



Effects of Dipeptidyl Peptidase 4 Inhibitors and Sodium-Glucose Linked coTransporter-2 Inhibitors on cardiovascular events in patients with type 2 diabetes mellitus: A meta-analysis



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ABSTRACT

Background: Dipeptidyl Peptidase 4 Inhibitors (DPP4-I) and Sodium-Glucose Linked coTransporter-2 Inhibitors (SGLT2-I) improve glycemic control in patients with type 2 diabetes mellitus (DM). However, only few studies were designed to assess the efficacy and safety of these drugs on cardiovascular (CV) events and mortality. The purpose of the current study was to evaluate the effects of DPP4-I and SGLT2-I on CV events and mortality by meta-analysis.

Methods: Randomized trials enrolling more than 200 patients, comparing DPP4-I or SGLT2-I versus placebo or active treatments in patients with DM, and reporting at least one event among all-cause and CV mortality, stroke, myocardial infarction (MI) and new onset of heart failure (HF), were included.

Results: 157 randomized trials (114 on DPP4-I and 43 on SGLT2-I) enrolling 140,470 patients (107,100 in DPP4-I and 33,370 in SGLT2-I studies) were included in the analysis. Compared to control, treatment with DPP4-I did not affect all-cause (RR: 1.010; 95% CI: 0.935–1.091) and CV (RR: 0.975; CI: 0.887–1.073) mortality as well as risk of MI (RR: 0.915; CI: 0.835–1.002), stroke (RR: 0.933; CI: 0.820–1.062) and HF (RR: 1.083; CI: 0.973–1.205). Treatment with SGLT2-I significantly reduced the risk of all-cause death by 28% (RR: 0.718; CI: 0.613–0.840), CV death by 33% (RR: 0.668; CI: 0.544–0.821), MI by 20% (RR: 0.803; CI: 0.668–0.965) and HF by 35% (RR: 0.652; CI: 0.517–0.823) without effect on stroke (RR: 1.158; CI: 0.912–1.469).

Conclusions: DPP4-I show a safe CV profile as they do not affect mortality and CV events, including HF, in patients with type 2 DM. SGLT2-I are associated with improved CV outcome and survival in DM patients.

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1. Introduction

Patients with type 2 diabetes mellitus (DM) are at increased risk of cardiovascular (CV) microvascular and macrovascular ischemic events and of CV-related mortality [1]. Furthermore, patients with DM are at increased risk of developing heart failure (HF), and in HF patients coexistence of DM substantially worsens prognosis [2]. In fact, in the Framingham study population, diabetic men aged 45 to 74 years had

more than twice the incidence of HF compared to the paired non-diabetic cohort, and diabetic women had a fivefold increased risk [2]. Increased risk of HF in diabetic population is likely multifactorial, and attributable to several factors including accelerated atherogenesis and coronary artery disease, hypertension, diabetic cardiomyopathy and extracellular fluid volume expansion [3].

The observation that glitazones use was associated with unfavorable CV outcome in DM patients prompted in 2012 the major world health regulatory agencies, namely the European Medicines Agency (EMA) and the Food and Drug Administration (FDA), to recommend post-marketing studies on new DM drugs designed to assess their CV safety [4–6].

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Dipeptidyl peptidase-4 inhibitors (DPP4-Is) are a class of oral antidiabetic agents largely used to improve glycemic control in patients with type 2 DM. Following EMA and FDA recommendation, 3 large phase III clinical trials have been conducted to assess the CV safety of these drugs in DM patients at high CV risk. Although none of these studies showed any effect on mortality or stroke or MI, inconsistent effects were observed on the risk of HF. In the SAVOR-TIMI 53 (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus - Thrombolysis in Myocardial Infarction 53) trial [7], saxagliptin, compared to placebo, was associated with a 23% increase in the rate of HF hospitalization in DM patients at high CV risk, whereas in the EXAMINE (Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care) trial [8] Alogliptin was associated with a numerical, albeit non-significant, increase of HF hospitalization in DM patients with recent acute coronary artery syndrome. However, in the more recent TECOS (Trial Evaluating Cardiovascular Outcomes with Sitagliptin) trial [9], no increase in HF hospitalization was observed in DM patients at increased CV risk treated with sitagliptin compared to placebo. Finally, in DM patients with systolic HF, vildagliptin unfavorably affected left ventricular remodeling [10]. Previous meta-analysis, published before the publication of the TECOS trial [9], reported a statistically significant increase of HF hospitalizations in DM patients treated with DPP4-Is [11].

