12.5 and 25 mg alogliptin as add-on therapy to SU treatment did not increase the incidence of hypoglycemia [14]. Additionally, the frequency of hypoglycemic events was substantially lower in alogliptin + metformin-treated patients (2.5% and 1.4% for alogliptin 12.5-mg and 25-mg groups, respectively) versus SU + metformin-treated patients (23.2%) in a 2-year study (Del Prato et al., 2014; Online Resource, Table S1, see the ESM), with the majority of the first hypoglycemia events occurring within the first 20 weeks of SU treatment [17]. In the same study, severe hypoglycemia was reported in five patients receiving an SU compared with one patient in the alogliptin 12.5-mg group and none in the 25-mg group [17]. Notably, in older patients, alogliptin 25-mg monotherapy had a substantially lower risk of hypoglycemia compared with SU monotherapy (Rosenstock et al., 2013; Online Resource, Table S1) [101].

Metformin and alogliptin are considered unlikely to cause serious hypoglycemia (Table 1) [39, 103]. This is supported by an international phase III study [18] and a Japanese phase II/III study [70] (Pratley et al., 2014, and Seino et al., 2012b; Online Resource, Table S1), where patients receiving alogliptin and metformin monotherapies had a similar incidence of hypoglycemia. Yet, in another Asian study (Ji

Table 2 Most common adverse events in a pooled analysis of randomized controlled phase II and III studies with alogliptin [95]

Adverse event	Placebo ($n=4349$)	Active comparator ($n=2496$)	Alogliptin 12.5 mg ($n=2944$)	Alogliptin 25 mg ($n=8068$)	Alogliptin total ($n=11,299$)[a]
Any TEAE, *n* (%)	3001 (69.0)	1716 (68.8)	1944 (66.0)	5486 (68.0)	7586 (67.1)
Nasopharyngitis	217 (5.0)	125 (5.0)	216 (7.3)	461 (5.7)	691 (6.1)
Hypertension	233 (5.4)	122 (4.9)	108 (3.7)	375 (4.6)	484 (4.3)
URTI	143 (3.3)	124 (5.0)	140 (4.8)	318 (3.9)	461 (4.1)
Headache	112 (2.6)	124 (5.0)	121 (4.1)	295 (3.7)	426 (3.8)
Diarrhea	144 (3.3)	141 (5.6)	110 (3.7)	302 (3.7)	415 (3.7)
UTI	138 (3.2)	109 (4.4)	116 (3.9)	277 (3.4)	402 (3.6)
Back pain	109 (2.5)	102 (4.1)	107 (3.6)	246 (3.0)	359 (3.2)
Arthralgia	84 (1.9)	85 (3.4)	85 (2.9)	199 (2.5)	287 (2.5)
Influenza	74 (1.7)	99 (4.0)	74 (2.5)	186 (2.3)	261 (2.3)
Dizziness	93 (2.1)	78 (3.1)	74 (2.5)	179 (2.2)	259 (2.3)
Renal impairment	177 (4.1)	6 (0.2)	7 (0.2)	220 (2.7)	227 (2.0)
Angina pectoris	197 (4.5)	10 (0.4)	10 (0.3)	214 (2.7)	225 (2.0)
Dyslipidemia	63 (1.4)	96 (3.8)	42 (1.4)	158 (2.0)	200 (1.8)
Hyperglycemia	136 (3.1)	43 (1.7)	11 (0.4)	145 (1.8)	156 (1.4)
Angina unstable	140 (3.2)	7 (0.3)	3 (0.1)	121 (1.5)	124 (1.1)
Hypoglycemia	164 (3.8)	100 (4.0)	22 (0.7)	192 (2.4)	215 (1.9)

Table shows TEAEs occurring in ≥ 3% of patients in any group. Table is ordered in descending frequency of TEAEs in the alogliptin total group

TEAE treatment-emergent adverse event, *URTI* upper respiratory tract infection, *UTI* urinary tract infection

[a]Also includes patients who received 6.25-, 50-, and 100-mg alogliptin doses

et al., 2017; Online Resource, Table S1), more patients in the metformin group (500 mg BID) experienced a hypoglycemic event (6.2%) compared with the alogliptin group (12.5 mg BID; 1.2%) [5]; further studies may be required to compare the risks of hypoglycemia in the Asian population.

Compared with SoC, alogliptin significantly lowered HbA1c levels without increasing hypoglycemia (0.3% vs. SoC 0.1%; $p=0.004$) after 104 weeks of treatment in the Study of Preventive Effects of Alogliptin on Diabetic Atherosclerosis (SPEAD-A), a 104-week multicenter, open-label, blinded endpoint, parallel study comparing alogliptin with SoC in Japanese patients with T2DM [77].

In summary, although alogliptin monotherapy is unlikely to cause serious hypoglycemia, treating physicians should remain vigilant if DPP-4is, such as alogliptin, are used as add-on treatments to SUs and insulin therapies, which have a moderate-to-high risk of hypoglycemia (Table 1) [102].

3.2 Weight Gain

Approximately 58–90% of patients with T2DM are overweight or obese [104]; hence, lifestyle changes to prevent weight gain are important for glycemic control and CV health [38, 56]. Phase II/III studies have demonstrated that alogliptin monotherapy and add-on/combination therapy decreased HbA1c levels with minimal changes in weight gain versus placebo [2, 7, 12, 14, 17, 21, 70]. However, it should be noted that DPP-4is may have lower efficacy in obese patients because DPP-4 induces insulin resistance in adipocytes that are found in the circulation of overweight and obese patients [105]. These findings are also supported by a retrospective study that demonstrated that the efficacy of DPP-4i monotherapy was significantly decreased in diets high in saturated fatty acids (multiple regression analysis; $p<0.01$) [106], highlighting the importance of diet therapy and avoiding weight gain [38, 39, 45, 106].

Weight gain is a major side effect with TZDs, SUs, and insulin therapies [38, 107], as summarized in Table 1. So far, there have only been three comparison studies between TZDs or SUs and alogliptin treatment. Data from an international phase III study (DeFronzo et al., 2012; Online Resource, Table S1, see the ESM) showed decrease in body weight was modest but significantly lower in patients receiving alogliptin (− 0.02 and − 0.7 kg for alogliptin 12.5 and 25 mg, respectively) versus the pooled pioglitazone group (+1.5 kg pooled 15, 30, and 45 mg pioglitazone) [9]. Similarly, in a 2-year study (Del Prato et al. 2014; Online Resource, Table S1), weight gain was significantly greater in patients treated with SU + metformin compared with alogliptin (12.5 or 25 mg) + metformin (both doses $p<0.001$) [17]. Of note, treatment with 25 mg alogliptin in older patients resulted in a modest but significant decrease in body weight

compared with SU therapy after 1 year of treatment (− 0.62 vs. 0.60 kg; $p < 0.001$) [101].

For alternative therapies, such as metformin, the risk of weight gain is neutral/less compared with neutral for DPP-4is (Table 1). This is supported by a phase III study (Pratley et al., 2014; Online Resource, Table S1), where metformin monotherapy led to the greatest weight reduction (− 0.80 and − 1.25 kg with metformin 500 and 1000 mg BID, respectively), while alogliptin monotherapy was weight neutral (− 0.01 kg with alogliptin 12.5 mg BID) [18]. Compared with SoC, the mean change in BMI was significantly lower in alogliptin-treated patients (0.3 ± 1.9 kg/m^2 vs. 20.3 ± 1.7 kg/m^2 in the SoC group; $p = 0.003$) [77].

Hence, as TZDs, SUs, and insulin are associated with weight gain [39], it is recommended that treating physicians remain vigilant with respect to weight gain, particularly in patients receiving add-on therapy to alogliptin or combination therapy.

3.3 CV Events

T2DM is strongly associated with micro- and macrovascular complications, with almost 50% of patients developing HF [50, 108]. In 2008, the US Food and Drug Administration (FDA) issued specific guidance for assessing the CV safety, pre- and post-approval, of new antidiabetic agents [2]. Subsequently, in 2018, the American Diabetes Association released an update of the "Standards of Medical Care in Diabetes" document, including, for the first time, new recommendations for patients with T2DM and heart disease around choosing medications proven to improve heart health [109]. These recommendations have been carried over to the 2019 update [110], emphasizing the importance of CV health in diabetes management. Currently, these guidelines recommend SGLT2is and GLP-1 receptor agonists [110]; meta-analyses investigating the CV safety of DPP-4is have demonstrated a neutral effect of these agents on major CV endpoints and all-cause death [111].

