Chapter 4

Dipeptidyl peptidase-4 inhibitors

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Introduction

Dipeptidyl peptidase (DPP)-4 inhibitors inhibit the activity of the enzyme responsible for the initial rapid degradation of the incretin hormones, thereby enhancing their antihyperglycemic effects. The first DPP-4 inhibitor to be approved for treatment of type 2 diabetes was sitagliptin in 2006 and there are now eight available: alogliptin, linagliptin, saxagliptin, and vildagliptin, all with relatively broad global availability, and anagliptin, gemigliptin, and teneligliptin with currently more restricted geographical availability. Several other inhibitors are in various stages of clinical development. This review will focus on the five most commonly used inhibitors.

Pharmacokinetics and pharmacodynamics

As a class, DPP-4 inhibitors comprise a group of structurally diverse, orally available small molecules [1]. They all bind reversibly to the DPP-4 enzyme, but whereas alogliptin, linagliptin, and sitagliptin form non-covalent interactions with sites in the catalytic pocket, saxagliptin and vildagliptin bind covalently. Alogliptin, linagliptin and sitagliptin have intrinsically long half-lives; they do not undergo appreciable metabolism and are eliminated slowly, resulting in sustained DPP-4 inhibition and allowing for a once daily dosing regimen (Table 4.1). In contrast, saxagliptin and vildagliptin are metabolized extensively.

Hepatic metabolism of saxagliptin generates an active metabolite which is half as potent as the parent compound. Following administration,

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	Metabolism	Elimination route	Half-life (hours)	DPP-4 inhibition (24-hours post-dose)	Dose*
alogliptin	Limited	Predominantly renal	~ 21	~ 75%	25 mg qd
linagliptin	Limited	Predominantly biliary (< 6% renal)	~ 12 (effective) > 100 (terminal)	> 80%	5 mg qd
saxagliptin	Active metabolite (hepatic via CYP3A4/5)	Metabolism (parent) Renal (parent + metabolite)	~ 2.5 (parent) ~ 3 (metabolite)	~ 70%	5 mg qd
sitagliptin	Limited	Predominantly renal	~ 12.5	> 80%	100 mg qd
vildagliptin	Inactive metabolite (CYP-independent hydrolysis)	Metabolism (parent) Renal (parent + metabolite)	~ 2	< 40% (~80% 12h post-dose)	50 mg bid

Table 4.1 Characteristics of dipeptidyl peptidase-4 (DPP-4) inhibitors. Data taken from [1] and the prescribing information of the individual inhibitors. *Dose may vary in some countries. bid, twice daily; qd, once daily.

approximately one-quarter of the inhibitor circulates as the intact saxagliptin molecule and one-half as the metabolite. Vildagliptin undergoes hydrolysis, forming a pharmacologically inactive metabolite; around one-fifth circulates as the active inhibitor. Consequently, both saxagliptin and vildagliptin have short half-lives (Table 4.1). Nevertheless, DPP-4 activity is inhibited for longer than would be predicted because the inhibitors remain bound to the enzyme until slow hydrolysis breaks the covalent bonds, meaning that saxagliptin can be used once daily and vildagliptin twice daily. Accordingly, despite the differences in half-life, direct comparison reveals that the extent of DPP-4 inhibition obtained with sitagliptin and vildagliptin is comparable (and greater than that achieved with saxagliptin) when the inhibitors are used at their therapeutic doses (once daily for saxagliptin and sitagliptin, twice daily for vildagliptin) [2].

The kidney plays an important role in the elimination of all of the inhibitors, with the exception of linagliptin. Thus, both alogliptin and sitagliptin are predominantly renally eliminated (as the parent

molecules) via mechanisms involving both active secretion as well as glomerular filtration, whereas saxagliptin and vildagliptin are subjected to metabolism, as described above, with subsequent renal clearance. In contrast, linagliptin is mostly protein-bound at its therapeutic dose, which minimizes its renal clearance (to <6%); the main route of elimination is biliary excretion [1].