Sodium-Glucose Linked coTransporter-2 Inhibitors (SGLT2-Is) represent the most recent class of oral antidiabetic drugs. The recently released EMPA-REG OUTCOME trial [12] reported a significant favorable effect of empagliflozin, compared to placebo, on the primary end point of CV death, myocardial infarction (MI) and stroke in DM patients with established ischemic CV disease. Notably, a remarkable 32% and 38% reduction of CV and all-cause mortality, respectively, were also reported in the trial. While the mechanisms of these protective effects are largely speculative, it is unclear whether they represent a class-effect or are peculiar for the drug tested in the trial.

Therefore, we performed a comprehensive meta-analysis of randomized clinical trials to assess the effect of DPP4-Is and SGLT2-Is on CV morbidity and mortality, in patients with type 2 DM.

2. Methods

2.1. Search strategy

The study was designed according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement [13]. MEDLINE, Cochrane, ISI Web of Science and SCOPUS databases were searched for articles published until January 2016 combining the following terms [(“Alogliptin” or “Linagliptin” or “saxagliptin” or “sitagliptin” or “vildagliptin” or “Dipeptidyl Peptidase 4 Inhibitors” or “Canagliflozin” or “Dapagliflozin” or “empagliflozin” or “Sodium-Glucose Linked coTransporter-2 Inhibitors” and “randomized”]. Additionally, ClinicalTrials.gov database was searched for the following term: “Alogliptin”, “Linagliptin”, “saxagliptin”, “sitagliptin”, “vildagliptin”, “Dipeptidyl Peptidase 4 Inhibitors”, “Canagliflozin”, “Dapagliflozin”, “empagliflozin”, “Sodium-Glucose Linked coTransporter-2 Inhibitors”. No language restrictions were applied.

2.2. Study selection

Study inclusion criteria were: randomized allocation to DPP4-Is or SGLT2-Is vs. placebo or other antidiabetic drugs; enrollment of more than 200 patients; report of at least one clinical event among all-cause death, CV death, MI, stroke and new onset of HF.

2.3. Data extraction

Articles were screened for fulfillment of inclusion criteria by three independent reviewers (GS, CDA, FDM). Reviewers compared selected

trials and discrepancies were resolved by the senior author (PPF). Corresponding authors were asked to provide full-text articles, if they were not available. From each study, information about methods, year of publication, number of patients in treatment and control arms, duration of follow-up, age, gender, CV risk factors, medications, body mass index (BMI), duration of DM were collected and entered into STATA (version 12.0, Statacorp, College Station, Texas) by one author (GS) and checked by another author (CDA). The outcomes abstracted were all-cause death, CV death, MI, stroke and new onset of HF.

2.4. Data synthesis and analysis

Relative Risks (RR) of the effect of randomized treatments were calculated using the metan routine (STATA Statacorp, version 12.0) to account the probability of events occurring in treatment group versus control group [14–16]. RR and 95% Confidence Interval (CI) for each outcome were calculated separately for each trial, with grouped data using the intention-to-treat principle [17]. Pooled RRs were logarithmically transformed and weighted for the inverse of variance. Overall estimates of effect were calculated with a fixed-effects model or with a random effects model when heterogeneity could not be explained. The assumption of homogeneity between the treatment effects in different trials was tested by Q statistic and further quantified by i^2 statistic. A significant heterogeneity was defined by a $p < 0.05$ at Q statistic; i^2 ranging from 0% to 40% might indicate not important heterogeneity, from 30% to 60% might represent moderate heterogeneity, from 50% to 90% might indicate substantial heterogeneity and from 75% to 100% might represent considerable heterogeneity [18]. The significance level for all outcome and heterogeneity analyses was set at $p \leq 0.05$.

2.5. Sensitivity analysis

To investigate the effects of individual drug on the outcomes, and whether the effects of DPP4-Is or SGLT2-Is differed when compared to placebo or to active treatments, meta-analyses were performed stratifying trials according to the type of DPP4-I or SGLT2-I, and according to the comparator (placebo or active treatment) used.

Random-effects meta-regression analysis was performed with the metareg command [19] (STATA Statacorp, version 14.0) to test the influence of age, gender and BMI on our results.

2.6. Publication bias

To evaluate potential publication bias, a weighted linear regression was used, with the natural log of the odds ratio as the dependent variable and the inverse of the total sample size as the independent variable. This is a modified Macaskill's test, which gives more balanced type I error rates in the tail probability areas in comparison with other publication bias tests [20]. The significance level for the publication bias analysis was set at $p < 0.05$.