The pivotal Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) study evaluated the effect of alogliptin in addition to SoC for diabetes (excluding DPP-4is and GLP-1 receptor agonists) on CV-related outcomes in 5380 T2DM patients who had recently experienced acute coronary syndrome. Rates of major adverse CV event (MACE) incidences (CV death, non-fatal myocardial infarction [MI], or non-fatal stroke) were similar between the alogliptin and placebo groups (11.3% and 11.8% of patients, respectively; hazard ratio [HR] 0.96; upper boundary of one-sided repeated CI 1.16; $p < 0.001$ for non-inferiority) [2]. Secondary and post hoc analyses from the EXAMINE study [2, 108, 112–114] further supported these findings, demonstrating no significant differences between alogliptin- and placebo-treated patients in the five-component composite CV endpoint (CV death, stroke, MI, unstable angina, and coronary revascularization; $p = 0.72$) [113], CV hospitalizations ($p = 0.70$) [113], and mortality (HR 0.88; 95% CI 0.71–1.09) [115]. In another subgroup, rates of CV death ($p = 0.01$) and all-cause mortality ($p = 0.033$) were significantly lower in the alogliptin group versus placebo [114] in patients receiving either metformin or an SU as SoC. It should be noted, however, that the composite outcome in a subgroup of high-risk patients with previous history of HF displayed trends of reduced CV death and increased hospital admission for HF in the post hoc analysis by Zannad et al., suggesting that survivor bias cannot be ruled out [108].

Previously, there had been concern with respect to the increased risk of CV complications with concomitant use of DPP-4is and angiotensin-converting enzyme (ACE) inhibitors, a commonly prescribed class of drug for HF. High doses of ACE inhibitors prevent degradation of substance P, and as it is a DPP-4 substrate, it was hypothesized that the combination of both inhibitors could lead to stimulation of substance P, activation of the sympathetic nervous system, and a subsequent increase in the risk of CV complications [22]. An ACE inhibitor was used by 62% of patients in the EXAMINE trial, and a stratified analysis from the EXAMINE study revealed no differences between the alogliptin and placebo groups with respect to composite rates for CV death and HF in patients also receiving ACE inhibitors ($p = 0.57$) [22].

There is ongoing debate whether DPP-4is increase the risk of HF and the underlying mechanisms [116, 117]. A meta-analysis of the effect of DPP-4is on HF risk using controlled trials and observational studies found either a similar risk of HF between DPP-4is and control medications in controlled studies, or a possible increased risk in observational studies [118]; however, the evidence was of low or very low quality, leading the authors to conclude that the effect was uncertain. Post-marketing reports of HF in patients receiving linagliptin, saxagliptin, sitagliptin, and vildagliptin submitted via the FDA AE reporting system (FAERS) suggest that the CV safety of this class requires further monitoring [119, 120], while a Korean population-based cohort study found no increased risk of HF with DPP-4is versus SUs [121]. In contrast, another population-based study from Korea demonstrated a significantly increased risk of hospitalization for HF with DPP-4is versus SUs [122]. Further studies designed to examine the CV effect of alogliptin are ongoing, including the TRACT study, which aims to clarify possible anti-atherogenic effects by means of fractional flow reserve in Japanese patients with T2DM [123]. Nevertheless, warnings about HF risk have been added to the labels of several DPP-4is, including saxagliptin [124], alogliptin [26], and vildagliptin [125]. In contrast, other therapies, particularly GLP-1 receptor agonists (e.g., semaglutide and liraglutide)

and SGLT2is (e.g., canagliflozin and empagliflozin), appear to have protective effects against CV disease [126].

There have been limited comparisons between alternative therapies and alogliptin for CV events, with a few studies each examining SoCs, metformin, SUs, or TZDs with alogliptin [9, 17, 18, 77, 101]. Similar to the pooled analysis described above [93], overall incidences of CV AEs were similar in Japanese patients with T2DM treated with alogliptin or SoC in the SPEAD-A study [77]. Moreover, alogliptin, but not SoC treatment, attenuated the progression of carotid intima-media thickness by week 104 relative to baseline [77]. In a comparison with metformin, the incidences of MACE were low in the alogliptin monotherapy group (one and two events in the alogliptin 25-mg once-daily and alogliptin 12.5-mg BID groups, respectively) in a phase III study (no MACE were reported for the metformin monotherapy group [18]; Pratley et al. 2014, Online Resource, Table S1, see the ESM). There was a trend towards lower confirmed MACE incidences (CV death, non-fatal MI, or non-fatal stroke) in the alogliptin + metformin group (0.7% and 0.9% for alogliptin 12.5 mg and 25 mg, respectively) compared to in the SU + metformin group (1.3%) in a 2-year phase III study [17]. In a separate phase III study (DeFronzo et al., 2012; Online Resource, Table S1), two cases of congestive HF were reported in pioglitazone-treated patients (one possibly related to therapy), while no cases were reported with alogliptin monotherapy and alogliptin add-on to pioglitazone [9]. Consensus statements recommend caution when administering TZDs to patients with New York Heart Association (NYHA) class I–II HF and to avoid use in NYHA class III–IV.

3.4 Bile Duct, Gallbladder, and Pancreatic Safety

In 2013, based on case reports and the results of one observational study, the FDA added warnings about acute pancreatitis to DPP-4i labeling [127, 128]. Since 2013, post-marketing reports have suggested an association between DPP-4is, including alogliptin, and acute pancreatitis [27, 129]. However, results from the EXAMINE study reported comparable incidences of acute pancreatitis between alogliptin- and placebo-treated patients with diabetes and high CV risk (alogliptin $n = 12/2701$ [0.4%]; placebo $n = 8/2679$ [0.3%]); more importantly, no cases were fatal [2]. Furthermore, no cases of pancreatitis were reported in a Japanese study comparing alogliptin + metformin-treated and placebo-treated patients [70].

There have been a few studies comparing the incidence of acute pancreatitis in alogliptin-treated and active comparator-treated patients; these include a pooled study and SU analyses. The incidence of acute pancreatitis in alogliptin-treated patients was low and similar to comparators (placebo and active) in a pooled analysis of 20 RCTs (0.22 vs. comparators 0.15 incidences per 100 PYs; Fig. 1 [93]). In alogliptin versus SU studies, one year-long study demonstrated no incidences of pancreatitis in both monotherapy groups [101]. Additionally, in a 2-year, phase III study (Del Prato et al., 2014; Online Resource, Table S1, see the ESM), pancreatitis occurred in one patient (0.1%) in the alogliptin 25-mg + metformin group and three (0.3%) in the SU + metformin group [17]. Nonetheless, treating physicians are advised to remain vigilant of the association between DPP-4is and acute pancreatitis when making treatment decisions.

Some observational studies and post-marketing reports have described an increase in the risk of pancreatic cancer and cholangiocarcinoma in patients exposed to DPP-4is [130]. However, other studies have failed to demonstrate an association between DPP-4i use and pancreatic cancer [131–133], and one Korean registry study even reported a reduction in the risk of malignancy for DPP-4is compared with metformin (HR 0.57; 95% CI 0.51–0.64) [134]. While further studies are required to determine if there is a genuine class or even drug-specific effect, doctors must be alert to the potential risk of late-onset pancreatic malignancy in T2DM patients receiving DPP-4i treatment. Use of DPP-4is does not appear to increase the risk of bile duct or gallbladder diseases (cholelithiasis, cholecystitis, and cholangitis) compared with the use of at least two oral antidiabetic drugs from other classes [135].

3.5 Skin-Related Adverse Events

Skin-related AEs, including allergic reactions, have been monitored as a result of concerns from preclinical evaluation in monkeys and reports of hypersensitivity reactions with other DPP-4is [36]. In a pooled analysis, alogliptin was associated with a low incidence of hypersensitivity reactions, with 0.2% of patients developing an anaphylactic reaction compared with 0% for placebo [36]. Data from post-marketing experiences with alogliptin show that skin and subcutaneous disorders were the most common events reported by system organ class (124 non-serious and 18 serious) [36].