Efficacy

Although there are some differences in the indications for the individual agents, as a class, DPP-4 inhibitors have been approved for use as monotherapy (for patients in whom metformin is not indicated or not tolerated) and as add-on combination therapy (dual and triple therapy with metformin, sulphonylureas, thiazolidinediones, insulin) if treatment goals are not met with metformin alone. Their efficacy, as monotherapy and in combination with other agents, has now been demonstrated in numerous clinical trials, where they typically result in reductions in HbA1c of 0.6–1.0% (dependent on baseline levels, with reductions of up to ~2% being seen in subjects with elevated HbA1c concentrations). In head-to-head comparisons, the DPP-4 inhibitors generally result in smaller HbA1c reductions in monotherapy compared to metformin but they have consistently been demonstrated to be equivalent to sulphonylureas and thiazolidinediones, particularly when used as add-on therapy to metformin (Figure 4.1) [3]. However, despite their similar glycemic efficacy, the DPP-4 inhibitors are not associated with hypoglycemia and are generally weight neutral, in contrast to the increased risk of hypoglycemia, which is characteristically seen with the sulphonylureas, and the weight gain associated with both sulphonylureas and thiazolidinediones [3].

Dipeptidyl peptidase-4 inhibitors monotherapy

While metformin will still be the preferred option for most patients, there is an increasing place for DPP-4 inhibitors to be used in monotherapy when metformin cannot be used. While their efficacy is similar to that of other agents which might be used in this situation, their tolerability/side effect profile is generally superior. Thus, in cases where monotherapy with metformin is not a suitable option, the glucose-dependent mechanism of

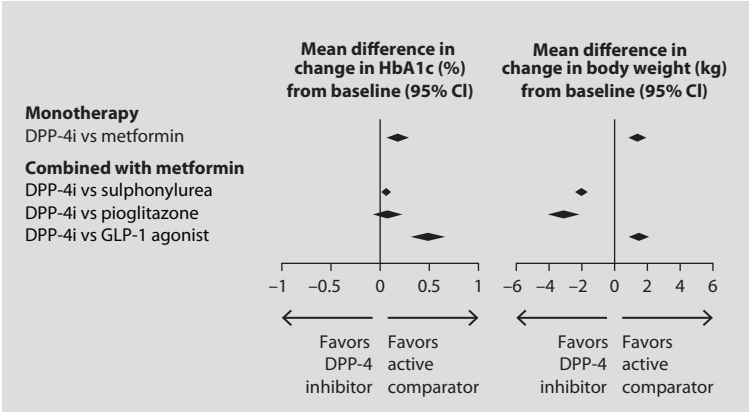

Figure 4.1 Meta-analysis showing glycated hemoglobin (HbA1c)-lowering efficacy and body weight effects of dipeptidyl peptidase inhibitors (DPP-4i) as monotherapy compared with metformin or as add-on therapy to metformin when compared with other commonly used antihyperglycemia agents combined with metformin. Based on data published from Phase III clinical trials of ≥16 weeks duration. Data are shown as mean difference between DPP-4 inhibitors and comparators in the change from baseline (± 95% confidence intervals [CI]). GLP-1, glucagon-like peptide. Figure modified with permission from Karagiannis et al [3] ©BMJ.

action associated with DPP-4 inhibitors may favor their use, particularly in patients where hypoglycemia should be avoided (eg, drivers of goods vehicles, operators of heavy machinery), in the elderly, and in those at higher risk from hypoglycemia due to comorbidities (eg, kidney disease).