3. Results

3.1. Characteristics of included trials (supplemental table S1)

Of 10,815 articles identified in the initial search, 457 were retrieved for more detailed evaluation and, finally, 157 randomized trials [1*–100*, 7–10,12,21] were included in the analyses, 114 on DPP4-Is and 43 on SGLT2-Is (Fig. 1). Of 140,470 patients, a total of 107,100 were enrolled in DPP4-I and 33,370 in SGLT2-I trials. Mean age was 57 ± 5 years in DPP4-I trials and 58 ± 4 years in SGLT2-I trials; 45% of patients enrolled in DPP4-I trials and 44% in SGLT2-I trials were women. Follow-up ranged from 4 to 209 weeks in DPP4-I trials and from 12 to 209 weeks in SGLT2-I trials. To compare baseline CV risk among phase III outcome trials, the yearly rate of all cause and CV mortality, as well

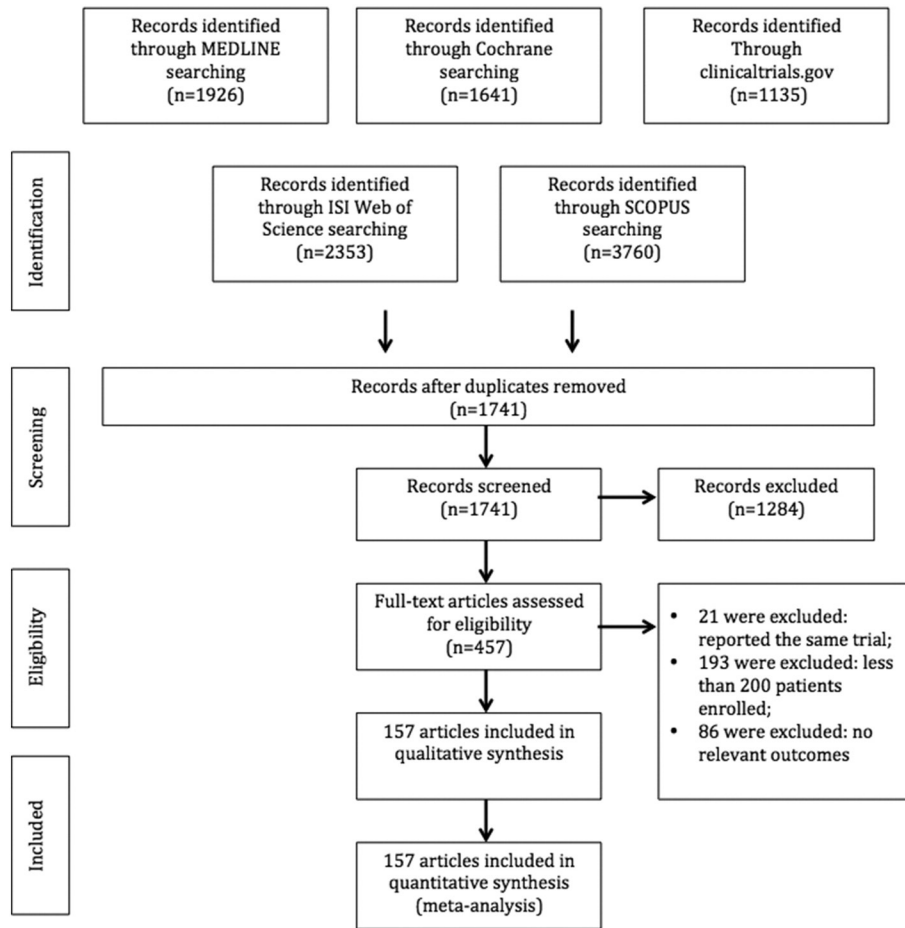


Fig. 1. Meta-analysis flow chart showing the search process.

as of MI, stroke and HF hospitalization in placebo arms are presented in Table 1.

3.2. Outcome analysis (Figs. 2,3)

3.2.1. DPP4-Is

All-cause death occurred in 2.7% of patients treated with DPP4-Is as compared to 3.0% of those enrolled in control arms. Thus, no significant difference in risk of all-cause death was observed between DPP4-Is and control drugs (fixed effect model - RR: 1.010; 95% CI: 0.935 to 1.091; comparison p: 0.806; pQ: 0.996; i²: 0%) (Supplemental Fig. S1). This effect was consistent in trials comparing DPP4-Is vs. placebo (fixed effect model - RR: 1.019; 95% CI: 0.942 to 1.103; comparison p: 0.636; pQ: 0.982; i²: 0%) and in those comparing DPP4-Is vs. active drugs (fixed effect model - RR: 0.836; 95% CI: 0.571 to 1.222; p comparison: 0.354; pQ: 0.354; i²: 0%).

Similarly, CV death occurred in 2.2% of patients randomized to DPP4-Is as compared to 2.5% of those taking control drugs, indicating no

significant difference in risk of CV death (fixed effect model - RR: 0.975; 95% CI: 0.887 to 1.073; p comparison: 0.609; pQ: 0.985; i²: 0%) (Supplemental Fig. S2). The lack of effect of DPP4-Is on CV death was consistently observed in trials comparing DPP4-Is vs. placebo (fixed effect model - RR: 0.979; 95% CI: 0.889 to 1.078; comparison p: 0.666; pQ: 0.922; i²: 0%) and in those comparing DPP4-Is vs. active drugs (fixed effect model - RR: 0.810; 95% CI: 0.467 to 1.404; p comparison: 0.452; pQ: 0.938; i²: 0%).

