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VIEWPOINT

Dypeptidylpeptidase-4 inhibitors and the cardiovascular system: How to manage the fil rouge

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Abstract Dypeptidylpeptidase-4 (DPP-4) inhibitors are a therapeutic option for improving glucose control in patients with type 2 diabetes. They can be prescribed at different stages of the natural history of the disease because of their low risk for hypoglycemia and associated weight gain. For all new drugs for diabetes, the US Food and Drug Administration requires the demonstration of the cardiovascular (CV) safety profile through pooled analyses of phase 3 studies or specifically designed trials.

A significant superiority over placebo has been observed with a sodium-dependent glucose transporter-2 inhibitor, empagliflozin, and two glucagon-like peptide-1 receptor agonists, liraglutide and semaglutide, thus suggesting cardioprotective effects for some antidiabetic drugs.

The neutral results of CV safety trials on DPP-4 inhibitors have been disappointing, appearing to contradict the data from pooled analyses and meta-analyses of early trials. The main aim of this review is to find a possible interpretation for the differences between the results of these early trials and the CV safety studies with DPP-4 inhibitors. We conclude that the hypothesis of additional beneficial effects by DPP-4 inhibitors (beyond the improvement of glucose control), on the CV system in low-risk patients in primary prevention, needs to be verified with specifically designed studies.

Introduction

Dypeptidylpeptidase-4 (DPP-4) inhibitors have been available since 2006. In Europe, currently approved DPP-4 inhibitors include sitagliptin, vildagliptin, saxagliptin, alogliptin, and linagliptin. In addition, anagliptin, gemigliptin, teneligliptin, and two once-weekly DPP-4 inhibitors (trelagliptin and omarigliptin) have been approved in some countries outside Europe.

To date, these drugs are predominantly used as second- or third-line agents in type 2 diabetes mellitus (T2DM), typically after metformin failure, including in combination with basal insulin. They are also approved as monotherapy when metformin is contraindicated (e.g. in patients with chronic kidney disease). They are versatile therapeutic options which can be prescribed at different stages in the natural history of T2DM because of their low risk for hypoglycemia and the associated weight gain [1].

After concerns about the long-term cardiovascular (CV) safety of rosiglitazone in 2007 [2], the US Food and Drug Administration (FDA) required a specific demonstration of CV safety for all newly approved drugs for T2DM. New

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molecules can be approved only if the incidence of CV events in phase 2–3 trials is not increased over comparators, with an upper limit of the confidence interval (CI) of the odds ratio (OR) not exceeding 1.8. If the upper CI of OR is between 1.3 and 1.8, a further, specific CV safety trial in high-risk patients must be performed, with the aim of reaching an upper CI of OR for major adverse CV events (MACE) below 1.3 for confirmation of marketing authorization [3].

Cardiovascular outcomes from studies in patients with type 2 diabetes

The primary endpoint of completed CV safety trials with drugs for diabetes has been non-inferiority versus placebo, except in the SAVOR-TIMI 53 (Saxagliptin Assessment of Vascular Outcomes Recorded in patients with diabetes mellitus – Thrombolysis In Myocardial Infarction-53) trial with saxagliptin [4], which had superiority as a co-primary endpoint. However, superiority with respect to placebo in the prevention of MACE has been listed as a secondary endpoint in all other trials. A significant superiority over placebo was observed with empagliflozin [5] and canaglifozin [6] and two glucagon-like peptide-1 receptor agonists liraglutide [7] and semaglutide [8], thus suggesting cardioprotective effects for some antidiabetic drugs. The incidence of MACE was reduced by 14%, 14%, 13%, and 26%with empagliflozin, canagliflozin, liraglutide, and semaglutide, respectively [5–8].

To date, four CV safety trials have been performed with DPP-4 inhibitors. TECOS (Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes) was a non-inferiority trial designed to assess cardiovascular outcomes of sitagliptin in patients with T2DM affected by CV disease [9] and the EXAMINE (Alogliptin after Acute Coronary Syndrome in Patients with Type 2 Diabetes) study similarly evaluated CV events after treatment with alogliptin, in addition to standard care in T2DM, in patients with a recent acute coronary syndrome [10]. SAVOR-TIMI 53 was designed as a phase 4 trial to test superiority of saxagliptin versus placebo in addition to standard therapy [4]. CARMELINA (The Cardiovascular and Renal Microvascular Outcome Study with Linagliptin in Patients with Type 2 Diabetes Mellitus at High Vascular Risk) assessed the effect on MACE of linagliptin, compared to placebo, in patients at high risk of either cardiovascular or kidney disease [11].

In addition, the CAROLINA (Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Patients With Type 2 Diabetes) [12] trial, investigating the effects of linagliptin on CV mortality/morbidity compared with sulfonylureas, is currently ongoing.

