Effects of Sodium-Glucose Co-Transporter-2 (Sglt2) Inhibitors on Major Cardiovascular Events in Type 2 Diabetic Patients a Meta-Analysis of Randomized Controlled Trials

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Abstract

Background: Sodium-glucose co-transporter-2 inhibitors (SGLT2i) reduce cardiovascular (CV) events in diabetic patients, with a consistent effect on heart failure (HF) related outcomes. However, the effects on ischemic CV events appear less certain, in particular in patients with history of HF. The aim of this meta-analysis is to investigate CV benefits of SGLT2i and to assess the effects in patients with and without established atherosclerotic cardiovascular disease (ASCVD), with and without HF, and with estimated glomerular filtration rate (eGFR) < or ³60 ml/min.

Methods: We searched PubMed, Embase, Cochrane, ISI Web of Science, SCOPUS, and clinicaltrial.gov databases. We performed a systematic review and meta-analysis of randomised, placebo-controlled, cardiovascular outcome trials (CVOT) of SGLT2i in diabetic patients, assessing the effects of SGLT2i on 3-point major adverse cardiac events (MACE) (CV death, non fatal myocardial infarction (MI), non fatal stroke) and composite of HF hospitalization or CV death.

Of 205 articles, 7 CVOTs were included in the meta-analysis.

Results: Compared to placebo, SGLT2i significantly reduced by 10% the risk of 3-point MACE (HR 0.90; p=0.025) and the risk of CV death or HF hospitalization by 24% (Hazard Ratio (HR) 0.76; p<0.001). SGLT2i significantly reduced HF hospitalization by 30% (HR 0.70; p<0.001), with consistent effects in all subgroups analyzed, CV death by 17% (HR 0.83; p=0.035) and all-cause mortality by 18% (HR 0.82; p=0.024). No significant effects were observed on MI and stroke.

Conclusions: SGLT2i significantly reduce CV outcome in diabetic patients. SGLT2i remarkably and consistently reduce HF hospitalization, in patients with and without HF at baseline and independently on the presence of ASCVD.

Background

Type 2 diabetes mellitus (DM) is a major risk factor for atherosclerotic cardiovascular disease (ASCVD) and heart failure (HF) (1). This latter condition may ensue as either preserved or reduced ejection fraction cardiomyopathy, as consequence of ischemic cardiac events and/or associated comorbidities, or representing a peculiar type of diabetic cardiomyopathy, that has been linked to metabolic, neurohormonal and inflammatory effects of DM and insulin resistance on cardiac function (2) (3). Sodium-glucose co-transporter-2 inhibitors (SGLT2i) have shown to reduce major cardiovascular (CV) events and slow renal function impairment in patients with type 2 DM (4). Among beneficial CV effects of SGLT2i, the most clinically relevant appears the remarkable reduction of HF hospitalizations, in patients without history of HF at baseline, that has been consistently shown in all CV outcome trials (CVOTs) (5) (6) (7) (8) (9). More recently, the DAPA-HF trial (10) purposely enrolled patients with HF and reduced ejection fraction, with and without type 2 DM at baseline, to assess the effects of dapagliflozin, compared to placebo, on a primary composite endpoint of CV death and worsening HF. The results of this trial for the first time demonstrated that the benefits of SGLT2i also extend to patients with systolic HF, with or without DM and independently on etiology. Similarly, the EMPEROR-Reduced (11), enrolled patients with HF and reduced ejection fraction, with and without type 2 DM at baseline, documented lower risk of CV death or hospitalization for HF in patients treated with empaglifozin than those in the placebo group, regardless the presence or the absence of DM.

Currently, based on four CVOTs (5) (6) (7) (8) and one meta-analysis (12), ESC/EASD guidelines (13) and ADA guidelines (14) recommend SGLT2i for primary prevention of CV events, including HF, in DM patients at high and very high CV risk. Yet, although the effects of SGLT2i on HF were consistent in clinical trials and registry data (15) (16) for all agents of the class, the effects on CV ischemic events appear less robust. In fact, a significant reduction of 3-points major CV events (MACE) (CV death, myocardial infarction (MI), stroke) was observed in three trials (EMPA-REG OUTCOME (5), CANVAS Program (6) and CREDENCE (7)) but not in two other trials (DECLARE-TIMI 58 (8), VERTIS CV (9). In addition, differently from HF endpoint, effects on MACE were only evident in patients with ASCVD at enrollment.

A previous meta-analysis (12), including 34322 patients enrolled in three CVOTs on SGLT2i, reported a significant 11% reduction of MACE with a statistically significant effect on MI (11%) and CV death (16%), with high heterogeneity among trials for this latter endpoint. Notably, no effects on MACE were observed in patients without ASCVD at baseline. In contrast, a substantial 29% and 36% reduction of HF hospitalizations was observed, respectively, in patients with and without ASCVD, without heterogeneity among trials. More recently, a meta-analysis (17) on 46969 diabetic patients enrolled in five trials documented a significant reduction of major adverse CV events risk in diabetic patients treated with SGLT2-inhibitors. Indeed, this meta-analysis demonstrated that the largest benefit across the class was for an associated reduction in risk for HF hospitalization and kidney outcomes. However, this meta-analysis (17), did not included data of DAPA-HF trial (10) and EMPEROR-Reduced trial (11), that provided yhe most robust data in patients with systolic HF.

