Metabolism Clinical and Experimental 109 (2020) 154295

Contents lists available at ScienceDirect

Metabolism Clinical and Experimental

journal homepage: www.metabolismjournal.com

Articles from the Incretin Hormones and Incretin-based Glucose-lowering Medications Special Issue, Edited by Michael Nauck, Manfredi Rizzo and Christos Mantzoros

The efficacy and safety of dipeptidyl peptidase-4 inhibitors compared to other oral glucose-lowering medications in the treatment of type 2 diabetes

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ARTICLE INFO

Article history:
Received 4 January 2020
Received in revised form 7 June 2020
Accepted 11 June 2020

ABSTRACT

Introduction: The dipeptidyl peptidase-4 inhibitors (DPP-4is), which belong to the class of incretin-based medications, are recommended as second or third-line therapies in guidelines for the management of type 2 diabetes mellitus. They have a favorable drug tolerability and safety profile compared to other glucose-lowering agents.
Objective: This review discusses data concerning the use of DPP-4is and their cardiovascular profile, and gives an updated comparison with the other oral glucose-lowering medications with regards to safety and efficacy. Currently available original studies, abstracts, reviews articles, systematic reviews and meta-analyses were included in the review.
Discussion: DPP4is are moderately efficient in decreasing the HbA1c by an average of 0.5% as monotherapy, and 1.0% in combination therapy with other drugs. They have a good tolerability and safety profile compared to other glucose-lowering drugs. However, there are possible risks pertaining to acute pancreatitis and pancreatic cancer.
Conclusion: Cardiovascular outcome trials thus far have proven the cardiovascular safety for ischemic events in patients treated with sitagliptin, saxagliptin, alogliptin, linagliptin and vildagliptin. Data showing increased rate of hospitalisation in the case of saxagliptin did not seem to be a class effect.

1. Introduction

Inhibitors of dipeptidyl peptidase-4 (DPP-4is), also known as "gliptins", belong to the group of incretin-based medications that act by stimulating the insulin secretion and inhibiting glucagon secretion in a glucose-dependent manner [1]. They improve glycaemic control in monotherapy or combined therapy with other medications without having a large number of adverse effects [2,3]. Glucagon-like peptide-1 (GLP-1) is a gut hormone which is released from L cells in the small intestine in response to digestion and absorption of food, leading to postprandial insulin release. This incretinic effect is reduced in patients with type 2 diabetes mellitus (T2DM), resulting in reduced glucose tolerance [4]. The second incretin hormone, the glucose-dependent insulinotropic polypeptide (GIP), is also degraded by DPP-4 [3,5]. Several clinical studies in the literature demonstrate that DPP-4is could increase the circulating concentrations of intact endogenous GLP-1 and GIP-1 by about 2- to 4- fold [6,7].

DPP-4is are currently recommended as second or third-line therapies in guidelines for the management of T2DM [8–11]. In some cases where DPP-4is may be used as first-line medications, especially when there is metformin intolerance or contra-indication, and a number of metformin/DPP-4i fixed-dose combinations are available [12]. DPP-4is are also recommended as triple therapy with metformin and sodium-glucose co-transporter type 2 (SGLT-2) inhibitors or with metformin and insulin. The current 2020 ADA guidelines on T2DM management strongly support the use of GLP-1 RA or SGLT2i, both with demonstrated CVD benefit, for patients with established ASCVD or indicators of high ASCVD risk (such as those ≥55 years of age with left ventricular hypertrophy or coronary, carotid, or lower-extremity artery stenosis >50%), established heart failure or kidney disease, independently of A1C and considering patient-specific factors [13].

The DPP-4is have good tolerability, few adverse events and an excellent safety profile compared to other glucose-lowering drugs, including the SGLT2 inhibitors [14–19]. There are, however, concerns about the

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https://doi.org/10.1016/j.metabol.2020.154295
0026-0495/

adverse effects of DPP-4isespecially regarding acute pancreatitis (AP) and pancreatic cancer [20–22]. In the important area of cardiovascular (CV) safety and efficacy, saxagliptin showed a raised risk of hospitalisation for heart failure (hHF) in people with diabetes with established cardiovascular disease (CVD) [23]. Last but not least, DPP-4is are associated potentially with arthralgias, and this is very important for diabetic patients in clinical practice [24].