The four completed safety trials have demonstrated the safety of DPP-4 inhibitors with respect to the incidence of MACE, but have failed to show any reduction in CV risk [4,9–11]. SAVOR-TIMI 53 showed a small (2.8% versus 1.9%) but significant increase in the incidence of hospital admissions for heart failure with saxagliptin [4]; the TECOS and CARMELINA trials did not show any sign of such a risk with sitagliptin and linagliptin, respectively [9,11], whereas the results of alogliptin in the EXAMINE trial were inconclusive with respect to heart failure [10]. Hospital admissions for heart failure were not among pre-defined endpoints of the EXAMINE study; a post-hoc analysis was performed after the publication of the results of the SAVOR-TIMI 53 study (see Table 1).

In contrast, pooled analyses of patient-level data from phase 2–3 randomized clinical trials with DPP-4 inhibitors have shown a non-significant trend toward a reduction of MACE for each molecule [13–16]. However, the number of events in each of these analyses was too small to draw definitive conclusions. A meta-analysis of trial-level data for all molecules of the class showed a significant and substantial reduction in MACE (- 29%) and all-cause mortality (–40%), suggesting a cardioprotective effect of DPP-4 inhibitors [17]. Results were in line with previous mechanistic studies, suggesting favorable actions of DPP-4 inhibitors on CV risk both through GLP-1 dependent effects on lipid, pressure, glycemic profile together with positive actions on endothelial and myocardial function) and GLP-1 independent mechanisms likely mediated by a chemokine protein, the stromal derived factor-1α (Fig. 1) [18]. Therefore, the results of these first four CV safety trials have been unexpected.

Discussion

The interpretation of differences between results of early trials and CV safety studies with DPP-4 inhibitors is complex. TECOS [9], EXAMINE [10], SAVOR-TIMI 53 [4], and CARMELINA [11] were primarily designed to demonstrate safety rather than efficacy of DPP-4 inhibitors, following the FDA requirement. Therefore, these studies aimed to explore the CV effects of investigational drugs, which occurred independently of glucose control. In fact, investigators were encouraged to adjust glucose-lowering treatments in all patients to maintain good glucose control, minimizing glycated hemoglobin (HbA1c) differences between study arms. Consequently, the use of concurrent glucose-lowering medications was greater in the placebo arm. Despite these protocols, a small difference in HbA1c between study arms was detected. However, the

Table 1 Items for interpretation of CVOTs with DPP4i versus phase III trial metaanalysis.

	CVOTs	Phase 3 trial metaanalysis
Population	high risk for CV events	Relatively younger, with shorter diabetes duration, and lower comorbidity
Aim	Cardiovascular safety	Efficacy in glucose control
Cardiovascular events	Prospectively and blindly adjudicated by an independent panel	Often reported as adverse events, which were not systematically adjudicated or were adjudicated post-hoc

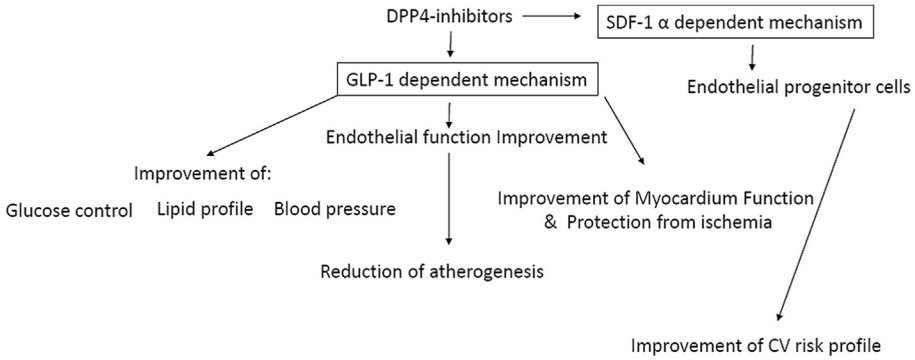

Figure 1 Effects of dipeptidyl peptidase-4 (DPP-4) inhibitors on the cardiovascular (CV) system. GLP-1, glucagon-like peptide-1; SDF1α, stromal derived factor-1α.

improvement of glucose control was smaller than that obtained in phase 3 trials with the same drugs.