Thus, the aim of the present meta-analysis was to investigate CV outcomes of SGLT2i in 7 CVOTs including 49108 diabetic patients and to assess the effects in subgroups of patients with and without established ASCVD, as well in those with and without HF at baseline, and in patients with estimated glomerular filtration rate (eGFR) < or ≥60 ml/min.

Methods

Search strategy and selection criteria

The meta-analysis was conducted according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) reporting guidelines (18). We searched PubMed, Embase, Cochrane, ISI Web of Science, SCOPUS, and clinicaltrial.gov databases to identify all eligible trials with a primary outcome including 3-point MACE and composite of HF hospitalization or CV death, comparing efficacy and safety of SGLT2i to placebo in patients with type 2 DM at high CV risk. The terms used for the research, as suggested by an expert medical librarian (A.P.), were: ‘SGLT2 inhibitors’, ‘sodium-glucose-cotransporter-2

inhibitors, 'gliflozin', 'empagliflozin', 'canagliflozin', 'dapagliflozin', 'ertugliflozin', 'placebo', 'cardiovascular disease', 'atherosclerotic cardiovascular disease', 'MACE', 'major adverse cardiovascular event', 'death', 'diabetes mellitus', 'heart failure', 'randomized controlled trials'. The reference lists of included studies were searched for additional studies. Searches were done up from 01 May 2020 until 30 August 2020.

Study inclusion criteria were Phase 3 randomized and controlled allocation to SGLT2i versus placebo enrolling more than 500 patients, articles published from January 2012 to June 2020, assessing at least one of following major CV outcomes: 3-point MACE, HF hospitalization, CV death, non-fatal myocardial infarction and stroke, all-cause mortality, in patients with type 2 DM. No language, background medication therapy, background CV risk or disease restrictions were applied. We excluded observational non-randomized studies registries, ongoing trials without results, duplicate series, meta-analysis, abstracts and oral communications. Articles were screened for fulfillment of inclusion criteria by four independent reviewers (P.D.N., S.D.A., I.E., L.B.). Reviewers compared selected trials and discrepancies were resolved by four authors (P.G., S.P., A.P., G.D.). Corresponding author was asked to provide full-text articles if not available. Neither ethics approval nor patient consent was required for this analysis. This meta-analysis was previously registered in PROSPERO (CRD42020189257).

Data analysis

The primary efficacy outcomes were: 1) 3-point MACE (composite of CV mortality, non-fatal MI or non-fatal stroke); 2) CV death or HF hospitalization. The secondary efficacy outcomes were:1) CV death 2) non-fatal MI 3) non-fatal stroke 4) HF hospitalization 5) all-cause death. The CANVAS Program (6) consisted of two trials, CANVAS and CANVAS-R, but are presented combined. In this trial the number of events, stratified for drug and placebo, is presented as patients per 1000 patient-years, differently from other studies. So, for this trial we don't reported the number of events. In addition, from DAPA-HF (10) and EMPEROR-Reduced (11), enrolling HF patients with and without type 2 DM, we extracted only data of type 2 DM patients (19) for available endpoints.

In the first step the meta-analysis was performed in the overall population, subsequently patients were stratified by presence of established ASCVD or multiple CV risk factors, previous history of HF, and by renal function (eGFR < 60 or >/= 60 ml/min), in order to explore the effects of SGLT2i in specific subgroups. In case of renal function, when required, effect estimates for subgroups within the same study were merged by use of a fixed-effects model.

When the data were not presented in main study, we extracted data from supplementary analyses and sub-studies of main trials (20), (21), (22), (23), (24), (25). The data of VERTIS CV (9) trial were extracted from presentation of study results, available online, because the article has not yet published.

Safety endpoints of interest consisted in lower limb amputations, bone fractures, diabetic ketoacidosis, genital infections, pancreatitis, severe hypoglycemia, urinary tract infections, and volume depletion.

Statistical heterogeneity between studies was assessed using the Cochrane Q statistic and I^2 statistic. Standard thresholds were considered for judging the percentage of total variability across studies not due to sampling error (I^2): 25% or lower for low heterogeneity, 26–50% for moderate heterogeneity and greater than 50% for high heterogeneity. The random effects model was a-priory selected to obtain pooled estimates of treatment effect (Hazard Ratios - HRs) with the 95% Confidence Intervals (95% CIs) for all efficacy outcomes. The Paule-Mandel method for estimating the between-study variance τ^2 was used. Due to the small number of studies, the Hartung and Knapp (HK) adjustment was employed.

Subgroup analyses for efficacy outcomes to assess effect modification by presence of established ASCVD or multiple CV risk factors, previous history of HF, and by renal function (eGFR < 60 or >/= 60 ml/min) were based on random effects models, applying the Paule-Mandel method and HK adjustment. A random effect model, with HK adjustment, was further applied to obtain pooled estimates of Risk Ratio (RR) with the corresponding 95% C.I. for the main safety outcomes. Due to the small number of studies no attempt to assess publication bias was made. Statistical analysis was performed using the R statistical programming environment, Version 3.5.2 (http://www.r-project.org). Package *meta*, Version 4.11 (26) was used for all the meta-analysis elaborations.