This review aims at discussing the latest data concerning the use of DPP-4is and to make an updated comparison with the other oral glucose-lowering medications, both for safety and efficacy. Currently available original studies, abstracts, reviews articles including systematic reviews and meta-analyses were examined.

2. Effectiveness of DPP-4is on glucose control

Intensive glucose control has been shown to reduce the risk of microvascular and macrovascular complications [25]. It is imperative to achieve the target glycated haemoglobin (HbA1c) from the very beginning of the disease, since the reduction in CV complications has been observed after many years of the primary intervention [26–28]. It was demonstrated that a reduction of 1% in HbA1c was associated with a 21% reduction in death and a 37% reduction in microvascular complications [25].

The target for glucose control is individualised since it depends on various parameters, such as age, the presence of CVD, the duration of the disease, risk for hypoglycemia and socioeconomic factors. Glucose targets are stricter in young patients with the newly diagnosed disease and higher in old-aged subjects with long-standing T2DM, CV complications and potentially shorter life expectancy [29].

DPP-4is have demonstrated moderate glycemic efficacy and reduce HbA1c on average by about 0.6–0.8% [30]. There is little risk of hypoglycemia, since the magnitude of action of DPP-4is depends on the glucose level [31]. Another significant feature of DPP-4is use is the lack of weight gain. Most important classes of antidiabetic drugs, such as sulfonylureas, thiazolidinediones and insulin are associated with weight gain. However, the impact of DPP-4is on weight is not as strong as with GLP-1 receptor agonists (GLP-1RA) (which are associated with weight loss) [32] and the SGLT2 inhibitors [33]. Therefore, the DPP4is stand in the middle between older and newer anti-diabetic agents in their glucose profile: glycemic reduction, with few hypoglycemic episodes and a weight neutral effect [34].

In addition to the HbA1c target, the durability of glycemic control is also an important parameter. Alogliptin is one of the drugs that had a sustained efficacy over a 2-year period when compared to glipizide in patients treated only with metformin [35]. When Saxagliptin was compared with dapagliflozin, dapagliflozin demonstrated greater durability of glucose control, both short-term and long-term analyses [36].

In the trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) study, treatment with sitagliptin was associated with improved glycaemic control and a delayed use of insulin in subjects receiving metformin monotherapy or combination therapy metformin with SU. The subjects treated with sitagliptin achieved lower HbA1c throughout follow-up without an increased risk for severe hypoglycemia, irrespective of baseline therapy. A down-titration of concomitant medications was encouraged in case of severe hypoglycemia, rather than discontinuation of the study drug [37]. Similarly, linagliptin as monotherapy or as add-on to other oral glucose-lowering agents resulted in sustained long-term glycemic control for up to 102 weeks [38]. However, in the CAROLINA (Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Patients With Type 2 Diabetes) CVOT study, there was hardly any difference in HbA1c reduction between glimepiride and linagliptin, indicating that glimepiride's effect was also as sustainable as that of linagliptin. However, subjects on glimepiride experienced significantly more hypoglycemia compared to those on linagliptin, associated with weight gain [39].

3. Safety of DPP-4is

3.1. Hypoglycemia

A significant advantage of DPP-4is is the decreased risk of hypoglycemia. It seems that DPP-4is reduce the risk of hypoglycemia about tenfold when compared to sulphonylureas [40,41] in both randomized clinical trials and observational studies [2,41]. Two specific observational studies performed in Taiwan and Sweden had demonstrated a low risk of severe hypoglycemia and a lower risk of a major CV event and all-cause mortality when they were compared to sulphonylureas [42,43]. Reduced the risk of hypoglycemia is important for all diabetic patients, but more in specific population groups, such as elderly, frail patients and patients with high-risk professions. Another significant meta-analysis of randomized controlled trials (RCTs) with DPP-4is and other oral glucose-lowering medications showed better glycemic control by DPP-4is compared to α-glucosidase inhibitors, including lower risks of gastrointestinal adverse effects [44]. About 39 placebo-controlled trials assessed and provided information on hypoglycemia. Some heterogeneity and increased risk ratios for hypoglycemia were noticed in the linagliptin and sitagliptin subgroups with concomitant use of insulin or a sulphonylurea. However, without concomitant use of insulin or a sulphonylurea, no elevated risk of hypoglycemia was observed for any agent [45].