MI occurred in 1.7% of patients randomized to DPP4-Is vs. 2.3% randomized to control treatments. This corresponded to an 8.5% reduction in risk of MI that approximated statistical significance (fixed effect model - RR: 0.915; 95% CI: 0.835 to 1.002; p comparison: 0.056; pQ: 0.969; i²: 0%) (Supplemental Fig. S3). The reduction in risk of MI was significant in trials comparing DPP4-Is vs. active treatments (RR: 0.548; 95% CI: 0.385 to 0.781; p comparison: 0.001; pQ: 0.998; i²: 0%), but not in those comparing DPP4-Is vs. placebo (fixed effect model - RR: 0.958; 95% CI: 0.872 to 1.054; p comparison: 0.380; pQ: 0.868; i²: 0%), suggesting a neutral effect of DPP4-Is on MI.

Rates of stroke were 1.0% in DPP4-I arm vs. 1.2% in control groups, indicating no statistical difference in risk (fixed effect model - RR: 0.933; 95% CI: 0.820 to 1.062; p comparison: 0.293; pQ: 0.995; i²: 0%) (Supplemental Fig. S4). Similar to what observed for MI, DPP4-Is significantly reduced the risk of stroke compared to active treatments (fixed effect model - RR: 0.561; 95% CI: 0.363 to 0.866; comparison p: 0.009; pQ: 0.987; i²: 0%), whereas DPP4-Is did not affect the rate of stroke compared to placebo (fixed effect model - RR: 0.980; 95% CI: 0.855 to 1.123; p comparison: 0.770; pQ: 0.987; i²: 0%).

Finally, HF occurred in 1.9% of patients randomized both to DPP4-Is and to placebo or active drugs. Thus, DPP4-Is did not affect the risk of HF (fixed effect model - RR: 1.083; 95% CI: 0.973 to 1.205; p comparison:

Table 1

Yearly event rate of all-cause death, cardiovascular death, myocardial infarction, stroke and new onset heart failure in the placebo arms of the major trials included in the meta-analysis.

| Trial | All-cause death | Cardiovascular death | Myocardial infarction | Stroke | New onset heart failure |
|----------------------------|-----------------|----------------------|-----------------------|--------|-------------------------|
| SAVOR-TIMI 53 ⁷ | 2.0% | 1.4% | 1.6% | 0.8% | 1.3% |
| EXAMINE ⁸ | 4.3% | 3.3% | 4.3% | 0.8% | 2.0% |
| TECOS ⁹ | 2.4% | 1.7% | 1.4% | 0.8% | 1.0% |
| EMPA-REG | 2.7% | 1.9% | 1.7% | 1.0% | 1.3% |
| OUTCOME ¹² | | | | | |

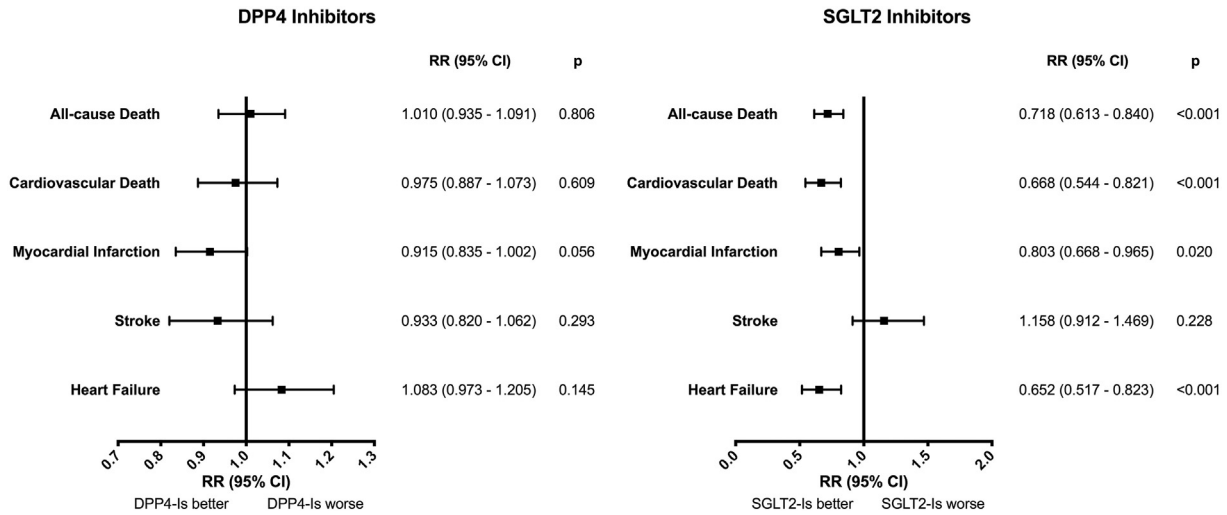


Fig. 2. Forrest plot showing the outcome analyses in Dipeptidyl Peptidase 4 Inhibitors (DPP4-I) and Sodium-Glucose Linked coTransporter-2 Inhibitors (SGLT2-I) meta-analyses.