Results

Of 205 articles evaluated for eligibility, 7 CVOTs (EMPA-REG OUTCOME (5), CANVAS Program (6), CREDENCE (7), DECLARE-TIMI 58 (8), VERTIS CV (9), DAPA-HF (10) and EMPEROR-Reduced (11) were eligible and included in the meta-analysis (Figure S1). EMPA-REG OUTCOME (5) and VERTIS CV (9) included only diabetic patients with established ASCVD, whereas CANVAS Program (6), DECLARE-TIMI 58 (8), and CREDENCE (7) included also patients with multiple CV risk factors without established ASCVD. DAPA-HF (10) and EMPEROR-Reduced (11) included only patients with HF and reduced ejection fraction with or without type 2 DM. CREDENCE trial (7) enrolled diabetic patients with chronic kidney disease, defined as an eGFR of 30 to < 90 ml/min/1,73 m^2 BSA and albuminuria. Meta-analysis included 50964 patients. Mean age of patients was 63.5 ± 0.63 years, 27% were female; mean baseline HbA1c was 8.22 ± 1.03. The median study duration was 2.8 (IQR 0.79) years. Detailed characteristics of trials and patients included in the trials are reported, respectively, in Table 1 and Table 2 (Supplementary material).

Table 1
Characteristics of trials included in the meta-analysis.

	EMPA-REG OUTCOME	CANVAS	DECLARE--TIMI 58	CREDENCE	DAPA-HF	VERTIS CV	EMPEROR Reduced
Publication year	2015	2017	2019	2019	2019		2020
Study design	Multicenter, randomized, double-blind, placebo-controlled trial to assess the effect of empagliflozin on CV events in adults with type 2 DM with established CV disease	Multicenter, randomized, double blind, placebo-controlled trial to assess the effect of canagliflozin on CV events in patients with type 2 DM, and established atherosclerotic CV disease or 50 years of age with at least two CV risk factors	Multicenter, randomized, double-blind, placebo-controlled trial to assess the effect of dapagliflozin on CV events in patients with type 2 DM and established atherosclerotic CV disease or multiple risk CV risk factors	Multicenter, randomized, double-blind, placebo-controlled trial to assess the effect of canagliflozin on renal and CV events in patients with type 2 DM and albuminuric chronic kidney disease	Multicenter, randomized, double-blind, placebo-controlled trial to assess efficacy and safety of dapagliflozin in patients with HF and a reduced ejection fraction, regardless of presence of DM	Multicenter, randomized, double-blind, placebo-controlled trial to assess the effect of ertugliflozin on CV events in patients with type 2 DM and established atherosclerotic CV disease	Multicenter, randomized, double-blind, placebo-controlled trial to assess efficacy and safety of empagliflozin in patients with HF and a reduced EF, regardless of presence of DM
Sample size	7020	10142	17160	4401	4744	8246	3730
Inclusion criteria	Type 2 DM; established CV disease. No glucose-lowering agents for at least 12 weeks before randomization and HbA1c of at least 7.0–9.0%, or stable glucose-lowering therapy for at least 12 weeks before randomization and HbA1c level of at least 7.0–10.0%	Type 2 DM; history or high risk of CV disease. HbA1c level ≥ 7.0% to ≤ 10.5% (1) not currently on antihyperglycemic agent or (2) on monotherapy or combination therapy with any approved class of agents	Type 2 DM; high risk for CV events defined as having either established CV disease and/or multiple risk factors. HbA1c level of at least 6.5% but less than 12.0%	Type 2 DM; HbA1c ≥ 6.5% to ≤ 12.0%; eGFR ≥ 30 to < 90 mL/min/1.73 m^2 (as determined using the CKD-EPI equation); Urinary albumin:creatinine ratio > 300 mg/g to ≤ 5000 mg/g	HF with an EF ≤ 40% and New York Heart Association class II, III, or IV symptoms. A plasma level of NT-proBNP of at least 600 pg/ml	Type 2 DM; established CVdisease. HbA1c of at least 7.0–10.5%, stable on antihyperglycemic agents or no background therapy for ≥ 8 weeks prior study participation	HF with an EF ≤ 40% and New York Heart Association class II-IV; HF hospitalization within 12 mounths; a plasma level of NT-proBNP ≥ 600 pg/ml if EF ≤ 30%, ≥ 1000 pg/ml if EF 31–35%, ≥ 2500 pg/ml if EF > 35%
Follow up period (yrs)	3.1	2.6	4.2	2.62	1.52	3.5	1.4
Primary outcomes	MACE-3 (CV death, non-fatal myocardial infarction [excluding silent myocardial infarction], non-fatal stroke)	MACE-3 (CV death, non-fatal myocardial infarction, non-fatal stroke)	MACE-3 (CV death, non-fatal myocardial infarction, non-fatal stroke); composite of CV death or hospitalization for HF	Composite outcome of end-stage kidney disease, doubling of the serum creatinine level, renal death or CV death	Composite of worsening HF or CV death	MACE-3 (CV death, non-fatal myocardial infarction, non-fatal stroke)	Composite of HF hospitalization (first event) and CV death

CV: cardiovascular; DM diabetes mellitus; HbA_{1c}: glicated haemoglobin; HF heart failure; EF: ejection fraction;eGFR: estimated glomerular filtration rate; NT-proBNP N-terminal pro-brain natriuretic peptide; MACE: major cardiovascular events, KCCQ: Kansas City Cardiomyopathy Questionnaire.