When the same authors compared sitagliptin with vildagliptin in patients with T2DM and severe renal insufficiency, either without or in combination with a sulphonylurea, thiazolidinediones, or insulin, no difference could be detected [45]. Moreover, DPP-4is combined with metformin or pioglitazone is not correlated with a significant risk of hypoglycemic episodes. Contrariwise, when they are combined with sulphonylureas, there were increased episodes of hypoglycemia compared to sulphonylurea in monotherapy, especially in those T2DM subjects with a slightly increased HbA1c at baseline [46]. In another meta-analysis of randomized controlled trials (RCTs), the combination of DPP-4is with insulin ameliorated the glycemic profile significantly, without an increased risk of weight gain or severe hypoglycemia compared with insulin monotherapy. Nevertheless, when it was compared with the combination alpha-glucosidase inhibitor/insulin, thiazolidinediones/insulin and GLP-1 RAs/insulin treatments, DPP-4is/insulin treatment had equivalent placebo-corrected effects on HbA1c and both fasting and postprandial plasma glucose (FPG and PPG) [47]. Combining DPP-4is with GLP-1RA is not recommended because they have a similar mechanism of action and the effect on HbA1c was not superior [48]; however longer-term studies are needed for confirmation. Finally, when DPP-4 is combined with SLGT-2 inhibitors, they have beneficial effects on glucose control, possibly due to their complementary mechanisms of action [49,50].

3.2. Gastrointestinal and pancreatic safety

A significant advantage of DPP-4is compared to the other class of incretin-based medications is that they do not cause gastrointestinal adverse effects like nausea and vomiting, possibly since they do not slow gastric emptying [51]. In a recent network meta-analysis and systematic review which included 165 RCTs (122,072 T2DM patients), the DPP-4is - alogliptin, linagliptin, sitagliptin and vildagliptin did not increase the rate of gastrointestinal adverse events when compared with placebo, GLP-1RA, metformin and alpha-glucosidase inhibitors (acarbose, voglibose) [52].

Another concern about incretin-based medications is represented by pancreatic events [20,21,52]. The US Food and Drug Administration (FDA) and the European Medicines Agency (EMA), in 2014, could not establish a clear relationship between DPP-4is and pancreatitis or pancreatic cancer. Subsequently, further studies were designed in order to resolve this controversy [53]. Firstly, two systematic reviews of phase 2 and 3 RCTs, with 19,241 and 20,526 patients, respectively, have shown that DPP-4is were not associated with an increased risk of AP.

A meta-analysis of 3 cohort studies, including 1,324,515 subjects demonstrated no significant relationship between DPP-4is use and increased risk of AP [54–56]. On the contrary, the results of a meta-analysis including the three CV outcome trials (CVOT) for saxagliptin (SAVOR TIMI 53), alogliptin (EXAMINE) and sitagliptin (TECOS), demonstrated that the incidence of AP was significantly increased in the gliptin-treated group compared with the placebo group in an average follow-up of 2–3 years; however, the difference in the absolute risk was relatively small (0.13%) [57].

In another recent meta-analysis including 36 double-blind RCTs and 54,664 subjects, there was no significant difference in pancreatic cancer (RR = 0.54, 95% CI = 0.28–1.04) with the use of DPP-4is. However, their use was associated with an increased risk of HF (RR = 1.13, 95% CI = 1.01–1.26) and AP (RR = 1.57, 95% CI = 1.03–2.39) [58]. In an additional analysis in the TECOS study, all suspected cases of AP and pancreatic cancer were studied prospectively for 14,671 participants during the follow-up time of 3 years and were adjudicated blindly. The rates for these events were uncommon and were not significantly different between the sitagliptin and placebo groups, although numerically more sitagliptin-treated participants developed pancreatitis and fewer developed pancreatic cancer. Meta-analysis suggests a small but absolute increased risk for pancreatitis associated with the DPP-4is use [59].

Several observational studies were done in order to clarify the association between DPP-4is and increased risk of AP. In a case-control study using Taiwan's National Health Insurance Research Database, the risk of AP was similar among current and past users of DPP-4is (adjusted odds ratio (aOR) for current users: 1.04; 95% CI [0.89–1.21]; past users: aOR 1.61 [0.93–2.77]) compared with non-users [60]. Similar results were reported in sensitivity analyses when various definitions of "current users" of DPP-4is were used. On the contrary, the adjusted risk of AP was found to be raised significantly in subjects with alcohol-related disease (aOR 5.36 [4.05–7.08]), gallstone disease (aOR 5.89 [4.71–7.35]), dyslipidemia with hypertriglyceridemia (aOR 1.80 [1.26–2.56]), pancreatic disease (a OR 17.29 [10.60–28.19]), and a higher Diabetes Complications Severity Index (DCSI) score (DCSI 3–4: a OR 1.49 [1.21–1.84]; DCSI ≥5: aOR 1.32 [1.01–1.73]) [60]. Therefore, it seems that underlying diseases and as well as the severity of T2DM, but not DPP-4is use, were associated with AP [60].