Combination therapy

Combination with metformin

DPP-4 inhibitors are positioned as second-line agents in many therapeutic guidelines, including the American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) position statement [4] and the American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) diabetes algorithms [5,6]. They are commonly used in addition to ongoing metformin therapy if therapeutic targets are not attained. Fixed-dose combinations with metformin are now available with all of the individual inhibitors, giving the option of a twice-daily dosing regimen (when combined with immediate-release metformin), or once daily use (when combined with the extended-release metformin formulation). The combination of

metformin with a DPP-4 inhibitor has its merits because it effectively targets the underlying pathology of type 2 diabetes, with metformin improving insulin resistance and directly reducing hepatic glucose output, while the DPP-4 inhibitors address islet dysfunction (and indirectly, endogenous glucose production) via insulinotropic and glucagonostatic effects mediated through GLP-1.

However, they do this without increasing the risk of hypoglycemia or weight gain. Indeed, the AACE consensus statement positions DPP-4 inhibitors ahead of the sulphonylureas because of their lower hypoglycemia risk and the absence of weight gain [5,6]. The metformin/DPP-4 inhibitor combination gives rise to greater HbA1c lowering than when either agent is used alone and, intriguingly, is associated with a reduced incidence of gastrointestinal side effects than when metformin is used as monotherapy [7]; the mechanism behind this effect has yet to be elucidated. Because of its greater efficacy compared to metformin monotherapy, initial combination therapy including a DPP-4 inhibitor is also recommended in patients with elevated HbA1c levels at diagnosis in some guidelines (eg, AACE/ACE) [5,6]. Indeed, when baseline HbA1c levels are >10%, reductions in HbA1c of >3% can be achieved with initial combination therapy, compared to ~2.5% when therapy is initiated with metformin alone [8,9].

Combination with sulphonylurea

The use of DPP-4 inhibitors together with sulphonylureas has also been approved as dual therapy or as part of triple therapy in combination with metformin. While the combination gives additional glycemic efficacy, the risk of hypoglycemia is increased in comparison to combinations not including a sulphonylurea. Thus, although DPP-4 inhibitors have a glucose-dependent mechanism of action (ie, insulin secretion is stimulated and glucagon secretion suppressed only when glucose levels rise above fasting levels), which minimizes the risk of hypoglycemia; this glucose-dependency is uncoupled in the presence of the sulphonylurea [10]. Accordingly, a reduction in the sulphonylurea dose is recommended when used concomitantly with a DPP-4 inhibitor.

Combination with insulin

Although perhaps not initially considered an obvious combination, the use of DPP-4 inhibitors together with insulin has been shown to be of benefit and is increasingly being used. A number of studies have examined the effect of adding a DPP-4 inhibitor in patients inadequately treated with insulin, showing that additional glycemic control can be obtained. While some studies reported a minor increase in hypoglycemia following the addition of the DPP-4 inhibitor [11], this was attributed to the study design (change in the insulin dose was not permitted unless hypoglycemia occurred); in studies where the insulin dose could be titrated, no such increase in hypoglycemia was noted [12]. This combination is associated with an insulin-sparing effect, and improvements in glycemic control can be obtained with smaller increments in insulin dosage following the addition of a DPP-4 inhibitor to insulin in placebo-controlled studies [13].

In studies designed to more closely mimic real world settings, the effect of intensification of insulin therapy has been compared against adding a DPP-4 inhibitor to ongoing therapy. These studies showed that not only could glycemic control be improved despite the lower insulin dose when a DPP-4 inhibitor was added, but the incidence of hypoglycemia was also reduced [14]. Beneficial effects are also seen when insulin is added to an ongoing regimen, which includes a DPP-4 inhibitor. Thus, in subjects inadequately treated with metformin and a DPP-4 inhibitor, the addition of insulin glargine resulted in additional HbA1c reductions without unduly increasing the risk of hypoglycemia or weight gain [15].