0.145; pQ: 0.952; i^2 : 0%) (Supplemental Fig. S5). This effect was consistent in trials comparing DPP4-Is vs. placebo (fixed effect model - RR: 1.103; 95% CI: 0.989 to 1.231; comparison p: 0.078; pQ: 0.952; i^2 : 0%) and in those comparing DPP4-Is vs. active drugs (fixed effect model - RR: 0.699; 95% CI: 0.421 to 1.163; p comparison: 0.168; pQ: 0.802; i^2 : 0%), indicating a neutral effect on HF.

3.2.2. SGLT-Is

All-cause death occurred in 1.9% of patients treated with SGLT2-Is compared to 2.6% of those randomized to control arms. This 0.7% absolute risk reduction corresponded to a significant 28.2% RR reduction (fixed effect model - RR: 0.718; 95% CI: 0.613 to 0.840; p comparison <0.001; pQ: 0.942; i^2 : 0%) (Supplemental Fig. S6).

Similarly, CV death occurred in 2.0% of patients assuming SGLT2-Is compared to 2.8% of those taking control drugs, indicating a significant 33.2% RR reduction (fixed effect model - RR: 0.668; 95% CI: 0.544 to 0.821; p comparison <0.001; pQ: 0.501; i^2 : 0%) (Supplemental Fig. S7).

1.7% of patients enrolled to SGLT2-Is vs. 2.1% of those using control treatments experienced MI. Thus, SGLT2-Is significantly reduced the risk of MI by 19.7% compared to controls (fixed effect model - RR: 0.803; 95% CI: 0.668 to 0.965; p comparison: 0.020; pQ: 0.919; i^2 : 0%) (Supplemental Fig. S8).

Rates of stroke were 1.4% in SGLT2-Is arms vs. 1.2% in control groups. Thus, patients treated with SGLT2-Is and those randomized to control

drugs showed no difference in risk of stroke (fixed effect model - RR: 1.158; 95% CI: 0.912 to 1.469; p comparison: 0.228; pQ: 0.943; i^2 : 0%) (Supplemental Fig. S9).

HF occurred in 1.1% of patients randomized to SGLT2-Is vs. 1.6% of those treated with a control drug, representing a significant 34.8% reduction in risk of HF (fixed effect model - RR: 0.652; 95% CI: 0.517 to 0.823; p comparison: <0.001; pQ: 0.978; i^2 : 0%) (Supplemental Fig. S10). 5 out of 43 studies on SGLT2-Is were conducted against placebo, thus preventing a separate analysis on studies using active drug as comparators.

3.3. Sensitivity analysis

When outcome meta-analyses were separately repeated for individual drug, vildagliptin significantly reduced the risk of MI (fixed effect model - RR: 0.427; 95% CI: 0.222 to 0.822; comparison p: 0.011; pQ: 0.802; i^2 : 0%) and stroke (fixed effect model - RR: 0.299; 95% CI: 0.103 to 0.865; comparison p: 0.026; pQ: 0.648; i^2 : 0%) without affecting all-cause and CV death and risk of new HF onset. Linagliptin significantly reduced the risk of stroke (fixed effect model - RR: 0.363; 95% CI: 0.184 to 0.715; comparison p: 0.003; pQ: 0.971; i^2 : 0%), but not the risk of all-cause and CV death, the risk of MI and new HF onset. Saxagliptin significantly increased the risk of new HF onset compared to control (fixed effect model - RR: 1.194; 95% CI: 1.011 to 1.409;