In another analysis of 114,141 subjects, the risk of AP was not significantly higher in T2DM subjects treated with DPP-4is than in those not treated. Greater interaction effects were seen between gender and age (HR 0.80, 95% confidence interval [CI] 0.64–0.99) and age and DCSI score (HR 0.83, 95% CI: 0.71–0.97) [61]. In subgroup analyses, significant risks of AP were noted in elderly DPP-4is users (aged 65 years and over) with HR 2.39 (95% CI: 1.11–5.15). Among women, the risk of AP was significantly higher among DPP-4is users compared with non-users (HR 2.27, 95% CI: 1.30–3.97) [61].

Other observational studies provide reassuring results for the use of DPP-4is. One of them is a retrospective study in Japan of an extensive medical claims database that compared the incidence of AP among those receiving DPP-4is and those receiving other oral antidiabetic agents. The incidence of AP and hospitalisations for AP were similar between the two groups [62]. Another nationwide population-based case-control study using medical databases in Denmark evaluated 12,868 patients with a first-time hospitalisation for AP between 2005 and 2012 with a population of 128,680 matched control subjects. The findings suggested that the use of incretin-based therapy appeared not to be associated with an increased OR of AP [63]. Finally, another large, international, multicenter, population-based cohort study was reported using combined health records from 7 participating sites in Canada, the United States, and the UK, with an overall cohort of 1,532,513 T2DM subjects initiating the use of antidiabetic drugs. The use of incretin-based drugs was not associated with an increased risk of AP compared with other oral antidiabetic drugs [64].

3.3. Cardiovascular safety

CVD is the leading cause of morbidity and mortality in patients with T2DM [65]. The improvement of blood glucose haemostasis results in amelioration of other CV risk factors. DPP-4is may have positive effects, either by effective glucose control or via direct effects on the CV system. DPP-4 enzyme is widely expressed in the blood vessels, myocardium and myeloid cells.

There are preclinical studies that have demonstrated at a molecular basis that DPP-4is have a clear positive association with CV abnormalities, improving vascular endothelial function and blood pressure. Moreover, DPP-4is, through GLP-1R activation, inhibit the development of atherosclerosis, which is associated with a reduction in intestinal lipoprotein secretion and inflammation [66–69].

However, the direct effects of DPP-4is on the vascular function in patients are controversial. Since the first reports from preclinical studies were promising and along with the high importance of the CV safety of antidiabetic drugs, large prospective CVOT were designed to evaluate the CV safety and effectiveness of DPP-4is in subjects with T2DM and CVD [70]. The first two large published clinical trials were EXAMINE (Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care) with alogliptin, and SAVOR-TIMI 53 (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction) with saxagliptin that has demonstrated that these two DPP-4is are non-inferior to placebo for CVD, but they do not have a CV benefit [23,71]. The CVOT trial for sitagliptin (TECOS), has shown similar findings concerning the primary CV outcome [72]. It is noteworthy that the overall CV safety of DPP-4is is proved even for T2DM subjects with moderate chronic kidney disease (CKD) for saxagliptin and sitagliptin [73,74]. A systematic review and meta-analysis of phase 2–3 trials, including T2DM subjects at a low CV risk and treated with DPP-4is medication, have demonstrated a significantly reduced the incidence of MACE (major adverse cardiac events) [75,76]. In RCTs that evaluated alogliptin, saxagliptin, and sitagliptin, there was no overall increased risk for MACE compared to placebo in T2DM patients at high CV risk or with known CVD, although an increased rate of hHF was associated with saxagliptin treatment [76]. The same findings have been emerged for the risk of stroke, while pooled analysis of smaller phase 2–3 RCTs demonstrated a trend toward benefit against stroke associated with the use of DPP-4is, although non-significant (OR 0.639, 95% CI 0.336–1.212) [77].