Use in specific patient populations

Renal impairment

All DPP-4 inhibitors can be used in patients with reduced renal function (Table 4.2), although once creatinine clearance declines below 50 mL/min, dose adjustment is required for those inhibitors with a renal route of elimination (alogliptin, saxagliptin, sitagliptin, vildagliptin). This is not for safety reasons, but rather to compensate for the increase in exposure which occurs once renal function declines [1]. Accordingly, for alogliptin and sitagliptin (which depend predominantly on the kidneys for their elimination), doses are reduced by one-half (moderate renal

impairment) and one-quarter (severe renal impairment, including end-stage renal disease and dialysis), whereas for saxagliptin and vildagliptin (which undergo metabolism as well as renal elimination), a single dose reduction is sufficient (Table 4.2). Renal function should be monitored to allow appropriate dose choice, although this is not required for linagliptin because of its primarily non-renal route of elimination. However, given the wide therapeutic window, it is doubtful that any drug accumulation would lead to unfavorable outcomes if the normal therapeutic doses are inadvertently used in subjects with impaired renal function [16].

The degree of improvement in glycemic control attained with DPP-4 inhibitors in renally impaired subjects, including those on dialysis, is similar to that observed in subjects without kidney disease and, as is also seen in individuals with normal renal function, DPP-4 inhibitors lower HbA1c levels to a comparable extent as other anti-hyperglycemic agents in patients with reduced kidney function [16]. In line with the glucose-dependency of their action, the incidence or severity of hypoglycemia is not increased, an important consideration in this patient group where renal impairment itself is a risk factor for hypoglycemia [16]. This, coupled with their good tolerability and absence of any increase in the incidence or severity of other adverse events makes them an attractive therapeutic option in patients with diabetes and kidney disease, particularly since many other agents may have restricted use or be contraindicated in this population [17].

Hepatic impairment

Generally speaking, reduced liver function is not a contraindication for the use of DPP-4 inhibitors, although experience in patients with severe hepatic impairment is more limited (Table 4.2). Vildagliptin has been associated with mild increases in liver transaminases, although not with any increase in actual hepatic adverse events [18]. Monitoring of liver function is, therefore, recommended prior to initiation of therapy of vildagliptin and its use is not recommended in patients with any degree of hepatic impairment, including pre-treatment elevated liver enzyme levels.

Elderly and vulnerable patients

DPP-4 inhibitors appear particularly well-suited for use in vulnerable patient groups because of their ease of use, low risk of hypoglycemia, and absence of side effects or weight gain. Management of elderly patients with diabetes can be challenging because this group is often characterized by the presence of long-standing diabetes, a high prevalence of comorbidities including an age-related decline in renal function, the use of multiple concomitant drugs, and progressive cognitive impairment. Moreover, given that many of these patients are also frail, the consequences of hypoglycemia (eg, falls resulting in hip fractures) can be more severe and occur with greater frequency.

Data from post-hoc subgroup analyses of Phase III clinical trials, as well as from specific prospective studies in elderly subjects, confirm not only the efficacy of DPP-4 inhibitors in this patient group, but importantly also show them to be well tolerated and without increased risk of hypoglycemia [19]. Along similar lines, the overall good safety profile of the DPP-4 inhibitors makes them a good option for treatment of individuals with psychiatric disorders where a risk of overdose may exist [20].

Safety

To date, the DPP-4 inhibitor class appears to have a good safety profile [21] and early suggestions that they may compromise immune function and be associated with increased risk of infections have not been realized [3]. Numerous pooled safety analyses, meta-analyses, and data-base analyses have generally indicated that the DPP-4 inhibitors are associated with good tolerability and have an adverse event profile, that is similar to that of placebo [22]. However, occasional findings and isolated post-marketing observations have led to some debate over potential safety issues [22].