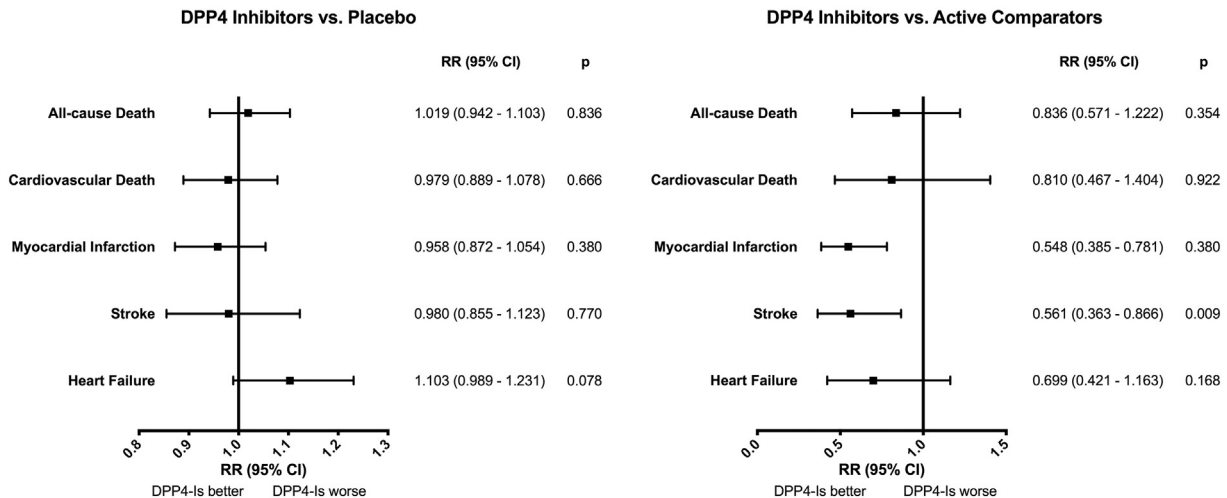


Fig. 3. Forrest plot showing the outcome analyses in Dipeptidyl Peptidase 4 Inhibitors (DPP4-Is) vs. Placebo and in DPP4-Is vs. Active Comparators meta-analyses.

comparison p : 0.037; pQ : 0.217; i^2 : 25%), but not the risk of all-cause and CV death, the risk of MI, stroke and new HF onset. Alogliptin and sitagliptin treatments had no impact on mortality and CV outcomes.

Among SGLT2-Is, empagliflozin significantly reduced the risk of all-cause death (fixed effect model - RR: 0.689; 95% CI: 0.580 to 0.818; comparison p < 0.001; pQ : 0.760; i^2 : 0%), CV death (RR: 0.618; 95% CI: 0.497 to 0.768; comparison p < 0.001; pQ : 0.693; i^2 : 0%) and HF (fixed effect model - RR: 0.656; 95% CI: 0.510 to 0.843; comparison p : 0.001; pQ : 0.693; i^2 : 0%), without a significant effect on the risk of MI and stroke. Canagliflozin significantly reduced the risk of MI (fixed effect model - RR: 0.483; 95% CI: 0.236 to 0.986; comparison p : 0.046; pQ : 0.667; i^2 : 0%), without effect on mortality and CV outcomes. Dapagliflozin did not significantly affect mortality or CV outcomes.

When analyses were repeated excluding EMPA-REG OUTCOME trial [12] that was the largest trial included in the SGLT2-Is meta-analysis, SGLT2-Is still significantly reduced the risk of MI by 49.3% (fixed effect model - RR: 0.607; 95% CI: 0.419 to 0.879; comparison p : 0.008; pQ : 0.963; i^2 : 0%) whereas the reduction in risk of HF was comparable to that observed in the EMPA-REG trial, and approximated statistical significance (fixed effect model - RR: 0.624; 95% CI: 0.376 to 1.036; comparison p : 0.068; pQ : 0.967; i^2 : 0%). No significant effect on the risk of all-cause death (fixed effect model - RR: 0.820; 95% CI: 0.584 to 1.152; p comparison: 0.254; pQ : 0.937; i^2 : 0%), CV death (fixed effect model - RR: 1.383; 95% CI: 0.715 to 2.676; p comparison: 0.335; pQ : 0.718; i^2 : 0%) and stroke (fixed effect model - RR: 1.086; 95% CI: 0.681 to 1.733; p comparison: 0.728; pQ : 0.930; i^2 : 0%) were observed when EMPA-REG trial was removed from the analysis.

At the meta-regression analysis, gender, age and BMI were shown not to be confounders of our outcome analysis (p > 0.05 for all the outcomes in both DPP4-Is and SGLT2-Is analyses).

3.4. Publication bias

A potential publication bias was identified for CV death and MI in the DPP4-I analysis and for MI in for the SGLT2-I analysis.

4. Discussion

The main findings of the present analysis show that DPP4-Is and SGLT2-Is have a safe CV profile and, for SGLT2-Is, a favorable effect on major CV outcomes.