The three above mentioned large clinical trials compared the safety of DPP-4is with placebo in T2DM subjects with established CVD. There is a need to compare DPP-4is with other oral antidiabetic agents in patients with lower CV risk in clinical practice. There are meta-analyses in the literature comparing DPP-4is and placebo or another glucose-lowering agent.

Regarding the comparison of DPP-4is with placebo, three meta-analyses evaluated CV outcomes in patients with T2DM and demonstrated a neutral CV effect [58,78,79]. In another meta-analysis, saxagliptin was associated with an increased risk of HF, while sitagliptin was associated with an important decreased risk of all-cause death compared to active controls [80].

Regarding the potential mechanism of CV protection, sitagliptin has been shown to significantly increase the flow-mediated dilation in association with an increase in the circulating CD34+ cells, which is a marker of endothelial progenitor cells, in patients with T2DM, thus implying a potentially positive effect [81]. A similar protective effect of sitagliptin is seen in diabetic patients with coronary artery disease since it improves the endothelial function by reducing the high-sensitivity C-reactive protein levels [67]. In addition to these basic and pathophysiological effects of sitagliptin, another cohort study of a total of 104,756 new diabetic subjects from the Taiwan National Health Insurance Research Database has shown a favorable outcome of sitagliptin on lowering CVD incidence in T2DM subjects [82].

Several studies compared DPP-4is with sulphonylureas. The latter are used commonly in clinical practice but have an uncertain CV safety profile [83]. A meta-analysis of 12 head-to-head comparison clinical studies of DPP-4is and sulphonylureas has shown beneficial effects of DPP-4is, concerning CV events [40]. Another meta-analysis that included both RCTs and cohort studies compared the combination of metformin with DPP-4is versus metformin and sulphonylurea combination. Combination therapy with metformin and DPP-4i significantly decreased the relative risk of nonfatal CV events, CVD mortality, and all-cause mortality, compared with the combination therapy of metformin and sulfonylurea. However, the number of fatal CV events (e.g. HF) was not significantly different between the two groups [84].

A large study including 40,028 Danish diabetic patients without prior myocardial infarction or stroke, demonstrated that the combination of metformin with DPP-4i was statistically associated with an RR of 0.65 (0.54–0.80) for mortality, an RR of 0.57 (0.40–0.80) for CV mortality and an RR of 0.70 (0.57–0.85) for the mixed endpoint (myocardial infarction, stroke and CV death). In other words, the combination of metformin plus DPP-4i was associated with a lower incidence of all-cause mortality, CV mortality, and the 3-point MACE, in comparison with metformin plus sulphonylurea [85]. Similar findings have emerged from the UK Clinical Practice Research Datalink (CPRD), which demonstrated a reduction in MACE and all-cause mortality for subjects under treatment with metformin and DPP-4i versus the use of metformin with sulphonylurea [86,87]. The Korean Health Insurance Database Study showed that DPP-4is combined with metformin decreased CVD risk compared to sulphonylureas added to metformin in T2DM patients [88]. The findings mentioned above are confirmed in a nationwide large study using Taiwan's National Health Insurance Research Database since DPP-4is led to lower risks for MACEs, ischemic stroke, and all-cause death (HR 0.63; 95% CI 0.55–0.72) compared the sulphonylureas and metformin combination, but the risk for myocardial infarction did not change significantly [42]. A nationwide observational study (20,422 patients with T2DM) showed that second-line treatment with DPP-4is as an add-on to metformin was associated with significantly lower risks of mortality and CV events compared with sulphonylureas, whereas basal insulin was associated with a higher risk of mortality [89]. Another cohort study in the UK examined the same combination therapy showing an HR for metformin plus DPP4i of 0.78 (95% CI 0.55; 1.11) for a major adverse cardiac event in comparison with the metformin-sulphonylurea regimen [90]. In multivariate-adjusted analyses of the UK Clinical Practice Research Datalink database, total event rates for MACE for this dual therapy were significantly lower than with sulphonylurea added to metformin, while the most important difference between the two groups of patients was the rate of myocardial infarction [91].