Acute pancreatitis

Post-marketing reports of acute pancreatitis in some patients taking incretin-based therapies led to warnings about the risk of pancreatitis being included in the prescribing information of all DPP-4 inhibitors (and GLP-1 receptor agonists) [22]; whether or not there is a causal relationship has still not been fully resolved. Animal studies have provided conflicting

Drug	Renal function monitoring	Renal impairment			Liver function monitoring	Hepatic impairment		Use with other drugs†
		Mild (CrCl ≥50 ml/min)	Moderate (CrCl ≥30-<50ml/min)	Severe/ESRD (CrCl <30ml/min)		Mild/ Moderate	Severe	
alogliptin	Yes	Yes	Yes, with dose adjustment (12.5 mg qd)	Yes, with dose adjustment (6.25 mg qd)	No	Yes	NR	–
linagliptin	No	Yes	Yes	Yes	No	Yes	Yes	Efficacy may be reduced if used with CYP3A4 inducer (eg, rifampin)
saxagliptin	Yes	Yes	Yes, with dose adjustment (2.5 mg qd)	Yes, with dose adjustment (2.5 mg qd)*	No	Yes	NR	Dose reduction (2.5mg qd) when used with strong CYP3A4/5 inhibitors (eg, ketoconazole; ritonavir).
sitagliptin	Yes	Yes	Yes, with dose adjustment (50 mg qd)	Yes, with dose adjustment (25 mg qd)	No	Yes	Not studied	–
vildagliptin	Yes	Yes	Yes, with dose adjustment (50 mg qd)	Yes, with dose adjustment (50mg qd)**	Yes	No*	No*	Dose reduction (50mg qd) when used with sulphonylurea

Table 4.2 Prescribing characteristics of commonly used dipeptidyl peptidase-4 (DPP-4) inhibitors. Data taken from prescribing information of the individual inhibitors; precise indications may vary by country). *Including those with transaminase levels ≥3 times upper limit of normal.†Dose reduction of sulphonylurea or insulin may be recommended when used together with a DPP-4 inhibitor. CrCl, creatinine clearance; CYP3A4/5, cytochrome P450, family 3, subfamily A, polypeptide 4/5; ESRD, end-stage renal disease; NR, not recommended. *Not recommended for patients requiring hemodialysis. **Use with caution for patients undergoing hemodialysis.

results: a few have described deleterious histological changes in the exocrine pancreas whereas others have been neutral, or even suggestive of protective actions in models of experimentally-induced pancreatitis [22]. These studies have mostly been carried out in rodents, however, and as such, are not necessarily predictive of the situation in humans. In the clinical trials [22], the incidence of acute pancreatitis has been very low, and pooled safety analyses have not given rise to any signal. Similarly, the majority of retrospective meta-analyses and observational studies have also concluded that there is no increased risk, although there have been one or two isolated reports contradicting this viewpoint [22].

Concern over this potential safety issue led the regulatory authorities in both the US and EU to undertake independent reviews of all the data, with the conclusion being that currently available data do not support a causal association between incretin-based therapies and pancreatitis [23]. A similar viewpoint has been taken by the major diabetes societies (eg, ADA, EASD, International Diabetes Federation), who have issued a joint statement indicating that there is presently no need to modify current treatment recommendations concerning the use of incretin-based therapies [24]. Encouragingly, the rates of acute pancreatitis were low in the three recently completed large cardiovascular safety studies with DPP-4 inhibitors [25–27]. There were, however, small numerical imbalances in the number of events and although these differences were not significant, it cannot be fully dismissed that a minor increase in risk may exisit. A recent pooled analysis (including the first two of these studies, as well as Phase II clinical trials) confirmed the low event rate (1.3 vs 1.2 events per 1,000 patient-years of exposure for DPP-4 inhibitors and comparators, respectively) and the apparent lack of increased risk (Figure 4.2) [28].