4.1. DPP4-Is and CV outcomes

DPP4-Is exert their effects by inhibiting the degradation of glucagon-like peptide-1 (GLP-1) and, consequently, by stimulating insulin secretion, inhibiting glucagon secretion and enhancing beta-cell mass [22]. The current analysis represents, to our knowledge, the largest and most comprehensive evaluation of the CV profile of DPP4-Is. From this analysis, treatment with DPP4-Is, as a class, resulted safe in patients with type 2 DM and high CV risk, as it did not affect all-cause or CV mortality, or the risk of stroke or HF, showing a trend toward reduction in the risk of MI. Interestingly, when the analysis was performed according to the comparator used (placebo or active treatments), DPP4-Is showed no effects on mortality and CV outcomes when compared to placebo, whereas DPP4-Is compared to active treatments significantly reduced risk of MI by 45% and the risk of stroke by 44%. It can be, therefore, hypothesized, that these drugs have a safer CV profile compared to other anti-diabetic agents that have been shown to or may adversely affect CV outcomes.

Use of DPP4-Is raised some safety concerns following the publication of the SAVOR-TIMI 53 trial [7], that reported a significant 27% increase of HF hospitalizations in type 2 DM patients with history of, or at risk for, CV events receiving saxagliptin and followed-up for a median of 2.1 years, although no differences in all-cause and CV mortality and morbidity (MI, stroke, hospitalization for unstable angina, coronary

revascularization) were observed between saxagliptin and placebo arms. However, it has to be acknowledged that the baseline treatment for DM was not homogeneous between the study groups, and that the higher use of pioglitazone in saxagliptin arm compared to the placebo arm might have contributed to the increased number of HF hospitalizations observed in saxagliptin-users. Nevertheless, a recent study based on assessment of the publicly available US-FDA Adverse Event Reporting System (FAERS) also reported an association between saxagliptin and HF [23]. In addition, data from the VIVID (Vildagliptin in Ventricular Dysfunction Diabetes Trial) trial [10] enrolling 254 patients with left ventricular dysfunction (NYHA classes I to III; left ventricular ejection fraction <35%) and type 2 DM, although not reporting significant differences in HF hospitalization risk, or in change of ejection fraction and natriuretic peptides plasma levels between patients receiving vildagliptin vs. placebo, showed an increase in left ventricular end-diastolic volume, end-systolic volume and stroke volume, relative to baseline, in patients treated with vildagliptin compared to the placebo group.

However, in the EXAMINE trial [8], enrolling 5,380 patients with type 2 DM, with either acute MI or unstable angina requiring hospitalization within the previous 15 to 90 days, who were randomized to Alogliptin or placebo, no significant differences in the primary outcome (CV death, MI and stroke), or in the single components of the primary outcome, all-cause mortality and HF hospitalizations were observed between treatment and placebo groups during a median follow-up of 1.5 years. Similarly, the recently published TECOS trial [9] investigating the CV safety of sitagliptin compared to placebo in 14,671 patients with established CV disease, and with a glycated hemoglobin level of 6.5 to 8.0% when treated with stable doses of one or two oral antihyperglycemic agents, followed-up for median of 3.0 years, reported no differences in the composite primary outcome of CV death, MI, stroke or hospitalization for unstable angina and no difference in the rate of HF hospitalizations.

The CV safety of DPP4-Is is consistent with experimental and clinical data since DPP4 activity has been associated with unfavorable CV effects in human and experimental studies [24,25]. In fact, treatment with sitagliptin in a rat model of HF determined a significant attenuation of HF-related cardiac dysfunction, cardiac remodeling and cardiomyocyte apoptosis and minimized pulmonary congestion [25]. Sitagliptin, compared to placebo, also attenuated renal dysfunction and favorably affected stroke volume, heart rate and the inotropic response to BNP in a pig model of pacing-induced HF [24]. These favorable effects have been attributed to inhibition of BNP degradation by DPP4-Is, preserving beneficial BNP actions [22]. Consistently, in 190 HF patients, dos Santos et al [25] reported an increase of 130% in circulating DPP4 activity of HF patients compared to healthy subjects, and an inverse correlation with left ventricular ejection fraction. In patients with DM, sitagliptin also increased the number of circulating progenitor cells and of plasma level of stromal-cell derived factor 1 [26], whereas in diabetic and non-diabetic patients with coronary artery disease sitagliptin favorably affected recovery of stunning myocardium [27] and slowed progression of carotid intima-media thickness [28]. In our individual drug analysis, no adverse effects on CV ischemic morbidity and on mortality were observed for any individual drug, whereas only saxagliptin resulted associated with a significant increase in HF hospitalizations. Obviously, these observations are hypothesis-generating and should prompt further investigation on individual drug on CV outcomes effects. Meanwhile, they underscore the need for continuing vigilance on individual DPP4-Is, particularly saxagliptin and vildagliptin.

4.2. Effects of SGLT2-is

SGLT2 is located in the early proximal tubule of the kidney where it reabsorbs the majority of filtered glucose. DM enhances renal glucose reabsorption by increasing the tubular glucose load and the expression of SGLT2. Thus, SGLT2-Is reduce hyperglycemia by decreasing renal

glucose reabsorption and, consequently, increasing urinary glucose excretion [29].