Finally, several studies have evaluated individual DPP-4is. A prospective study examining saxagliptin did not find a higher acute myocardial infarction risk for this treatment compared with patients who use other selected glucose-lowering drugs during the first 5 years after U.S. FDA approval of the drug [92]. Additionally, subjects who initiated therapy with saxagliptin had no increased risk of a major adverse cardiac effect in their clinical follow-up; it is noteworthy that in this study the risk of HF was not included in the primary or secondary endpoints [93]. Similar, another research for saxagliptin has shown that this drug did not increase change the rate of the ischemic events, despite a rise in the hHF [23].

3.4. Heart failure

An important point for the CV efficacy and safety of DPP-4is is their association with HF since their class effect remains controversial. In the SAVOR-TIMI 53 trial, more subjects in the saxagliptin group were hospitalised for HF compared to placebo. This difference was present after 12 months but lost its significance with time (time-varying interaction $p = 0.017$) [23]. However, in the EXAMINE study a non-significant trend toward a higher rate of hHF in alogliptin group compared to the placebo group was observed, in diabetic patients at high CV risk with recent acute coronary syndrome [71]. In contrast to these two clinical studies, TECOS did not show a difference between sitagliptin and placebo group concerning hHF in diabetic patients with CVD [72]. Post-hoc analyses of these studies showed positive results for DPP-4is [92,93]. In SAVOR-TIMI, 53 the patients who were at increased risk for hHF already had established HF, estimated glomerular filtration rate (eGFR) ≤ 60 mL/min and/or elevated levels of NT-proBNP at baseline [94]. In a post hoc analysis of the EXAMINE study, alogliptin had no significant association with composite events, such as CV death and hHF [95]. A subgroup analysis of sitagliptin in TECOS did not reveal increased risk for hHF [96].

Since the association between saxagliptin and increased risk of HF has provoked considerable controversy, an alternative measure to evaluate the risk of hHF was examined [94–96]. When another method for HR evaluation was used in all three extensive clinical studies, no differences in the risk of hHF between alogliptin, saxagliptin or sitagliptin and placebo were reported [97].

An extensive systematic review and meta-analysis of 43 RCTs and 12 observational studies evaluated the possible connection between the use of DPP-4is and the risk of HF or hHF in T2DM subjects. The overall conclusion was that DPP-4is might raise the hHF risk in diabetic subjects, with either established CVD or those with multiple vascular risk factors compared to placebo [98]. Another large meta-analysis including 54 studies with 74,737 T2DM participants, DPP-4is was associated with a non-significant trend for an increased risk of HF compared both to placebo or other anti-diabetic drugs (RR 1.106; 95% CI 0.995–1.228; $p = 0.062$). However, in this meta-analysis and subgroup analysis, only saxagliptin was associated with a significantly increased risk of HF (RR 1.215; 95% CI, 1.028–1.437; $p = 0.022$) [99]. A third meta-analysis of 100 randomized control trials, including EXAMINE, SAVOR-TIMI 53 and TECOS, demonstrated a 13% increase in hHF in the group of DPP-4is-treated subjects compared to control subjects. However, there is no clear correlation between DPP-4is and increased risk of HF [100]. Although the effect of DPP-4is on HF remains controversial, it is suggested that they be used with prudence in T2DM subjects who are at high risk of HF.

The three main large clinical trials included diabetic subjects largely without recognized HF at baseline. More specifically, in SAVOR-TIMI, 53 saxagliptin-treated diabetic subjects with prior HF and/or increased NT-proBNP levels at baseline, were at higher risk for hHF [94]. When compared to placebo, saxagliptin was associated with an increased rate of HF of 1.5% in subjects with previous HF compared with 0.6% in those without prior HF (p for interaction = 0.67). However, in a post hoc analysis of EXAMINE, neither new-onset not worsening HF in subjects with a history of HF were seen after alogliptin use [101].

The Vildagliptin in Ventricular Dysfunction Diabetes (VIVIDD) trial, a small randomized controlled study evaluated the safety of vildagliptin in T2DM patients with established HF [102]. The primary endpoint, which was the mean increase in the ejection fraction at 52 weeks, confirmed noninferiority in the vildagliptin-treated group compared to placebo (4.1 vs 3.5, $p = 0.670$). The vildagliptin-treated subjects showed significant elevations in left ventricular end-diastolic volume (LVEDV, $p = 0.007$), end-systolic volume (LVESV, $p = 0.06$) and stroke volume ($p = 0.002$). Although improvements in LVEDV and LVESV are usually considered to be unfavourable, reflecting decreased systolic function, the primary endpoint demonstrated that vildagliptin did not have an unfavourable effect on left ventricular ejection fraction (LVEF) [102]. More studies are needed concerning the safety of DPP-4is in subjects with HF and left ventricular systolic dysfunction as well as those with HF and preserved LVEF.