Cancer

While toxicology studies, clinical trials, and pooled safety analyses have not given cause for concern (Figure 4.3) [21,22], the question of whether DPP-4 inhibitors may be associated with chronic pancreatitis and increased risk of pancreatic cancer has been raised. This issue has also been thoroughly investigated by the FDA and EMA, as well as by

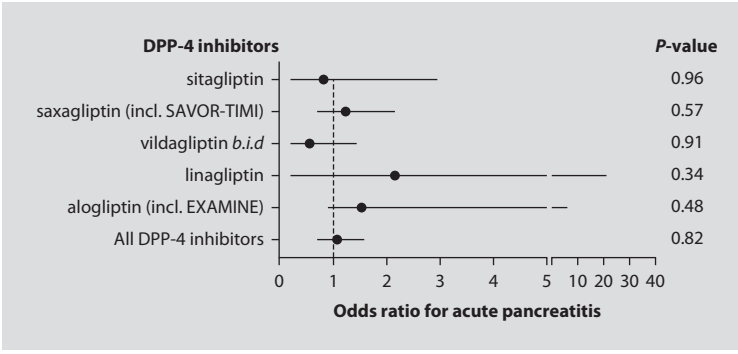

Figure 4.2 Pooled analysis showing risk of acute pancreatitis for DPP-4 inhibitors compared against placebo and active comparators. Based upon data of pancreatitis events from Phase III clinical trials on linagliptin, saxagliptin, sitagliptin, together with data extracted from a published pooled safety analysis (vildagliptin) and two cardiovascular outcome studies (SAVOR-TIMI, EXAMINE). Data are shown as odds ratios (OR) ± 95% confidence intervals. bid, twice a day. Figure modified with permission from Meier and Nauck [28] ©Springer.

the major diabetes societies; no evidence was found to suggest a causal link [23,24]. Additionally, there were no signals for any increase in cancer risk, including pancreatic cancer in any of the three completed cardiovascular safety trials [25–27].

Cardiovascular safety

Pooled safety analyses, as well as retrospective meta-analyses of clinical trials and healthcare providers' databases, have all consistently indicated that DPP-4 inhibitors are not associated with any increase in cardiovascular adverse events, and have even pointed towards a risk reduction [29]. However, these studies are generally of relatively short duration and do not typically include subjects at elevated cardiovascular risk or those with established cardiovascular disease. Large prospective outcome studies of longer duration in high risk populations (EXAMINE: alogliptin [30]; CARMELINA: linagliptin [31]; SAVOR-TIMI: saxagliptin [32]; TECOS: sitagliptin [33], all placebo-controlled; and CAROLINA: linagliptin [34] vs active comparator [glimepiride]) have, therefore, been undertaken to evaluate cardiovascular safety. Vildagliptin is not marketed in the US; hence; there is no large cardiovascular outcome trial with this compound.

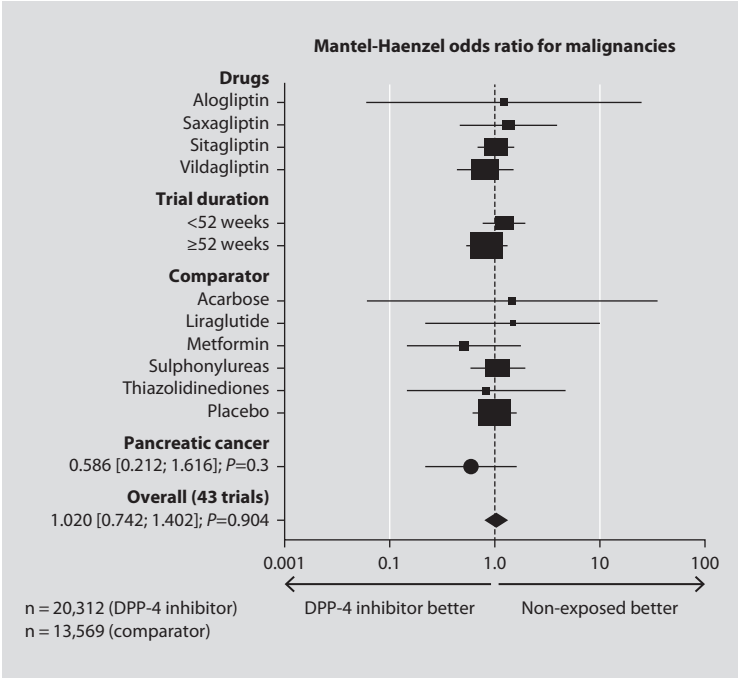

Figure 4.3 Meta-analysis showing risk of malignancies for DPP-4 inhibitors compared against placebo and active comparators. Based on data published from Phase III clinical trials of ≥24 weeks duration. Data are shown as odds ratios ± 95% confidence intervals. Figure adapted with permission from Monami et al [21] ©Informa.