Recent studies suggest that DPP-4 inhibition is associated with bullous pemphigoid [136–141]. Although the *HLA-DQB1*03:01* gene is not commonly associated with general bullous pemphigoid or T2DM, a study conducted in Japanese patients revealed a potential association between DPP-4i treatment and onset of non-inflammatory bullous pemphigoid [137]. Several observational studies, including reports of adverse drug reactions in pharmacovigilance databases, have demonstrated differential effects of individual DPP-4is on the risk of bullous pemphigoid, implying a drug-specific effect [136–141]. The risk of bullous pemphigoid appears to be highest among patients exposed to vildagliptin, whereas patients exposed to alogliptin appear to have a relatively low risk of developing the complication. Further

research is required to understand the mechanisms underlying these observations.

3.6 Inflammatory Bowel Disease

Gastrointestinal side effects are an AESI and one of the main factors influencing patient preference [82]. Alogliptin treatment has demonstrated comparable rates of diarrhea to pioglitazone after 26 weeks of treatment, as reported in the DeFronzo et al., 2012 study (alogliptin 12.5 or 25 mg + pioglitazone [15, 30, and 45 mg] and pooled pioglitazone monotherapy groups [2.3%, 5.1%, and 3.6%, respectively]) [9]. Additionally, patients treated with alogliptin (12.5 and 25 mg) and an SU as add-on to metformin had similar incidences of diarrhea (6.9%, 6.8% and 7.2%, respectively) [17].

To date, there has only been one observational study examining the association between DPP-4is and inflammatory bowel disease (IBD) activity [142]. Abrahami et al. reported that the HR for IBD in patients receiving DPP-4i therapy versus other antidiabetic treatments was 1.75 (95% CI 1.22–2.49), which gradually increased, peaking 3–4 years after starting DPP-4i treatment (HR 2.90; 95% CI 1.31–6.41); yet, the HR decreased after the 4-year peak [142]. The increased incidence rate for IBD in patients receiving DPP-4i treatment may be a consequence of the involvement of DPP-4 in several immune responses [143]. Further studies are required to examine the association between IBD and DPP-4is, especially as the long-term use of DPP-4is increases, and treating physicians should remain aware of this potential association when making treatment decisions.

3.7 Renal Failure

Diabetes is one of the leading causes of CKD, which affects 40% of patients [144]. A pooled analysis has suggested that diabetes, hypertension, or a combination of the two were the cause of over 80% of ESRD cases [145].

At the time of writing, there were few studies of alogliptin treatment in patients with CKD; however, in the studies available, alogliptin has been generally well-tolerated and efficacious [27, 36, 146–148]. For example, no increases in occurrence of AEs including hypoglycemia were reported at week 48 in a study examining alogliptin treatment (monotherapy and add-on therapy [mitiglinide and/or α-GI]) in Japanese HD-CKD patients ($n = 30$); a significant reduction in interdialytic body weight gain ($p = 0.04$) was observed in the alogliptin as add-on treatment arm. Moreover, HbA1c and glycated albumin levels were significantly reduced versus baseline levels ($p < 0.0001$) [146]. These observations are further supported by the results of a 2-year study examining alogliptin treatment in Japanese HD-CKD patients, in which treatment was well-tolerated and HbA1c levels had significantly decreased after 2 years ($p < 0.05$) [147]. In the real-world setting, alogliptin treatment maintained renal function after 6 months of treatment in Japanese non-dialysis CKD patients [148]. Of note, in the 25-mg alogliptin group, pruritus was the only AESI with ≥ 1% incidence in patients with mild or moderate renal impairment versus patients with normal renal function at baseline [36]. Further studies are warranted to examine the effect of alogliptin on renal function in a real-world setting.

Dose adjustments for many of the recommended antidiabetic agents [27, 149] are mandated in renally impaired patients with T2DM. In the published literature, there are limited comparisons examining the effect of alogliptin versus other antidiabetic agents on renal function in patients with T2DM and no CKD. For example, there was no statistically significant difference in estimated GFR from baseline to week 104 between alogliptin (-1 ± 10 mL/min/1.73 m^2) and SoC (0 ± 10 mL/min/1.73 m^2; $p = 0.27$) in the SPEAD-A study [77]. Additionally, cumulative incidences of ESRD were comparable between alogliptin + metformin and SU + metformin groups in a 2-year observational study (4.78% and 4.66% for alogliptin [12.5 and 25 mg, respectively] + metformin and 4.86% for SU + metformin [90], respectively).

3.8 Hepatotoxicity

The liver plays a key role in the pathogenesis of diabetes, with the care of diabetes both affected by, or causing effects on, the liver [150]. Hepatic abnormalities, such as cirrhosis, are estimated to account for 4.4–12.5% of deaths in patients with diabetes [151].

Results from pharmacokinetic studies have demonstrated that alogliptin exposure was not affected in patients with mild or moderate hepatic impairment [27, 37] (Child–Pugh grade A and B), and therefore dose adjustments are not required in this setting. However, the pharmacokinetic profile of alogliptin has not yet been examined in patients with severe hepatic impairment (Child–Pugh grade C) and therefore alogliptin is not currently recommended for this patient population [27]. Findings from a single-arm, 12-month, multicenter study evaluating alogliptin (25 mg) efficacy in patients with T2DM and non-alcoholic fatty acid disease suggested that alogliptin may prevent progression of non-alcoholic fatty liver disease with early T2DM [152].

In the EXAMINE study, there was a numerical increase in the number of patients with increased liver enzymes with alogliptin versus placebo (although there were no statistical differences in serum aminotransferase values > 3 × the upper limit of normal at any time) [2], and there were subsequent post-marketing reports of alogliptin-associated hepatotoxicity [153] that prompted some debate; a subsequent analysis

of the FAERS showed no hepatotoxicity signal for alogliptin and significant associations for sitagliptin, saxagliptin, and vildagliptin [154]. Currently, there is insufficient evidence to confirm whether alogliptin was the cause of the fatal and non-fatal hepatic failure documented in post-marketing reports; nevertheless, alogliptin should be administered with caution in patients with abnormal liver tests [27] and should be discontinued in patients with suspected hepatotoxicity [27].

3.9 Risk Evaluation for All DPP4is in Real-World Studies

Observational studies have shown that DPP-4is are associated with fewer gastrointestinal side effects than metformin, GLP-1 receptor agonists, and acarbose, and less hypoglycemia than SUs and insulin (reviewed by Scheen, 2018 [117]). Weight gain is also less with DPP-4is than with SUs, glitazones, and insulin [117]. Any potential increased risk of acute pancreatitis has not been confirmed in observational studies [117]. While the data from observational studies regarding HF is somewhat conflicting, there does not appear to be an increased risk of HF or hospitalization for HF with DPP-4is compared with other glucose-lowering agents in this setting [117]. With regard to CV outcomes, observational studies show reductions with DPP-4is versus other glucose-lowering agents in MACE, MI, stroke, and CV- and all-cause mortality.

In the ATTAK-J study, 12 months of alogliptin had no significant effect on body weight, blood pressure, or liver function [25]. Both total and low-density lipoprotein (LDL)-cholesterol were significantly reduced from baseline at 12 months (− 6.84 and − 7.22 mg/dL, respectively; $p = 0.023$ and $p = 0.001$). There was a significant increase in serum creatinine and a significant decrease in estimated GFR. The incidence of hypoglycemia was 0.6%. A reduction in LDL-cholesterol was also seen in the long-term observational study of Japanese patients with T2DM receiving alogliptin (106.5 ± 25.0 to 96.3 ± 20.9 mg/dL; $p = 0.0406$) [24].

4 Expert Opinion

With more classes of antidiabetic agents available than ever before, physicians have to consider multiple factors, such as glycemic control, patient preferences, safety profile, risk of hypoglycemia, and necessity for weight loss [38, 58], when determining patient-centric, optimal management of T2DM [38, 39, 45, 58]. Alogliptin is an effective therapy that acts synergistically with agents including metformin and pioglitazone to provide superior efficacy compared with component monotherapies, as well as SU + metformin combination therapy [5, 9, 15, 17, 18, 66, 77].

From a safety perspective, alogliptin is generally well-tolerated, with a low risk of hypoglycemia, weight gain, acute pancreatitis, and hepatotoxicity [1–3, 7, 8, 11–14, 17, 18, 21, 27, 37, 67, 69, 70, 93, 101]. Dose adjustments are required in patients with moderate renal impairment to ESRD, and caution is required in patients with renal and/or hepatic impairment [27, 36, 146–148]. Although the EXAMINE study and post hoc analyses demonstrated that alogliptin is well-tolerated in patients with a high HF risk [2, 108, 112–115], there are not currently enough data available to determine the cause and effect of alogliptin on the risk of HF [117]. Similarly, while there are new potential concerns for DPP-4i treatments, such as bullous pemphigoid and IBD [137, 142], further evaluation is required.