	EMPA-REG OUTCOME	CANVAS	DECLARE--TIMI 58	CREDENCE	DAPA-HF	VERTIS CV	EMPEROR Reduced
Secondary outcomes	MACE-4 (CV death, non-fatal myocardial infarction, non-fatal stroke, hospitalization for unstable angina)	Death from any cause; CV death; progression of albuminuria; composite of CV death or HF hospitalization	Renal composite outcome, defined as a sustained decrease of 40% or more in eGFR, new end-stage renal disease, or death from renal or CV causes; death from any cause	Composite of CV death or HF hospitalization; CV death, myocardial infarction or stroke; HF hospitalization; end stage kidney disease, renal death or CV death; dialysis, kidney transplantation or renal death	Composite of CV death or HF hospitalization; total number of HF hospitalizations and CV deaths; the change from baseline to 8 months in the total symptom score KCCQ; a composite of worsening renal function, end-stage renal disease, or renal death; any-cause death	Composite of CV death or HF hospitalization; CV death; renal composite (renal death, doubling of serum creatinine, dialysis/transplant)	All adjudicated hospitalization for HF (first and recurrent events). Rate of the decline in the estimated eGFR during double-blind treatment
Trial registry reference	NCT01131676	NCT01989754	NCT01730534	NCT02065791	NCT03036124	NCT01986881	NCT03057977

CV: cardiovascular; DM diabetes mellitus; HbA_{1c}: glicated haemoglobin; HF heart failure; EF: ejection fraction;eGFR: estimated glomerular filtration rate; NT-proBNP N-terminal pro-brain natriuretic peptide; MACE: major cardiovascular events, KCCQ: Kansas City Cardiomyopathy Questionnaire.

Table 2
Baseline characteristics of patients of included trials.

	EMPA-REG OUTCOME (n = 7020)	CANVAS (n = 10142)	DECLARE-TIMI-58 (n = 17160)	CREDENCE (n = 4401)	DAPA-HF* (n = 2139) *	VERTIS CV (n = 8246)	EMPEROR Reduced (n = 1856)**
Age (yrs), mean (SD)	63.1 (8.7)	63.3 (8.3)	63.9 (6.8)	63 (9.2)	66.5 (9.8)	64.4 (8.05)	NA
Sex (female), n (%)	2005 (28.5)	3631 (35.8)	6332 (36.9)	1492 (33.9)	477 (22)	2477 (30)	NA
BMI (kg/m^2)	30.6 (5.3)	32 (5.9)	32.1 (6.0)	31.3 (6.2)	29.3 (6.0)	32 (5.5)	NA
Diabetes, n (%)	7020 (100)	10142 (100)	17160 (100)	4401 (100)	2139 (100)	8246 (100)	1856 (100)
Hypertension, n (%)	6667 (95)	9125 (90)	NA	4260 (96.8)	NA	NA	NA
Dyslipidemia, n(%)	5684 (81)	NA	NA	NA	NA	NA	NA
Smoke, n (%)	NA	1806 (17.8)	NA	639 (14.5)	NA	NA	NA
HbA_{1c}, mean (SD)	8.075 (0.8)	8.2 (0.9)	8.3 (1.2)	8.3 (1.3)	7.4 (1.5)	8.2 (0.95)	NA
eGFR ($ml/min/1.73^{mq}$), mean (SD)	NA	76.5 (20.5)	85.2 (15.9)	56.2 (18.2)	63.3 (19.3)	75.9 (20,85)	NA
Established ASCVD, n (%)	6964 (99.2)	7324 (72.1)	6974 (40.6)	2220 (50.4)	1326 (62)#	8246 (100)	NA
CV risk factors only, n (%)	56 (0.8)	2818 (27.7)	10186 (59.6)	2181 (49.6)	813 (38)#	0	NA
Previous CCS, n (%)	5308 (75.6)	5721 (56.4)	5658 (32.9)	NA	NA	6279 (76.1)	NA
Previous MI, n (%)	3273 (46.6)	NA	NA	NA	NA	3962 (48)	NA
Previous HF, n(%)	706 (10.05)	1461 (14.4)	1724 (10.0)	652 (14.8)	2139 (100)	1979 (24)	NA
Previous cerebrovascular disease, n (%)	1637 (23.3)	1958 (19.3)	1301 (7)	NA	NA	1875 (22.7)	NA
Previous peripheral arterial disease, n (%)	1461 (20.8)	2113 (20.8)	1025 (6)	NA	NA	1537 (18.6)	NA
Insuline use, n (%)	3387 (48.2)	5095 (50.2)	7013 (40.8)	NA	540 (25.2)	3933 (47.7)	NA
Metformin use, n (%)	5193 (73.9)	7825 (77.2)	14068 (81.9)	NA	1016 (47.6)	6312 (76.5)	NA
Sulfonylurea use, n (%)	3006 (42.8)	4361 (43)	7322 (42.6)	NA	440 (20.5)	3380 (41)	NA
TZD use, n (%)	299 (4.3)	NA	NA	NA	NA	NA	NA
DPP-4 inhibitor use, n (%)	796 (11.3)	1261(12.4)	2888 (16.8)	NA	310 (14.4)	902 (10.9)	NA
GLP-1 RA use, n (%)	196 (2.7)	407 (4)	750 (4.3)	NA	21 (0.9)	263 (3.2)	NA
Median duration of follow up (yrs)	3.1	2.6	4.2	2.62	1.52	3.5	1.4
Participants with a primary outcome	772	1011	1559	585	486	980	465
Primary outcome (HR and 95% CI)	0.86 (0.74–0.99)	0.86 (0.75–0.97)	0.93 (0.84–1.03)	0.70 (0.59–0.82)	0.75 (0.63–0.90)	0.97 (0.85–1.11)	0.72 (0.60–0.87)