Reassuringly, the first three of these outcome trials to report their findings (EXAMINE [25], SAVOR-TIMI [35], and TECOS [27]) have confirmed that neither alogliptin (5,400 patients with recent acute coronary syndrome; mean follow-up 1.5 years), saxagliptin (16,500 patients with pre-existing cardiovascular disease or multiple risk factors; mean follow-up period of 2.1 years), nor sitagliptin (14,600 patients with established cardiovascular disease; mean follow-up of 3.0 years) was associated with any increase in mortality compared to placebo (hazard ratios for the primary composite cardiovascular outcome [cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, and in EXAMINE, hospitalization for unstable angina] of 0.96, 1.00 and 0.98, respectively). However, neither was there any reduction in cardiovascular risk.

Unexpectedly, a small increase in the rate of hospitalization for heart failure was noted in SAVOR-TIMI (hazard ratio 1.27; 95% CI, 1.07–1.51), with further analysis suggesting that subjects at greatest risk were those with previous heart failure, an estimated glomerular filtration rate ≤60 mL/min, or elevated baseline levels of N-terminal pro B-type natriuretic peptide [35,36]. Notably, however, the increased risk of hospitalization for heart failure in SAVOR-TIMI was not associated with any increase in adverse outcomes and its clinical significance is unknown [35,36]. In post hoc analyses of the results of EXAMINE, despite a small numerical imbalance, the rate of hospitalization for heart failure did not differ significantly between alogliptin and placebo treatment (hazard ratio 1.19; 95% CI, 0.90–1.58), and there was no indication that alogliptin led to any increase in new hospital admissions for heart failure or worsened outcomes for patients with a previous history of heart failure [37]. There was no signal for any increase in the risk of hospitalization for heart failure in TECOS, with the incidence (3.1%) being identical in both arms of the trial (hazard ratio 1.00; 95% CI, 0.83–1.20) [27]. At present, there is no obvious mechanistic explanation for the increased heart failure hospitalization seen in SAVOR-TIMI and it remains uncertain whether there is any causal relationship to DPP-4 inhibition, per se.

Conclusions

DPP-4 inhibitors have been on the market for nearly a decade and have now become an established therapy option for diabetes. Clinical experience has shown them to be effective, both when used in monotherapy or to provide additional glycemic control when used in combination. They can be used at all stages of disease progression, from diagnosis through to patients with long-standing diabetes, and are effective in all patient groups, including those with renal or hepatic impairment. DPP-4 inhibitors probably belong to the class of antihyperglycemic agents which currently has the best studied safety profile, showing them to be well tolerated: they generally do not provoke hypoglycemia, they are weight neutral and, so far, seem to be associated with a broadly benign adverse effect profile. Potential safety concerns over the possibility of a

small increased risk of acute pancreatitis still remain to be resolved; at present, no causal relationships have been established.

Ongoing pharmacovigilance, together with accumulating data from the large outcome trials, will reveal more about the long-term safety of the DPP-4 inhibitors. However, even if any of the potential safety concerns are proven, it should be borne in mind that the absolute risks involved are small, so the clinical relevance of any potential small increase is likely to be limited and should be evaluated for the individual patient based on a risk-benefit judgment. DPP-4 inhibitors, therefore, provide another choice for individualized therapy to help the patient achieve and maintain their glycemic targets which, in the longer term, may help to reduce diabetic complications and improve quality of life.

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