Alogliptin generally exhibits a favorable safety profile, with an incidence of 286.1 TEAEs per 100 PYs [93], compared with active comparators (283.3 TEAEs per 100 PYs). For alogliptin, the risk of hypoglycemia is decreased versus SoCs and SUs [17, 77, 101] or comparable versus metformin [18, 39, 70, 155]; risks for acute pancreatitis are low and comparable to SUs [17]; gastrointestinal AE risks are comparable to SUs and TZDs [9, 17]; CV risks are less than with SoCs and metformin [18, 77], and possibly with SUs and TZDs [9, 17], although alogliptin cannot be considered to have the same cardioprotective effects as GLP-1 receptor agonists and SGLT2is [126]. Furthermore, weight gain risks are less with alogliptin versus TZDs, SUs, and SoCs [9, 17, 77], but increased versus metformin [18]; as the efficacy of DPP-4i monotherapy is decreased in diets high in saturated fatty acids, avoidance of weight gain through diet therapy is an important consideration.

The main limitation of the current benefit-risk assessment is the lack of statistical analyses, including data reported in post-marketing databases, such as the FAERS. However, we anticipate that this assessment is a useful aid to physicians when choosing an optimal therapy for T2DM management for their patient.

5 Conclusions

Alogliptin treatment is one of the suitable medications for patients with T2DM who require glycemic control, with a low risk of hypoglycemia, weight gain, and gastrointestinal AEs, and for those who prefer a once-daily oral regimen, with caution required in those who have underlying CV risks. Notably, alogliptin has demonstrated greater efficacy in Asian patients than in non-Asian patients with T2DM, while maintaining a similar tolerability profile. This suggests that DPP-4is, including alogliptin, represent important

treatment options, especially for Asian patients with T2DM, for whom they have potential as a first-line therapy.

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Compliance with Ethical Standards

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References

1. DeFronzo RA, Fleck PR, Wilson CA, Mekki Q. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor alogliptin in patients with type 2 diabetes and inadequate glycemic control: a randomized, double-blind, placebo-controlled study. Diabetes Care. 2008;31(12):2315–7.
2. White WB, Cannon CP, Heller SR, Nissen SE, Bergenstal RM, Bakris GL, et al. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. N Engl J Med. 2013;369(14):1327–35.
3. Kaku K, Itayasu T, Hiroi S, Hirayama M, Seino Y. Efficacy and safety of alogliptin added to pioglitazone in Japanese patients with type 2 diabetes: a randomized, double-blind, placebo-controlled trial with an open-label long-term extension study. Diabetes Obes Metab. 2011;13(11):1028–35.
4. Kaku K, Sumino S, Katou M, Nishiyama Y, Kinugawa Y. Randomized, double-blind, phase III study to evaluate the efficacy and safety of once-daily treatment with alogliptin and metformin hydrochloride in Japanese patients with type 2 diabetes. Diabetes Obes Metab. 2017;19(3):463–7.
5. Ji L, Li L, Kuang J, Yang T, Kim DJ, Kadir AA, et al. Efficacy and safety of fixed-dose combination therapy, alogliptin plus metformin, in Asian patients with type 2 diabetes: a phase 3 trial. Diabetes Obes Metab. 2017;19(5):754–8.
6. Pratley RE, Reusch JE, Fleck PR, Wilson CA, Mekki Q. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor alogliptin added to pioglitazone in patients with type 2 diabetes: a randomized, double-blind, placebo-controlled study. Curr Med Res Opin. 2009;25(10):2361–71.
7. Rosenstock J, Rendell MS, Gross JL, Fleck PR, Wilson CA, Mekki Q. Alogliptin added to insulin therapy in patients with type 2 diabetes reduces HbA(1C) without causing weight gain or increased hypoglycaemia. Diabetes Obes Metab. 2009;11(12):1145–52.
8. Bosi E, Ellis GC, Wilson CA, Fleck PR. Alogliptin as a third oral antidiabetic drug in patients with type 2 diabetes and inadequate glycaemic control on metformin and pioglitazone: a 52-week, randomized, double-blind, active-controlled, parallel-group study. Diabetes Obes Metab. 2011;13(12):1088–96.
9. DeFronzo RA, Burant CF, Fleck P, Wilson C, Mekki Q, Pratley RE. Efficacy and tolerability of the DPP-4 inhibitor alogliptin combined with pioglitazone, in metformin-treated patients with type 2 diabetes. J Clin Endocrinol Metab. 2012;97(5):1615–22.
10. Pan C, Han P, Ji Q, Li C, Lu J, Yang J, et al. Efficacy and safety of alogliptin in patients with type 2 diabetes mellitus: a multicentre randomized double-blind placebo-controlled phase 3 study in mainland China, Taiwan, and Hong Kong. J Diabetes. 2017;9(4):386–95.
11. Pratley RE, McCall T, Fleck PR, Wilson CA, Mekki Q. Alogliptin use in elderly people: a pooled analysis from phase 2 and 3 studies. J Am Geriatr Soc. 2009;57(11):2011–9.
12. Seino Y, Fujita T, Hiroi S, Hirayama M, Kaku K. Efficacy and safety of alogliptin in Japanese patients with type 2 diabetes mellitus: a randomized, double-blind, dose-ranging comparison with placebo, followed by a long-term extension study. Curr Med Res Opin. 2011;27(9):1781–92.
13. Nauck MA, Ellis GC, Fleck PR, Wilson CA, Mekki Q. Efficacy and safety of adding the dipeptidyl peptidase-4 inhibitor alogliptin to metformin therapy in patients with type 2 diabetes inadequately controlled with metformin monotherapy: a multicentre, randomised, double-blind, placebo-controlled study. Int J Clin Pract. 2009;63(1):46–55.
14. Pratley RE, Kipnes MS, Fleck PR, Wilson C, Mekki Q. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor alogliptin in patients with type 2 diabetes inadequately controlled by glyburide monotherapy. Diabetes Obes Metab. 2009;11(2):167–76.
15. Rosenstock J, Inzucchi SE, Seufert J, Fleck PR, Wilson CA, Mekki Q. Initial combination therapy with alogliptin and pioglitazone in drug-naive patients with type 2 diabetes. Diabetes Care. 2010;33(11):2406–8.
16. Seino Y, Fujita T, Hiroi S, Hirayama M, Kaku K. Alogliptin plus voglibose in Japanese patients with type 2 diabetes: a randomized, double-blind, placebo-controlled trial with an open-label, long-term extension. Curr Med Res Opin. 2011;27(Suppl 3):21–9.
17. Del Prato S, Camisasca R, Wilson C, Fleck P. Durability of the efficacy and safety of alogliptin compared with glipizide in type 2 diabetes mellitus: a 2-year study. Diabetes Obes Metab. 2014;16(12):1239–46.
18. Pratley RE, Fleck P, Wilson C. Efficacy and safety of initial combination therapy with alogliptin plus metformin versus either as monotherapy in drug-naive patients with type 2 diabetes: a randomized, double-blind, 6-month study. Diabetes Obes Metab. 2014;16(7):613–21.
19. Kaku K, Mori M, Kanoo T, Katou M, Seino Y. Efficacy and safety of alogliptin added to insulin in Japanese patients with type 2 diabetes: a randomized, double-blind, 12-week, placebo-controlled trial followed by an open-label, long-term extension phase. Expert Opin Pharmacother. 2014;15(15):2121–30.
20. Takahara M, Shiraiwa T, Katakami N, Kaneto H, Matsuoka TA, Shimomura I. Efficacy of adding once- and thrice-daily voglibose in Japanese type 2 diabetic patients treated with alogliptin. Endocr J. 2014;61(5):447–56.
21. Van Raalte DH, van Genugten RE, Eliasson B, Moller-Goede DL, Mari A, Tura A, et al. The effect of alogliptin and pioglitazone