NA: not available; BMI: body mass index; HbA_{1c}: glycated haemoglobin; eGFR: estimated glomerular filtration rate; ASCVD atherosclerotic cardiovascular disease; CV: cardiovascular; CCS chronic coronary syndrome; MI myocardial infarction; HF heart failure, TZD: Thiazolidinedione; DPP-4: dipeptidyl peptidase 4; GLP-1 RA: glucagon-like peptide-1 receptor agonist; HR: hazard ratio; CI: confidence interval.

* Data of diabetic patients enrolled in DAPA-HF.

** Data of diabetic patients enrolled in EMPEROR-Reduced.

#These numbers refer to HF of ischemic or non-ischemic/unknown etiology.

Effects of SGLT2i on CV events in the whole population.

Five CVOTs (5) (6) (7) (8) (9) reported the effects on 3-point MACE. SGLT2i significantly reduced by 10% the risk of 3-point MACE compared to placebo (HR 0.90, 95% Confidence Interval (CI) 0.82–0.98; p = 0.025), with low heterogeneity among trials (I^2 = 2%) (Fig. 1A).

The analysis of the effects on the composite of CV death or HF hospitalization, reported in all CVOTs (5) (6) (7) (8) (9) (10) (11), demonstrated a significant 24% risk reduction with SGLT2i (HR 0.76, 95% CI 0.70–0.84; p < 0.001), with a moderate degree of heterogeneity among trials (I^2 = 31%) (Fig. 1B).

Among the single components of the 3-point MACE, the risk of non-fatal MI (Fig. 2A) (HR 0.91, 95%CI 0.81–1.03; p = 0.094) and non-fatal stroke (Fig. 2B) (HR 1.01, 95%CI 0.86–1.18; p = 0.899), reported in four CVOTs (5) (6) (8) (9), were not significantly affected by SGLT2i, with no heterogeneity among trials for both outcomes. HF hospitalizations, reported in 6 CVOTs (5) (6) (7) (8) (9) (10), were significantly reduced by 30% by SGLT2i (HR 0.70, 95%CI 0.64–0.76; p < 0.001), with no heterogeneity among trials (I^2 = 0%) (Fig. 2C). The risk of CV death (Fig. 2D), reported in 6 CVOTs (5) (6) (7) (8) (9) (10), was significantly reduced by SGLT2i (HR 0.83, 95%CI 0.70–0.98; p = 0.035) but with a high degree of heterogeneity among trials (I^2 = 55%). Finally, the risk of all-cause mortality, reported in five CVOTs (5) (6) (7) (8) (10), was significantly reduced by SGLT2i (HR 0.82, 95%CI 0.71–0.96; p = 0.024), although with a high degree of heterogeneity among trials (I^2 = 54%) (Fig. 2E).

Effect of SGLT2 inhibitors on efficacy outcomes in selected subgroups.

Effect of SGLT2i on CV outcomes in patients with and without ASCVD.

This analysis was restricted to 5 CVOTs (5) (6) (7) (8) (9), two of them enrolling only patients with established ASCVD (EMPA-REG OUTCOME (5) and VERTIS CV (9)) and three (6) (7) (8) enrolling patients with established ASCVD or with multiple CV risk factors only. In these latter trials, the percentage of patients with ASCVD varied from 40–72%.

The effect of SGLT2i on the 3-point MACE composite outcome was evident in patients with ASCVD (HR 0.88, 95%CI 0.81–0.96; p = 0.016) without a significant reduction of risk in subjects with multiple CV risk factors only (HR 0.91, 95% CI 0.54–1.51; p = 0.489); however, no significant interaction was found between the two groups (p for interaction = 0.84) (Fig. 3A).