The reduction of HbA1c in T2DM has been shown to be associated with a reduction in the incidence of MACE [19]. In trials designed to explore the long-term effects of the improvement of glucose control in T2DM, the reduction of the incidence of MACE obtained with a 0.9% reduction of HbA1c was approximately 10%. It is possible that those trials actually underestimated the CV benefit of improved glucose control. The intensification of diabetes therapy was obtained with drugs (i.e. predominantly sulfonylureas and insulin) that induced an increase in hypoglycemic risk. Hypoglycemia, which determines sympathoadrenergic activation and endothelial dysfunction, has been associated with increased CV mortality [20]. In addition, sulfonylureas have also been associated with an increased risk of stroke [21] and all-cause mortality [22], which may be explained by their actions on myocardial and cerebral ATP-dependent K^+ channels [18].

Based on these considerations, the effect of the reduction of HbA1c on the incidence of MACE could be greater than that previously estimated, which could explain, at least partly, the results of some CV safety trials performed in recent years [23].

It has been suggested that differences in results between early trials and CV safety studies with DPP-4 inhibitors could depend on the duration of treatment: a significant reduction of myocardial infarction risk was detected in shorter but not in longer studies [24]. However, survival curves reported for CV safety trials did not suggest any early short-term reduction in the incidence of MACE [4,8,9]. In addition, longer-term non-CV phase 3 trials showed a reduction in the incidence of myocardial infarction similar to that of shorter studies [25]. This suggests that trial duration is not a real issue for differences in outcome, which must be ascribed to other characteristics of trial design.

A further point is represented by the characteristics of the patients enrolled in different trials. The FDA guidance indicates that CV safety must be demonstrated in patients at high risk for CV adverse events; that is, at high CV risk [3]. Despite differences in inclusion criteria across trials, all available CV safety studies with DPP-4 inhibitors enrolled a majority of patients with prior CV events, with a relevant proportion of subjects with renal impairment, long duration of disease, concomitant treatment, comorbidities, and multiple CV risk factors.

The enrollment of patients at high risk for CV events had the further advantage of limiting sample size and trial duration owing to the higher event rate. For example, with an expected annual event rate of 3%, CV safety (with FDA criteria) can be demonstrated with a sample of 5400 patients and a 5-year follow-up; if the event rate is 2%, the number of patients must be increased to 8000, or the follow-up to 8.8 years [26].

Conversely, patients typically enrolled in phase 2 and early phase 3 trials are usually relatively younger, with shorter diabetes duration, and lower comorbidity. It is possible that the use of DPP-4 inhibitors at an early stage in the natural history of diabetes could exert greater positive effects on the CV system, which are no longer detected in patients with established atherosclerosis.

The FDA specifies that in CV safety trials, CV events must be prospectively and blindly adjudicated by an independent panel, whereas in phase 2 and 3 efficacy trials, CV events were often reported as adverse events, which were not systematically adjudicated or were adjudicated post-hoc. For this reason, the meta-analyses performed on outcomes that are different from the main endpoints of the trials must always be interpreted cautiously, particularly when a formal adjudication of the analyzed events was not performed.

In addition, concurrent treatments for CV prevention could have masked some potential benefits of DPP-4 inhibitors. It is conceivable that a drug capable of reducing the incidence of CV disease does not show any additional effect when combined with a number of other drugs (e.g. statins, β-blockers, angiotensin-converting-enzyme inhibitors or angiotensin receptor blockers, antiplatelet agents, etc.), which may act partly through the same mechanisms. However, significant reductions of cardiovascular events were observed with other drugs (SGLT-2 inhibitors and long-acting GLP-1 receptor agonists), despite a similar management of concomitant risk factors.

Based on all those considerations, the possibility that DPP-4 inhibitors have a favorable effect on the incidence of

CV events in low-risk patients with diabetes in primary prevention cannot be ruled out. Unfortunately, the demonstration of such a benefit, which has been suggested by some epidemiological surveys [27–29], cannot be easily identified with a randomized trial, which, in a low-risk population, would require a very large sample size with a very long follow-up period. On the other hand, observational studies may easily produce biased results. In a comparison between two cohorts, SLGT-2 inhibitors have shown a greater effect on cardiovascular morbidity and mortality than DPP4 inhibitors [30]. In the same cohort and other similar studies in relatively low-risk populations, SGLT-2 inhibitors were associated with reductions in all-cause mortality much wider than those observed in clinical trials [31–33]. However, the reliability of those results has been questioned, both for flaws in study design [33] and for the inherent weakness of observational studies, which cannot rule out prescription bias [34]. The question of the effects of DPP4 inhibitors on cardiovascular events in low-risk populations could well remain without a definitive answer.

In conclusion, available data show that DPP-4 inhibitors are a safe option for lowering blood glucose in patients with diabetes, including those at high CV risk. It is possible that DPP-4 inhibitors have some additional beneficial effects (beyond the improvement of glucose control) on the CV system in low-risk patients in primary prevention; however, this hypothesis would need to be verified with specifically designed studies, which are not likely to be performed.

Conflicts of interest

None.

Disclosure

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