combination therapy on various aspects of beta-cell function in patients with recent-onset type 2 diabetes. Eur J Endocrinol. 2014;170(4):565–74.
22. White WB, Wilson CA, Bakris GL, Bergenstal RM, Cannon CP, Cushman WC, et al. Angiotensin-converting enzyme inhibitor use and major cardiovascular outcomes in type 2 diabetes mellitus treated with the dipeptidyl peptidase 4 inhibitor alogliptin. Hypertension. 2016;68(3):606–13.
23. Inagaki N, Ueki K, Tanizawa Y, Watada H, Nakamura J, Yamada Y, et al. Protocol for a large-scale prospective observational study with alogliptin in patients with type 2 diabetes: J-BRAND Registry. BMJ Open. 2014;4(9):e004760.
24. Takebayashi K, Suzuki T, Naruse R, Hara K, Suetsugu M, Tsuchiya T, et al. Long-term effect of alogliptin on glycemic control in Japanese patients with type 2 diabetes: a 3.5-year observational study. J Clin Med Res. 2017;9(9):802–8.
25. Takeda H, Sasai N, Ito S, Obana M, Takuma T, Takai M, et al. Efficacy and safety of alogliptin in patients with type 2 diabetes: analysis of the ATTAK-J study. J Clin Med Res. 2016;8(2):130–40.
26. European Medicines Agency. Vipidia (alogliptin): EU summary of product characteristics. 2014. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002182/WC500152271.pdf. Accessed 28 Mar 2019.
27. Takeda Pharmaceuticals America Inc. Nesina (alogliptin), prescribing information. 2013. https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022271s000lbl.pdf. Accessed 28 Mar 2019.
28. Pharmaceuticals and Medical Devices Agency. Pharmaceuticals and Medical Devices Agency approved labels: Nesina® label https://www.pmda.go.jp/PmdaSearch/iyakuDetail/ResultDataSetPDF/400256_3969012F1025_1_18. Accessed 28 Mar 2019.
29. European Medicines Agency. Vipdomet (alogliptin/metformin HCl): EU summary of product characteristics. 2014. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002654/WC500152141.pdf. Accessed 28 Mar 2019.
30. Takeda Pharmaceuticals America Inc. Kazano (alogliptin and metformin HCl), prescribing information. 2013. https://general.takedapharm.com/KAZANOPI. Accessed 28 Mar 2019.
31. Takeda Pharmaceuticals America Inc. Oseni (alogliptin and pioglitazone), prescribing information. 2013. https://general.takedapharm.com/OSENIPI Accessed 28 Mar 2019.
32. Pharmaceuticals and Medical Devices Agency. Pharmaceuticals and Medical Devices Agency approved labels: Liovel® label. https://www.pmda.go.jp/PmdaSearch/iyakuDetail/ResultDataSetPDF/400256_3969103F1024_1_16. Accessed 28 Mar 2019.
33. Pharmaceuticals and Medical Devices Agency. Pharmaceuticals and Medical Devices Agency: Inisync® label. https://www.pmda.go.jp/PmdaSearch/iyakuDetail/ResultDataSetPDF/400256_3969105F1023_1_05. Accessed 28 Mar 2019.
34. European Medicines Agency. Incresync (alogliptin/pioglitazone): EU summary of product characteristics. 2014. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002178/WC500152197.pdf. Accessed 28 Mar 2019.
35. Covington P, Christopher R, Davenport M, Fleck P, Mekki QA, Wann ER, et al. Pharmacokinetic, pharmacodynamic, and tolerability profiles of the dipeptidyl peptidase-4 inhibitor alogliptin: a randomized, double-blind, placebo-controlled, multiple-dose study in adult patients with type 2 diabetes. Clin Ther. 2008;30(3):499–512.
36. European Medicines Agency. Vipidia: Committee for Medicinal Products for human use (CHMP). 2013. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002182/WC500152273.pdf. Accessed 28 Mar 2019.
37. Scheen AJ. Pharmacokinetics and clinical use of incretin-based therapies in patients with chronic kidney disease and type 2 diabetes. Clin Pharmacokinet. 2015;54(1):1–21.
38. American Diabetes Association. Standards of medical care in diabetes 2018. Diabetes Care. 2018;41:S1–159.
39. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care. 2015;38(1):140–9.
40. Sanchez-Rangel E, Inzucchi SE. Metformin: clinical use in type 2 diabetes. Diabetologia. 2017;60(9):1586–93.
41. Chaudhury A, Duvoor C, Reddy Dendi VS, Kraleti S, Chada A, Ravilla R, et al. Clinical review of antidiabetic drugs: implications for type 2 diabetes mellitus management. Front Endocrinol. 2017;8:6.
42. Kodama K, Tojjar D, Yamada S, Toda K, Patel CJ, Butte AJ. Ethnic differences in the relationship between insulin sensitivity and insulin response: a systematic review and meta-analysis. Diabetes Care. 2013;36(6):1789–96.
43. Seino Y, Kuwata H, Yabe D. Incretin-based drugs for type 2 diabetes: focus on East Asian perspectives. J Diabetes Investig. 2016;7(Suppl 1):102–9.
44. Suzuki K, Akiyama M, Ishigaki K, Kanai M, Hosoe J, Shojima N, et al. Identification of 28 new susceptibility loci for type 2 diabetes in the Japanese population. Nat Genet. 2019;51(3):379–86.
45. Haneda M, Noda M, Origasa H, Noto H, Yabe D, Fujita Y, et al. Japanese clinical practice guideline for diabetes 2016. J Diabetes Investig. 2018;9(3):657–97.
46. Nishimura R, Kato H, Kisanuki K, Oh A, Hiroi S, Onishi Y, et al. Treatment patterns, persistence and adherence rates in patients with type 2 diabetes mellitus in Japan: a claims-based cohort study. BMJ Open. 2019;9(3):e025806.
47. Tanabe M, Motonaga R, Terawaki Y, Nomiyama T, Yanase T. Prescription of oral hypoglycemic agents for patients with type 2 diabetes mellitus: a retrospective cohort study using a Japanese hospital database. J Diabetes Investig. 2017;8(2):227–34.
48. Kim YG, Hahn S, Oh TJ, Kwak SH, Park KS, Cho YM. Differences in the glucose-lowering efficacy of dipeptidyl peptidase-4 inhibitors between Asians and non-Asians: a systematic review and meta-analysis. Diabetologia. 2013;56(4):696–708.
49. Cahn A, Cernea S, Raz I. An update on DPP-4 inhibitors in the management of type 2 diabetes. Expert Opin Emerg Drugs. 2016;21(4):409–19.
50. Fowler MJ. Microvascular and macrovascular complications of diabetes. Clin Diabetes. 2008;26(2):77–82.
51. Trikkalinou A, Papazafiropoulou AK, Melidonis A. Type 2 diabetes and quality of life. World J Diabetes. 2017;8(4):120–9.
52. World Health Organisation. Diabetes factsheet. 2017. http://www.who.int/news-room/fact-sheets/detail/diabetes. Accessed 28 Mar 2019.
53. Charvat H, Goto A, Goto M, Inoue M, Heianza Y, Arase Y, et al. Impact of population aging on trends in diabetes prevalence: a meta-regression analysis of 160,000 Japanese adults. J Diabetes Investig. 2015;6(5):533–42.
54. Zheng Y, Ley SH, Hu FB. Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. Nat Rev Endocrinol. 2018;14(2):88–98.
55. Ma RC, Chan JC. Type 2 diabetes in East Asians: similarities and differences with populations in Europe and the United States. Ann N Y Acad Sci. 2013;1281:64–91.
56. World Health Organisation. Global report on diabetes. 2016. http://apps.who.int/iris/bitstream/handle/10665/204871/97892