Differently, both in patients with ASCVD and in patients with multiple CV risk factors, SGLT2i showed a favourable effect on the composite of CV death or HF hospitalizations (HR 0.77, 95% CI 0.65–0.90, p = 0.009 vs. HR 0.81, 95% CI 0.69–0.96, p = 0.032, respectively; p for interaction = 0.42) (Fig. 3B). Substantial reduction of HF hospitalizations was consistently observed both in patients with ASCVD and in patients with multiple CV risk factors (HR 0.70, 95% CI 0.62–0.78, p = 0.001 and HR 0.63, 95% CI 0.59–0.67, p = 0.001) with a greater effect in patients with multiple CV risk factors (p for interaction = 0.03) (Fig. 3C). No differences were documented for other secondary endpoints (Figure S2).

Effect of SGLT2i on CV outcomes in patients with and without HF.

Of seven CVOTs included in the meta-analysis (5) (6) (7) (8) (9) (10) (11), two enrolled only patients with HF at baseline (10) (11) (19), whereas in other trials the percentage of HF patients varied from 10–24%. Independently from HF presence at enrollment, no effects of SGLTi were found on 3-point MACE (HR 0.95, 95%CI 0.78–1.16, p = 0.504 in patients with HF at baseline vs. HR 0.89, 95%CI 0.78–1.01, p = 0.060 in non-HF patients; p for interaction = 0.33) (Fig. 4A).

In contrast, the effect of SGLTi on CV death or HF hospitalization was significant in patients with HF at baseline (HR 0.75, 95%CI 0.66–0.86, p = 0.004), whereas in non-HF patients the risk reduction almost reached statistical significance (HR 0.81, 95%CI 0.63–1.04; p = 0.077), with no significant interaction among the two groups (p for interaction = 0.42) (Fig. 4B).

A remarkable significant reduction of HF hospitalizations was observed in both groups (HR 0.71, 95%CI 0.57–0.90, p = 0.019 in patients with HF at baseline vs. HR 0.70, 95%CI 0.50–0.98, p = 0.046 in non-HF patients; p per interaction = 0.42) (Fig. 4C). CV death trended to be reduced in both groups, although the effect did not reach statistical significance (HR 0.81, 95%CI 0.64–1.02, p = 0.065 in patients with HF at baseline vs. HR 0.82, 95%CI 0.42–1.61, p = 0.340 in non-HF patients; p for interaction = 0.93) (Figure S3A).

The effect of SGLT2i on all-cause mortality was significant in patients with HF at baseline (HR 0.79, 95%CI 0.69–0.91; p = 0.012) without a significant reduction of risk in non-HF patients (HR 0.86, 95% CI 0.54–1.36; p = 0.284); no significant interaction was found among the two groups (p for interaction = 0.50) (Figure S3B).

Effect of SGLT2i on CV in patients with eGFR < 60 ml/min/1,73 m^2 BSA and ≥60 ml/min/1,73 m^2 BSA.

The effect of SGLTi on the 3-point MACE composite outcome, reported in four CVOTs (6) (7) (8) (9) was significant for patients with eGFR ≥ 60ml/min/1,73 m^2 (HR 0.93, 95%CI 0.90–0.96; p = 0.006) without a significant reduction of risk in patients with eGFR < 60ml/min/1,73 m^2 (HR 0.86, 95%CI 0.63–1.17; p = 0.211); however, no significant interaction was found among the two groups (p for interaction = 0.42) (Fig. 5A). No effects of SGLTi were found on the on the composite of CV death or HF hospitalization, reported in three CVOTs (7) (8) (9) in both patients with eGFR ≥60 ml/min/1,73 m^2 or eGFR < 60 ml/min/1,73 m^2 (HR 0.85, 95%CI 0.66–1.10, p = 0.110 vs. HR 0.77, 95%CI 0.45–1.33, p = 0.177, respectively; p for interaction = 0.49) (Fig. 5B).

Safety analysis (Figure S4).

Safety analysis showed no significant effect of SGLT2i on amputation (RR 1.1, 95%CI 0.99–1.22), bone fractures (RR 1.26, 95%CI 0.59–2.70), pancreatitis (RR 0.88, 95%CI 0.34–2.29), severe hypoglycemia (RR 0.97, 95%CI 0.45–2.11), urinary tract infections (RR 1.16, 95%CI 0.79–1.71), and volume depletion (RR 1.05, 95%CI 0.98–1.12). In contrast, SGLT2i had a significant effect on genital tract infections (RR 4.35, 95%CI 2.46–7.71) with a high degree of heterogeneity among trials (I^2 = 54%) and on diabetic ketoacidosis (RR 2.25, 95%CI 1.21–4.19).

Discussion

The findings of the current meta-analysis, including 49108 diabetic patients enrolled in seven CVOT, show that SGLT2i significantly reduce the 3-point MACE endpoint (10%), as well the composite endpoint of CV death or HF hospitalization (23%) in patients with type 2 DM.

Among the single components of 3-point MACE, CV death was significantly reduced (17%), confirming previous analysis (12). However, no significant effects were observed for non-fatal MI at variance with a previously reported significant reduction (12). Similar to previous analysis, our findings demonstrate a neutral effect on stroke, and a significant reduction of all-cause mortality (18%). Notably, the favourable effect on MACE was mostly evident in patients with ASCVD with no significant effects in those without.