3.5. Other safety concerns- bone metabolism, fracture, and arthralgia

Two large meta-analyses evaluated the association between DPP-4is and fracture events. The first included 51 RCTs (36,402 patients) and the

second looked at 62 RCTs with 62,206 patients. There was no significant difference in the risk of fracture between diabetic patients who used DPP-4is and controls (RR 0.95; 95% CI 0.83–1.10) [102,103].

An emerging issues with the use of DPP-4is is the induction of joint pain [104]. A large meta-analysis of 69 studies and 28,006 patients, has demonstrated that vildagliptin had an association with an increased incidence of arthralgia compared with other antidiabetic drugs [105], whereas a more recent systematic review and meta-analysis of a total of 67 RCTs, that included 79,110 subjects showed that DPP-4is, in general, had a clear and statistical significant connection with a slightly raised risk of overall arthralgias (RR 1.13; 95% CI: 1.04–1.22; $p = 0.003$), but a nonsignificant with an increased risk of severe arthralgias (RR 1.44; 95% CI: 0.83–2.51; $p = 0.20$) [106]. However, other cohort studies do not support these findings, as mentioned above [107,108].

4. Special populations

4.1. Patients with CKD

DPP-4is are a desirable option for the treatment of T2DM due to their low risk of hypoglycemia. This issue is even more pertinent in diabetic patients with CKD. An important meta-analysis demonstrated that DPP-4is afforded glucose control similar to other anti-diabetic drugs in T2DM subjects with renal insufficiency, without an increased risk of hypoglycemia [109]. However, in another meta-analysis of 12 RCTs and 4403 patients with CKD and 239 on dialysis, DPP-4is were inferior in glucose control compared with the other antidiabetic drugs, but with a lower risk of hypoglycemia [110].

When linagliptin was added to standard care in subjects with T2DM at high risk of CV events (with advanced coronary artery disease or a history of MI) and albuminuria, or they had impaired kidney function, the incidence of these events did not increase over of 2 years. Specifically, linagliptin was not inferior to placebo for both the primary (MACE) and secondary (composite renal) outcomes. It should be highlighted that the study population included older patients and those with severe CKD, and linagliptin demonstrated a reassuring long-term CV and safety profile, with a reduction in the progression of albuminuria, no increase in hypoglycemia, and no dose adjustment. These data are of particular importance for clinical practice as they support the CV and kidney safety of this drug in T2DM subjects at high CV risk and with kidney disease [111].

4.2. Patients with non-alcoholic fatty liver disease (NAFLD)

Clinical studies with sitagliptin at a dose of 100 mg/day showed no significant reduction in hepatic steatosis or fibrosis in diabetic subjects after 12 or 24 weeks of therapy [112–114]. DPP-4i (sitagliptin) provided glucose control comparable to sulphonylurea (glimepiride) but had a beneficial effect on intrahepatic lipid content, in overweight Japanese patients with diabetes [115]. Last but not least, vildagliptin 50 mg twice a day demonstrated positive effects on NAFLD progression in subjects with diabetes by decreasing hepatic triglyceride and transaminases levels [116].

4.3. Elderly

In the TECOS study [117], 14% of patients were older than 75 years. Sitagliptin treatment did not significantly impact the risk of death (1.05 [0.83–1.32]), severe hypoglycemia (1.03 [0.62–1.71]), and hHF (0.99 [0.65–1.49]).The authors concluded that this treatment was safe for use and could have a positive effect on sarcopenia in this specific age group [118]. Sitagliptin significantly ameliorated glycemic control and was well tolerated in T2DM subjects aged >/= 65 years [119].