41565257_eng.pdf;jsessionid=57E375117D877275E79C2D9581F6E2B9?sequence=1. Accessed 28 Mar 2019.
57. Garcia-Perez LE, Alvarez M, Dilla T, Gil-Guillen V, Orozco-Beltran D. Adherence to therapies in patients with type 2 diabetes. Diabetes Ther. 2013;4(2):175–94.
58. Irons BK, Minze MG. Drug treatment of type 2 diabetes mellitus in patients for whom metformin is contraindicated. Diabetes Metab Syndr Obes. 2014;7:15–24.
59. Feng J, Zhang Z, Wallace MB, Stafford JA, Kaldor SW, Kassel DB, et al. Discovery of alogliptin: a potent, selective, bioavailable, and efficacious inhibitor of dipeptidyl peptidase IV. J Med Chem. 2007;50(10):2297–300.
60. Lee B, Shi L, Kassel DB, Asakawa T, Takeuchi K, Christopher RJ. Pharmacokinetic, pharmacodynamic, and efficacy profiles of alogliptin, a novel inhibitor of dipeptidyl peptidase-4, in rats, dogs, and monkeys. Eur J Pharmacol. 2008;589(1–3):306–14.
61. Okondo MC, Johnson DC, Sridharan R, Go EB, Chui AJ, Wang MS, et al. DPP8/9 inhibition induces pro-caspase-1-dependent monocyte and macrophage pyroptosis. Nat Chem Biol. 2017;13(1):46–53.
62. Bergman AJ, Stevens C, Zhou Y, Yi B, Laethem M, De Smet M, et al. Pharmacokinetic and pharmacodynamic properties of multiple oral doses of sitagliptin, a dipeptidyl peptidase-IV inhibitor: a double-blind, randomized, placebo-controlled study in healthy male volunteers. Clin Ther. 2006;28(1):55–72.
63. Karim A, Covington P, Christopher R, Davenport M, Fleck P, Li X, et al. Pharmacokinetics of alogliptin when administered with food, metformin, or cimetidine: a two-phase, crossover study in healthy subjects. Int J Clin Pharmacol Ther. 2010;48(1):46–58.
64. Karim A, Laurent A, Munsaka M, Wann E, Fleck P, Mekki Q. Coadministration of pioglitazone or glyburide and alogliptin: pharmacokinetic drug interaction assessment in healthy participants. J Clin Pharmacol. 2009;49(10):1210–9.
65. Chen XW, He ZX, Zhou ZW, Yang T, Zhang X, Yang YX, et al. Clinical pharmacology of dipeptidyl peptidase 4 inhibitors indicated for the treatment of type 2 diabetes mellitus. Clin Exp Pharmacol Physiol. 2015;42(10):999–1024.
66. Del Prato S, Fleck P, Wilson C, Chaudhari P. Comparison of alogliptin and glipizide for composite endpoint of glycated haemoglobin reduction, no hypoglycaemia and no weight gain in type 2 diabetes mellitus. Diabetes Obes Metab. 2016;18(6):623–7.
67. Eliasson B, Moller-Goede D, Eeg-Olofsson K, Wilson C, Cederholm J, Fleck P, et al. Lowering of postprandial lipids in individuals with type 2 diabetes treated with alogliptin and/or pioglitazone: a randomised double-blind placebo-controlled study. Diabetologia. 2012;55(4):915–25.
68. Kaku K, Katou M, Igeta M, Ohira T, Sano H. Efficacy and safety of pioglitazone added to alogliptin in Japanese patients with type 2 diabetes mellitus: a multicentre, randomized, double-blind, parallel-group, comparative study. Diabetes Obes Metab. 2015;17(12):1198–201.
69. Seino Y, Hiroi S, Hirayama M, Kaku K. Efficacy and safety of alogliptin added to sulfonylurea in Japanese patients with type 2 diabetes: a randomized, double-blind, placebo-controlled trial with an open-label, long-term extension study. J Diabetes Investig. 2012;3(6):517–25.
70. Seino Y, Miyata Y, Hiroi S, Hirayama M, Kaku K. Efficacy and safety of alogliptin added to metformin in Japanese patients with type 2 diabetes: a randomized, double-blind, placebo-controlled trial with an open-label, long-term extension study. Diabetes Obes Metab. 2012;14(10):927–36.
71. Cai Y, Zeng T, Wen Z, Chen L. Ethnic differences in efficacy and safety of alogliptin: a systematic review and meta-analysis. Diabetes Ther. 2018;9(1):177–91.
72. Fujibayashi K, Hayashi M, Yokokawa H, Naito T. Changes in antidiabetic prescription patterns and indicators of diabetic control among 200,000 patients over 13 years at a single institution in Japan. Diabetol Metab Syndr. 2016;8:72.
73. Hampp C, Borders-Hemphill V, Moeny DG, Wysowski DK. Use of antidiabetic drugs in the U.S., 2003-2012. Diabetes Care. 2014;37(5):1367–74.
74. Higgins V, Piercy J, Roughley A, Milligan G, Leith A, Siddall J, et al. Trends in medication use in patients with type 2 diabetes mellitus: a long-term view of real-world treatment between 2000 and 2015. Diabetes Metab Syndr Obes. 2016;9:371–80.
75. Oishi M, Yamazaki K, Okuguchi F, Sugimoto H, Kanatsuka A, Kashiwagi A. Changes in oral antidiabetic prescriptions and improved glycemic control during the years 2002-2011 in Japan (JDDM32). J Diabetes Investig. 2014;5(5):581–7.
76. Yamamoto-Honda R, Takahashi Y, Mori Y, Yamashita S, Yoshida Y, Kawazu S, et al. Changes in antidiabetic drug prescription and glycemic control trends in elderly patients with type 2 diabetes mellitus from 2005-2013: an analysis of the National Center Diabetes Database (NCDD-03). Intern Med. 2018;57(9):1229–40.
77. Mita T, Katakami N, Yoshii H, Onuma T, Kaneto H, Osonoi T, et al. Alogliptin, a dipeptidyl peptidase 4 inhibitor, prevents the progression of carotid atherosclerosis in patients with type 2 diabetes: the study of preventive effects of alogliptin on diabetic atherosclerosis (SPEAD-A). Diabetes Care. 2016;39(1):139–48.
78. Berhan A, Berhan Y. Efficacy of alogliptin in type 2 diabetes treatment: a meta-analysis of randomized double-blind controlled studies. BMC Endocr Disord. 2013;13:9.
79. Kay S, Strickson A, Puelles J, Selby R, Benson E, Tolley K. Comparative effectiveness of adding alogliptin to metformin plus sulfonylurea with other DPP-4 inhibitors in type 2 diabetes: a systematic review and network meta-analysis. Diabetes Ther. 2017;8(2):251–73.
80. Rehman MB, Tudrej BV, Soustre J, Buisson M, Archambault P, Pouchain D, et al. Efficacy and safety of DPP-4 inhibitors in patients with type 2 diabetes: meta-analysis of placebo-controlled randomized clinical trials. Diabetes Metab. 2017;43(1):48–58.
81. World Health Organisation. Adherence to long-term therapies: evidence for action. 2003. http://apps.who.int/iris/bitstream/handle/10665/42682/9241545992.pdf;jsessionid=6216B66E93FFFE5ADF1768F0530EE415?sequence=1. Accessed 28 Mar 2019.
82. Flood EM, Bell KF, de la Cruz MC, Ginchereau-Sowell FM. Patient preferences for diabetes treatment attributes and drug classes. Curr Med Res Opin. 2017;33(2):261–8.
83. Dibonaventura MD, Wagner JS, Girman CJ, Brodovicz K, Zhang Q, Qiu Y, et al. Multinational internet-based survey of patient preference for newer oral or injectable type 2 diabetes medication. Patient Prefer Adherence. 2010;4:397–406.
84. Goto H, Mita T, Fujitani Y, Fujimoto S, Takahashi K, Satoh H, et al. Effects of linagliptin versus voglibose on treatment-related quality of life in patients with type 2 diabetes: sub-analysis of the L-STEP study. Endocr J. 2018;65(6):657–68.
85. Pan F, Chernew ME, Fendrick AM. Impact of fixed-dose combination drugs on adherence to prescription medications. J Gen Intern Med. 2008;23(5):611–4.
86. International Diabetes Foundation. Global factsheet (English), IDF 8th Edition 2017. 2017. http://diabetesatlas.org/resources/2017-atlas.html. Accessed 28 Mar 2019.
87. Li R, Zhang P, Barker LE, Chowdhury FM, Zhang X. Cost-effectiveness of interventions to prevent and control diabetes mellitus: a systematic review. Diabetes Care. 2010;33(8):1872–94.
88. Pedrazzoli M, Pasquini F, Minda K. Assessment of the economic value of Dpp-4 inhibitor alogliptin compared with sitagliptin, saxagliptin, and linagliptin. Value Health. 2014;17(7):A337.