The second primary endpoint of this meta-analysis was the composite of CV death or HF hospitalization, that was substantially reduced (23%). This effect was consistent in ASCVD patients and in patients with multiple CV risk factors only, in patients with HF at baseline and almost reached statistical significance in those without HF history at baseline.

The separate analysis of HF hospitalization confirmed the substantial favourable effects of SGLT2i, showing a remarkable 30% reduction (HR 0.70, 95%CI 0.64–0.76; $p < 0.001$) without heterogeneity among trials. Notably, the reduction of HF hospitalization among trials ranged from 20–35%, indicating a relevant and consistent clinical benefit. Reduction of HF hospitalization was observed independently on the baseline clinical characteristics and risk profile of patients, as it occurred in all examined subgroups.

The findings of the current analysis help clarify the favourable impact of SGLT2i on clinical outcomes of type 2 DM patients, at various stage of their CV risk profile. In particular, they demonstrate that clinical benefits are mostly driven by the consistent and remarkable effects on HF hospitalizations. In fact, this class of drugs have demonstrated to reduce very substantially the progression from stage A and/or B of HF, according to ACC/AHA guidelines (27), to clinically manifest HF in diabetic patients, thus representing a novel opportunity for primary prevention of HF in this high risk group of patients. In addition, the 30% reduction of HF hospitalization in patients with HF at baseline, together with the 25% reduction of the composite of CV death and HF hospitalization, extend the benefit of SGLT2i to treatment of patients with HF and reduced ejection fraction on top of optimized HF therapy. These effects on HF prevention and therapy are of potentially relevant impact to reduce the escalating clinical and economic burden of HF worldwide.

Insights on the pathogenetic mechanisms of clinical benefit are beyond the scope of the meta-analysis. In fact, several hypotheses have been made to explain CV effects of SGLT2i (28) (29) but no definitive explanations have been reached. Conceivably, the concurrent favourable effect on HF and renal disease likely explain the significant benefit on CV and all-cause mortality observed in the current and previous meta-analysis (30). In contrast, no significant effects are apparent on ischemic non-fatal events, including stroke and MI, that were not significantly reduced in any CVOT.

Use of SGLT2i appear to be generally safe, although a significant increase of genital infections and of ketoacidosis has been observed.

Comparison with previous meta-analysis

Two recent meta-analysis (17, 31) reported the effects of SGLT2i in diabetic and non diabetic patients, with and without HF. McGuire et al. (17) reported the effects of SGLT2i in 46969 patients included in 5 studies, excluding two trials (10, 11) from analysis. On the other hand, Zannad et al. (31) in a meta-analysis, including only these two trials for a total of 3995 diabetic plus HF patients, but not including relevant subgroups of similar patients from other 5 studies that were included in our analysis. Thus, the current study reports the largest number of patients and, in particular, more than twice patients with diabetes and HF.

Limitations

We acknowledge that use of trial rather than patient data is a limitation of meta-analysis. In addition, subgrouping of patients is based on investigator reporting of ASCVD and HF, that may be responsible for misclassification of individual patients. Within the subgroup of patients with HF, we could not make a separate analysis in patients with reduced or not reduced systolic function and therefore the effects of SGLT2i in patients with preserved or mildly reduced ejection fraction remain not adequately investigated. Finally, due to the small number of studies included in this meta-analysis, no attempt was made to formally evaluate potential publication bias.

Conclusions

In summary, our findings further strengthen ESC/EASD (13) and ADA guidelines (14), that recommend SGLT2i in high and very high risk diabetic patients, supporting the benefits of this class of drugs at early stages of diabetic disease. The beneficial effects on HF and mortality should prompt adherence to guidelines and implementation of SGLT2i therapy in clinical practice to reduce the burden of CV disease in type 2 diabetic patients.

Abbreviations

SGLT2: Sodium-Glucose Co-Transporter-2

CV: Cardiovascular

HF: heart failure

ASCVD: atherosclerotic cardiovascular disease

eGFR: estimated glomerular filtration rate

CVOT: cardiovascular outcome trials

MACE: Major adverse cardiac events

MI: myocardial infarction

HR: Hazard Ratio

DM: diabetes mellitus

HK: Hartung and Knapp

RR: Risk Ratio

CI: Confidence Interval

Declarations

Ethics approval and consent to participate:

Neither ethics approval nor patient consent was required for this analysis.

Consent for publication:

NA

Availability of data and materials:

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests:

The authors declare that they have no competing interests" in this section.

Funding:

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Authors' contributions:

PG, SP, MP: conception, design and data analysis. Manuscript writing.

DB: statistical analysis.

AP: database management and manuscript editorial revision

PDN, SDA, IE, LB, GD, AA, GA: article research and screening for fulfillment of inclusion criteria

CM, SD: critical revision of final draft

PPF: conception, design and final manuscript revision.

All authors read and approved the final manuscript.