Several studies demonstrated the benefits of SGLT2-Is for improving glycemic control in type 2 DM, but the assessment of the effects of these drugs on mortality and CV outcomes is limited to one randomized clinical trial, the EMPA-REG OUTCOME [12]. In this trial, 7,020 patients with established ischemic CV disease were randomized to receive empagliflozin or placebo over a median follow-up of 3.1 years. Treatment with empagliflozin, compared to placebo, was associated with a significant 14% reduction of the primary outcome (composite of all-cause death, non-fatal MI or non-fatal stroke), and with a 32% reduction of all-cause mortality, 38% reduction of CV death and 35% reduction of HF hospitalization that were secondary end-points, without significant effect on MI or stroke.

In the current meta-analysis SGLT2-Is significantly reduced the risk of all-cause death by 28%, CV death by 33%, MI by 20%, HF by 35%, without effect on the risk of stroke. When analyses were repeated excluding EMPA-REG OUTCOME trial [12], that accounted for 70–90% of total weight in the meta-analysis, SGLT2-Is still significantly reduced the risk of MI by 49% whereas the 37% reduction in risk of HF approximated statistical significance and was of the same magnitude of that observed in the EMPA-REG trial. The potential mechanisms that sustain CV effects of SGLT2-Is are largely speculative, and remain to be elucidated. Beyond their effects on glycemic control, SGLT2-Is have also been demonstrated to induce weight loss [21], reduce uric acid plasma levels [30] and blood pressure [31] without affecting heart rate [29], but the magnitude of these effects hardly explain the benefits observed in the EMPA-REG study [32]. Several SGLT2-Is are currently under investigation for treatment of DM that vary in their specificity for SGLT2 vs. SGLT1, ranging from 1:20 for sotagliflozin to 1:2700 for empagliflozin [33]. The incomplete specificity of these drugs for SGLT2 allows concomitant inhibition of SGLT1-dependent glucose absorption at high concentrations in the small bowel and in the late proximal tubule, that is further beneficial for reducing glucose levels. However, SGLT1 are also localized in the cardiac myocyte sarcolemma and their expression has been demonstrated to be two- to three-fold upregulated in DM and in presence of myocardial ischaemia in both humans and mouse models [34]. In patients with severe HF, the functional improvement after implantation of left ventricular assist devices led to a two-fold increase in myocardial SGLT1 mRNA, suggesting that upregulation of SGLT1 may be an adaptive response to injury [34]. Thus, it is uncertain whether these effects may contribute to the clinical benefits observed in clinical studies. Post-hoc subgroup analysis from EMPA-REG will likely provide a direction to interpret the clinical benefit obtained with empagliflozin, while further investigation is required to assess if the beneficial effects of SGLT2-Is observed in this meta-analysis are drug specific (empagliflozin) or represent a class-effect. To this regard, however, it is particularly interesting that the reduction in HF hospitalization risk was consistently observed when EMPA-REG OUTCOME [12] was removed from the analysis, suggesting a class effect of these drugs on HF risk. The ongoing phase III clinical trials CANVAS (CANagliflozin cardioVascular Assessment Study), DECLARE (Dapagliflozin Effect on CardiovascuLAR Events) and NCT01986881 (Ertugliflozin) are investigating the effects of different SGLT2-Is on CV outcomes in patients with DM at high CV risk and will clarify the CV profile of this class of drugs.

4.3. Study limitations and strengths

The current analysis was based on aggregate and not on patient level data. In addition, only 5 studies [7–10,12] included in the meta-analysis were designed to assess the impact of DPP4-Is and SGLT2-Is on CV events and/or mortality. The short follow-up of several trials included in the analysis should also be acknowledged, since optimal evaluation of mortality and CV outcomes may require longer observation. Additionally, our analysis was intended to investigate the CV effects of DPP4-Is and SGLT2-Is as classes of drugs. Therefore, within-class

differences should be interpreted with caution. Yet, our study presents also some relevant strengths, as it represents the largest, most comprehensive and most updated meta-analysis on this topic. In addition, the lack of heterogeneity as well as the detailed sensitivity analysis further reinforce the robustness of our observations.

4.4. Conclusions

DPP4-Is, as a class, show a safe CV profile as they do not affect mortality and CV events, including HF, in patients with type 2 DM. Although mainly driven by a single outcome trial, SGLT2-Is are associated with improved CV outcome and survival in DM patients.

Contributions

GS conceived and designed the research project, collected and analyzed data and wrote the first draft of the manuscript. CDA and FDM collected data. MF, SD, CM, FF, TL, LHL, BT and GMCR reviewed the manuscript. PPF conceived and designed the research project and reviewed and approved the final content of the manuscript. PPF is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Conflicts of interest

None to declare.

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None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.ijcard.2016.06.208>.

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