89. Lavernia F, Adkins SE, Shubrook JH. Use of oral combination therapy for type 2 diabetes in primary care: meeting individualized patient goals. Postgrad Med. 2015;127(8):808–17.
90. Gordon J, McEwan P, Hurst M, Puelles J. The cost-effectiveness of alogliptin versus sulfonylurea as add-on therapy to metformin in patients with uncontrolled type 2 diabetes mellitus. Diabetes Ther. 2016;7(4):825–45.
91. Kwon CS, Seoane-Vazquez E, Rodriguez-Monguio R. Cost-effectiveness analysis of metformin + dipeptidyl peptidase-4 inhibitors compared to metformin + sulfonylureas for treatment of type 2 diabetes. BMC Health Serv Res. 2018;18(1):78.
92. Teramachi H, Ohta H, Tachi T, Toyoshima M, Mizui T, Goto C, et al. Pharmacoeconomic analysis of DPP-4 inhibitors. Pharmazie. 2013;68(11):909–15.
93. Munsaka M, Smith N, Lee D, Wilson C. Abstract 777 – Safety and tolerability of alogliptin in patients with type 2 diabetes: pooled analysis of 20 double-blind randomised controlled clinical studies. Diabetologia. 2016;59(Suppl 1):S371. https://doi.org/10.1007/s00125-016-4046-9.
94. Smith N, Pratley R, Wilson C, Mekki Q. A long-term, open-label extension study to investigate the long-term safety of alogliptin subjects with type 2 diabetes. Diabetologia. 2017;60(S357-8):Abstract 780.
95. Takeda Pharmaceutical Company. Alogliptin global investigator brochure. Edition 15.0, 12 September 2018. Accessed.
96. Craddy P, Palin HJ, Johnson KI. Comparative effectiveness of dipeptidylpeptidase-4 inhibitors in type 2 diabetes: a systematic review and mixed treatment comparison. Diabetes Ther. 2014;5(1):1–41.
97. Willemen MJ, Mantel-Teeuwisse AK, Straus SM, Meyboom RH, Egberts TC, Leufkens HG. Use of dipeptidyl peptidase-4 inhibitors and the reporting of infections: a disproportionality analysis in the World Health Organization VigiBase. Diabetes Care. 2011;34(2):369–74.
98. Miller CD, Phillips LS, Ziemer DC, Gallina DL, Cook CB, El-Kebbi IM. Hypoglycemia in patients with type 2 diabetes mellitus. Arch Intern Med. 2001;161(13):1653–9.
99. Bron M, Marynchenko M, Yang H, Yu AP, Wu EQ. Hypoglycemia, treatment discontinuation, and costs in patients with type 2 diabetes mellitus on oral antidiabetic drugs. Postgrad Med. 2012;124(1):124–32.
100. Bremer JP, Jauch-Chara K, Hallschmid M, Schmid S, Schultes B. Hypoglycemia unawareness in older compared with middle-aged patients with type 2 diabetes. Diabetes Care. 2009;32(8):1513–7.
101. Rosenstock J, Wilson C, Fleck P. Alogliptin versus glipizide monotherapy in elderly type 2 diabetes mellitus patients with mild hyperglycaemia: a prospective, double-blind, randomized, 1-year study. Diabetes Obes Metab. 2013;15(10):906–14.
102. Salvo F, Moore N, Arnaud M, Robinson P, Raschi E, De Ponti F, et al. Addition of dipeptidyl peptidase-4 inhibitors to sulphonylureas and risk of hypoglycaemia: systematic review and meta-analysis. BMJ. 2016;353:i2231.
103. Howlett HC, Bailey CJ. A risk-benefit assessment of metformin in type 2 diabetes mellitus. Drug Saf. 1999;20(6):489–503.
104. International Diabetes Foundation. Diabetes Atlas: Second edition 2003. 2013. https://www.idf.org/e-library/epidemiology-research/diabetes-atlas/23-atlas-2nd-edition-year.html. Accessed 28 Mar 2019.
105. Sell H, Bluher M, Kloting N, Schlich R, Willems M, Ruppe F, et al. Adipose dipeptidyl peptidase-4 and obesity: correlation with insulin resistance and depot-specific release from adipose tissue in vivo and in vitro. Diabetes Care. 2013;36(12):4083–90.
106. Kuwata H, Okamoto S, Seino Y, Murotani K, Tatsuoka H, Usui R, et al. Relationship between deterioration of glycated hemoglobin-lowering effects in dipeptidyl peptidase-4 inhibitor monotherapy and dietary habits: retrospective analysis of Japanese individuals with type 2 diabetes. J Diabetes Investig. 2018;9(5):1153–8.
107. Yau H, Rivera K, Lomonaco R, Cusi K. The future of thiazolidinedione therapy in the management of type 2 diabetes mellitus. Curr Diab Rep. 2013;13(3):329–41.
108. Zannad F, Cannon CP, Cushman WC, Bakris GL, Menon V, Perez AT, et al. Heart failure and mortality outcomes in patients with type 2 diabetes taking alogliptin versus placebo in EXAMINE: a multicentre, randomised, double-blind trial. Lancet. 2015;385(9982):2067–76.
109. American Diabetes Association. 2018 standards of medical care in diabetes, with notable new recommendations for people with cardiovascular disease and diabetes. 2017. http://www.diabetes.org/newsroom/press-releases/2017/american-diabetes-association-2018-release-standards-of-medical-care-in-diabetes.html. Accessed 24 July 2019.
110. American Diabetes Association. 9. Pharmacologic approaches to glycemic treatment: Standards of medical care in diabetes-2019. Diabetes Care. 2019;42(Suppl 1):S90–S102.
111. Avogaro A, Fadini GP. The pleiotropic cardiovascular effects of dipeptidyl peptidase-4 inhibitors. Br J Clin Pharmacol. 2018;84(8):1686–95.
112. Heller SR, Bergenstal RM, White WB, Kupfer S, Bakris GL, Cushman WC, et al. Relationship of glycated haemoglobin and reported hypoglycaemia to cardiovascular outcomes in patients with type 2 diabetes and recent acute coronary syndrome events: the EXAMINE trial. Diabetes Obes Metab. 2017;19(5):664–71.
113. Shimada YJ, Cannon CP, Liu Y, Wilson C, Kupfer S, Menon V, et al. Ischemic cardiac outcomes and hospitalizations according to prior macrovascular disease status in patients with type 2 diabetes and recent acute coronary syndrome from the Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care trial. Am Heart J. 2016;175:18–27.
114. White WB, Heller SR, Cannon CP, Howitt H, Khunti K, Bergenstal RM. Alogliptin in patients with type 2 diabetes receiving metformin and sulfonylurea therapies in the EXAMINE trial. Am J Med. 2018;131(7):813–9.e5.
115. White WB, Kupfer S, Zannad F, Mehta CR, Wilson CA, Lei L, et al. Cardiovascular mortality in patients with type 2 diabetes and recent acute coronary syndromes from the EXAMINE trial. Diabetes Care. 2016;39(7):1267–73.
116. Scheen AJ. Cardiovascular effects of gliptins. Nat Rev Cardiol. 2013;10(2):73–84.
117. Scheen AJ. The safety of gliptins: updated data in 2018. Expert Opin Drug Saf. 2018;17(4):387–405.
118. Li L, Li S, Deng K, Liu J, Vandvik PO, Zhao P, et al. Dipeptidyl peptidase-4 inhibitors and risk of heart failure in type 2 diabetes: systematic review and meta-analysis of randomised and observational studies. BMJ. 2016;352:i610.
119. Baksh SN, McAdams-DeMarco M, Segal JB, Alexander GC. Cardiovascular safety signals with dipeptidyl peptidase-4 inhibitors: a disproportionality analysis among high-risk patients. Pharmacoepidemiol Drug Saf. 2018;27(6):660–7.
120. Raschi E, Poluzzi E, Koci A, Antonazzo IC, Marchesini G, De Ponti F. Dipeptidyl peptidase-4 inhibitors and heart failure: analysis of spontaneous reports submitted to the FDA Adverse Event Reporting System. Nutr Metab Cardiovasc Dis. 2016;26(5):380–6.
121. Kim YG, Yoon D, Park S, Han SJ, Kim DJ, Lee KW, et al. Dipeptidyl peptidase-4 inhibitors and risk of heart failure in patients with type 2 diabetes mellitus: a population-based cohort study. Circ Heart Fail. 2017;10(9):e003957.
122. Kim KJ, Choi J, Lee J, Bae JH, An JH, Kim HY, et al. Dipeptidyl peptidase-4 inhibitor compared with sulfonylurea in combination with metformin: cardiovascular and renal outcomes in a propensity-matched cohort study. Cardiovasc Diabetol. 2019;18(1):28.