4.4. Brief critical discussion

The results of recent meta-analysis showed that addition of DPP4i to insulin was associated with significantly improved glycemic control, no further weight gain and no hypoglycemia in T2DM patients [120]. These benefits of DPP4i were independent of study design, duration, specific drug used, and type and dose of insulin, supporting the use of these drugs as an add-on therapy to insulin in daily clinical practice. As mentioned above, guideline updates based on recent CVOTs, support the use of GLP-1 RA or SGLT2i as add-on to metformin therapy in T2DM patients with established CVD. However, additional treatment options and therapy intensification is required, especially in T2DM patients without established CVD, included both DPP-4i and sulfonylureas [121]. The results of the CAROLINA trial providing important information on the comparative CV safety of a commonly prescribed sulfonylurea and a DPP-4i should be highlighted, since few head-to-head trials have compared the effects of different oral glucose-lowering agents on CV outcomes in T2DM. In addition, guidelines suggest the use of DPP-4i in metformin failure in patients who do not require antidiabetic therapy with proven CV benefit and have increasingly replaced sulfonylureas as second line therapy. Additionally, in later stages of T2DM, DPP-4i are recommended in triple therapy regimens with metformin and SGLT-2i or with metformin and insulin. On the other hand, treatment with DPP-4i should be discontinued when GLP-1RA therapy is initiated. DPP-4i can be used as monotherapy when metformin is not tolerated or is contraindicated. Some studies indicate the importance of initial metformin-DPP-4i combination use in subjects with renal impairment and the elderly [12].

Further, it should be highlighted that the linagliptin study (CARMELINA) included subjects with renal disease as well as prior CV events and confirms its overall CV safety, without any associated HF risk. However, the findings from the studies using sitagliptin and saxagliptin as well as the three DPP4i CVOTs (SAVOR, TECOS, CARMELINA) have highlighted a safety signal regarding risk of pancreatitis.

The long-term safety findings are important because of the initial a concern that DPP-4 inhibition might lead to adverse events. This concern was based on the action of DPP-4 in cleaving biologically active peptides with alanine or proline as the second amino acid from the N-terminal end apart from GLP-1 and GIP, such as neuropeptide Y, substance P, gastrin-releasing peptide, and chemokines [122]. However, as these bioactive peptides are also inactivated by other pathways, the DPP-4 action is not as important for their inactivation as it is for GLP-1 and GIP, which could explain why the risk for adverse events with DPP-4i was not different from the risk with placebo [123]. In addition, potential serious acute safety concerns have been raised regarding AP, respiratory tract infections, and acute kidney injury. However, recent studies have not shown that initiation of a DPP4i is associated with such risks compared to sulfonylureas or other glucose-lowering therapies [124]. Furthermore, the overall risk of infections was not increased compared with placebo, metformin, sulfonylureas, thiazolidinedione and alpha glucosidase inhibitor treatment [125]. Longer follow-up observation is required to confirm their safety. The combination between DPP-4i and SGLT2i has been suggested as a potential early glucose-lowering treatment in T2DM due to their complementary mechanism of action [126]. Clinical studies have also demonstrated good glycemic control in association with low risk for hypoglycemia with this combination [127,128]. Therefore, it appears that DPP4is are a safe choice when used in the glucose-lowering stepped-up algorithm [129]. It should be noted that progression of T2DM is inexorable, and further research is needed to understand its predictors so that personalized diabetes management can be instituted [37].

5. Conclusion

DPP4is are moderately efficacious in decreasing HbA1c by an average of 0.5% as monotherapy, and by 1.0% in combination therapy. The

main advantages of this class are a low risk of hypoglycemia, ease of administration, and good tolerability, making it a suitable for treating older patients or those who have moderate to advanced CKD. Most of the DPP4is have been proven to be safe from the CV standpoint in large CVOTs. Data regarding the increased rate for hHF did not seem to be a class effect, although caution should be exercised in the case of saxagliptin. The association between DPP4is and AP/pancreatic cancer is controversial; the risk for these adverse events appears to be increased significantly in patients with alcohol-related disease, gallstone disease, and hypertriglyceridemia.

Funding

This review was written independently. The authors did not receive any financial or professional help in the preparation of the manuscript.

Author contribution statement

APS, AS, RAS, DN, AMP, AAR all contributed equally to this paper.

CRediT authorship contribution statement

Anca Pantea Stoian: Writing - review & editing.**Alexandros Sachinidis:**Writing - review & editing.**Roxana Adriana Stoica:**Writing - review & editing.**Dragana Nikolic:**Writing - review & editing.**Angelo Maria Patti:**Writing - review & editing.**Ali A. Rizvi:**Writing - review & editing.

Declaration of competing interest

The authors have given talks, attended conferences and participated in several advisory boards and trials sponsored by various pharmaceutical companies. Prof. APS is currently Vice President of Romanian National Diabetes Committee. The authors declare no conflict of interest, financial or otherwise.

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