123. Nozue T, Fukui K, Takamura T, Sozu T, Hibi K, Kishi S, et al. Effects of alogliptin on fractional flow reserve evaluated by coronary computed tomography angiography in patients with type 2 diabetes: rationale and design of the TRACT study. J Cardiol. 2017;69(3):518–22.
124. European Medicines Agency. Onglyza (saxagliptin): EU summary of product characteristics. 2018. https://www.ema.europa.eu/en/documents/product-information/onglyza-epar-product-information_en.pdf. Accessed 28 Mar 2019.
125. European Medicines Agency. Jalra (vildagliptin): EU summary of product characteristics. 2018. https://www.ema.europa.eu/en/documents/product-information/jalra-epar-product-information_en.pdf. Accessed 28 Mar 2019.
126. Kim GS, Park JH, Won JC. The role of glucagon-like peptide 1 receptor agonists and sodium-glucose cotransporter 2 inhibitors in reducing cardiovascular events in patients with type 2 diabetes. Endocrinol Metab (Seoul). 2019;34(2):106–16.
127. Garg R, Chen W, Pendergrass M. Acute pancreatitis in type 2 diabetes treated with exenatide or sitagliptin: a retrospective observational pharmacy claims analysis. Diabetes Care. 2010;33(11):2349–54.
128. Ryder RE. The potential risks of pancreatitis and pancreatic cancer with GLP-1-based therapies are far outweighed by the proven and potential (cardiovascular) benefits. Diabet Med. 2013;30(10):1148–55.
129. Faillie JL, Azoulay L, Patenaude V, Hillaire-Buys D, Suissa S. Incretin based drugs and risk of acute pancreatitis in patients with type 2 diabetes: cohort study. BMJ. 2014;348:g2780.
130. Nagel AK, Ahmed-Sarwar N, Werner PM, Cipriano GC, Van Manen RP, Brown JE. Dipeptidyl peptidase-4 inhibitor-associated pancreatic carcinoma: a review of the FAERS database. Ann Pharmacother. 2016;50(1):27–31.
131. Azoulay L, Filion KB, Platt RW, Dahl M, Dormuth CR, Clemens KK, et al. Incretin based drugs and the risk of pancreatic cancer: international multicentre cohort study. BMJ. 2016;352:i581.
132. Overbeek JA, Bakker M, van der Heijden A, van Herk-Sukel MPP, Herings RMC, Nijpels G. Risk of dipeptidyl peptidase-4 (DPP-4) inhibitors on site-specific cancer: a systematic review and meta-analysis. Diabetes Metab Res Rev. 2018;34(5):e3004.
133. Pinto LC, Rados DV, Barkan SS, Leitao CB, Gross JL. Dipeptidyl peptidase-4 inhibitors, pancreatic cancer and acute pancreatitis: a meta-analysis with trial sequential analysis. Sci Rep. 2018;8(1):782.
134. Lee DY, Yu JH, Park S, Han K, Kim NH, Yoo HJ, et al. The influence of diabetes and antidiabetic medications on the risk of pancreatic cancer: a nationwide population-based study in Korea. Sci Rep. 2018;8(1):9719.
135. Faillie JL, Yu OH, Yin H, Hillaire-Buys D, Barkun A, Azoulay L. Association of bile duct and gallbladder diseases with the use of incretin-based drugs in patients with type 2 diabetes mellitus. JAMA Intern Med. 2016;176(10):1474–81.
136. Bene J, Moulis G, Bennani I, Auffret M, Coupe P, Babai S, et al. Bullous pemphigoid and dipeptidyl peptidase IV inhibitors: a case-noncase study in the French Pharmacovigilance Database. Br J Dermatol. 2016;175(2):296–301.
137. Ujiie H, Muramatsu K, Mushiroda T, Ozeki T, Miyoshi H, Iwata H, et al. HLA-DQB1*03:01 as a biomarker for genetic susceptibility to bullous pemphigoid induced by DPP-4 inhibitors. J Invest Dermatol. 2018;138(5):1201–4.
138. Arai M, Shirakawa J, Konishi H, Sagawa N, Terauchi Y. Bullous pemphigoid and dipeptidyl peptidase 4 inhibitors: a disproportionality analysis based on the Japanese adverse drug event report database. Diabetes Care. 2018;41(9):e130–2.
139. Garcia M, Aranburu MA, Palacios-Zabalza I, Lertxundi U, Aguirre C. Dipeptidyl peptidase-IV inhibitors induced bullous pemphigoid: a case report and analysis of cases reported in the European pharmacovigilance database. J Clin Pharm Ther. 2016;41(3):368–70.
140. Kridin K, Bergman R. Association of bullous pemphigoid with dipeptidyl-peptidase 4 inhibitors in patients with diabetes: estimating the risk of the new agents and characterizing the patients. JAMA Dermatol. 2018;154(10):1152–8.
141. Lee SG, Lee HJ, Yoon MS, Kim DH. Association of dipeptidyl peptidase 4 inhibitor use with risk of bullous pemphigoid in patients with diabetes. JAMA Dermatol. 2019;155(2):172–7.
142. Abrahami D, Douros A, Yin H, Yu OHY, Renoux C, Bitton A, et al. Dipeptidyl peptidase-4 inhibitors and incidence of inflammatory bowel disease among patients with type 2 diabetes: population based cohort study. BMJ. 2018;360:k872.
143. Moran GW, O'Neill C, Padfield P, McLaughlin JT. Dipeptidyl peptidase-4 expression is reduced in Crohn's disease. Regul Pept. 2012;177(1–3):40–5.
144. Gross JL, de Azevedo MJ, Silveiro SP, Canani LH, Caramori ML, Zelmanovitz T. Diabetic nephropathy: diagnosis, prevention, and treatment. Diabetes Care. 2005;28(1):164–76.
145. International Diabetes Foundation. Care and prevention. Diabetes and the kidneys https://www.idf.org/our-activities/care-prevention/diabetes-and-the-kidney.html. Accessed 28 March 2019.
146. Fujii Y, Abe M, Higuchi T, Mizuno M, Suzuki H, Matsumoto S, et al. The dipeptidyl peptidase-4 inhibitor alogliptin improves glycemic control in type 2 diabetic patients undergoing hemodialysis. Expert Opin Pharmacother. 2013;14(3):259–67.
147. Nakamura Y, Inagaki M, Shimizu T, Fujita K, Inoue M, Gotoh H, et al. Long-term effects of alogliptin benzoate in hemodialysis patients with diabetes: a 2-year study. Nephron Clin Pract. 2013;123(1–2):46–51.
148. Sakai Y, Suzuki A, Mugishima K, Sumi Y, Otsuka Y, Otsuka T, et al. Effects of alogliptin in chronic kidney disease patients with type 2 diabetes. Intern Med. 2014;53(3):195–203.
149. Goodchild E, Chowdhury T. Managing diabetes in the presence of renal impairment. Prescriber. 2017;28:24–30.
150. Baig NA, Herrine SK, Rubin R. Liver disease and diabetes mellitus. Clin Lab Med. 2001;21(1):193–207.
151. Tolman KG, Fonseca V, Dalpiaz A, Tan MH. Spectrum of liver disease in type 2 diabetes and management of patients with diabetes and liver disease. Diabetes Care. 2007;30(3):734–43.
152. Mashitani T, Noguchi R, Okura Y, Namisaki T, Mitoro A, Ishii H, et al. Efficacy of alogliptin in preventing non-alcoholic fatty liver disease progression in patients with type 2 diabetes. Biomed Rep. 2016;4(2):183–7.
153. Barbehenn E, Almashat S, Carome M, Wolfe S. Hepatotoxicity of alogliptin. Clin Pharmacokinet. 2014;53(11):1055–6.
154. Raschi E, Poluzzi E, De Ponti F. Comment on: "Pharmacokinetics in patients with chronic liver disease and hepatic safety of incretin-based therapies for the management of type 2 diabetes mellitus". Clin Pharmacokinet. 2015;54(4):447–8.
155. Ayers D, Kanters S, Goldgrub R, Hughes M, Kato R, Kragh N. Network meta-analysis of liraglutide versus dipeptidyl peptidase-4 inhibitors for the treatment of type 2 diabetes in Japanese patients. Curr Med Res Opin. 2017;33(9):1653–61.