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Figures

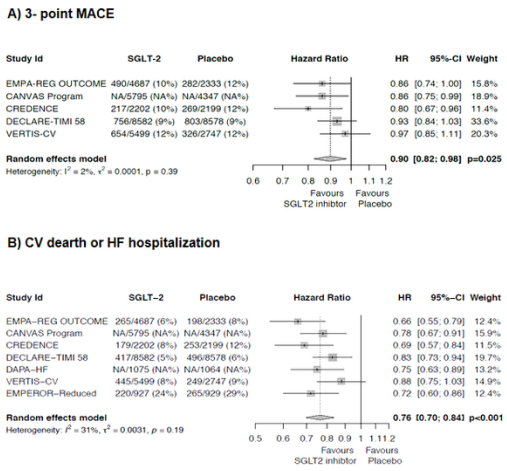

Figure 1

Meta-analysis of SGLT2i trials on 3-point MACE (A) and CV death or HF hospitalization (B). MACE: major adverse cardiovascular events; CV: cardiovascular; MI: myocardial infarction; HF: heart failure.

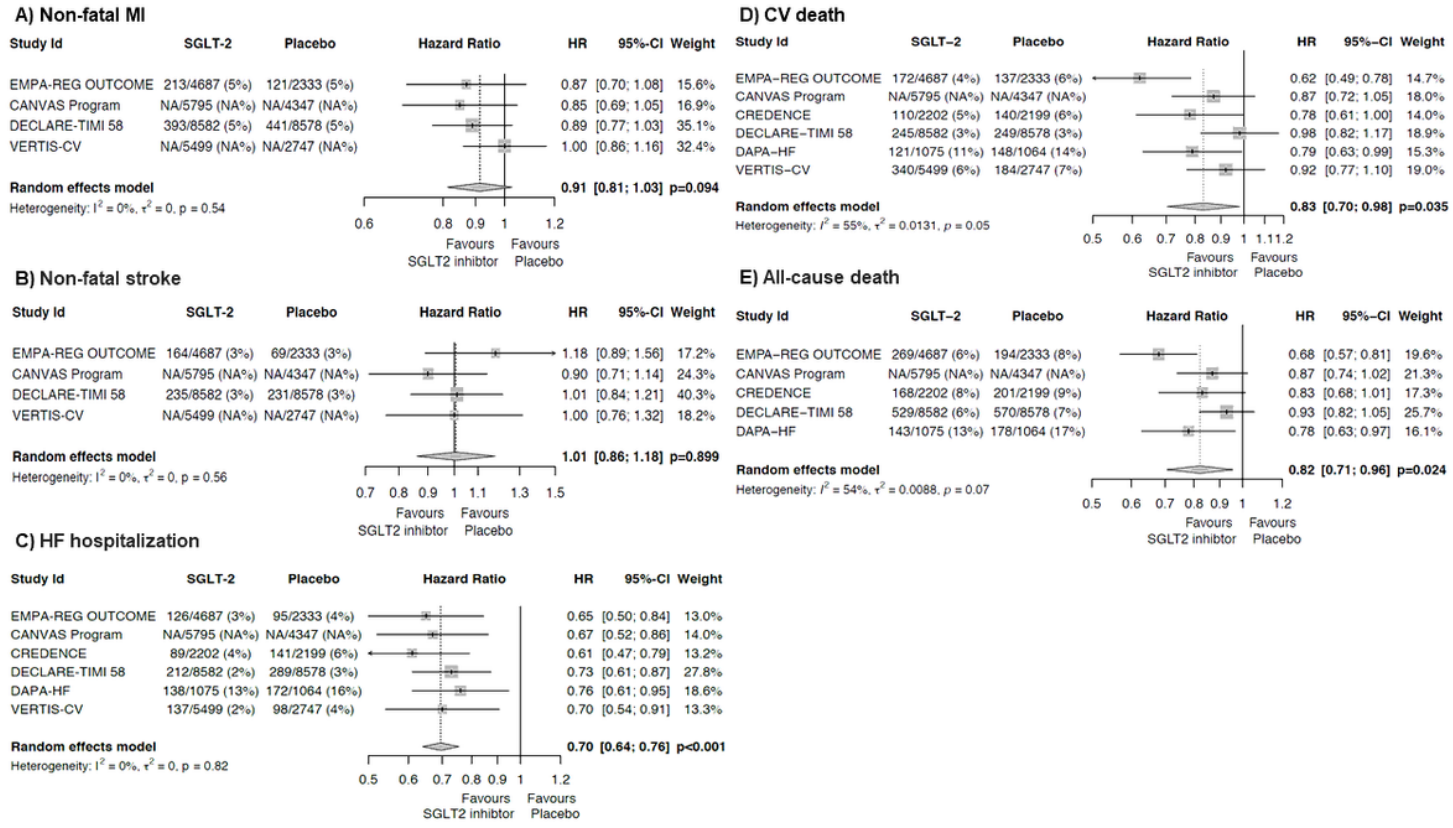

Figure 2

Meta-analysis of SGLT2i trials on CV secondary outcomes. (A) CV death; (B) Non-fatal MI; (C) Non-fatal stroke; (D) HF hospitalization; (E) All-cause death. CV: cardiovascular; MI myocardial infarction; HF: heart failure.

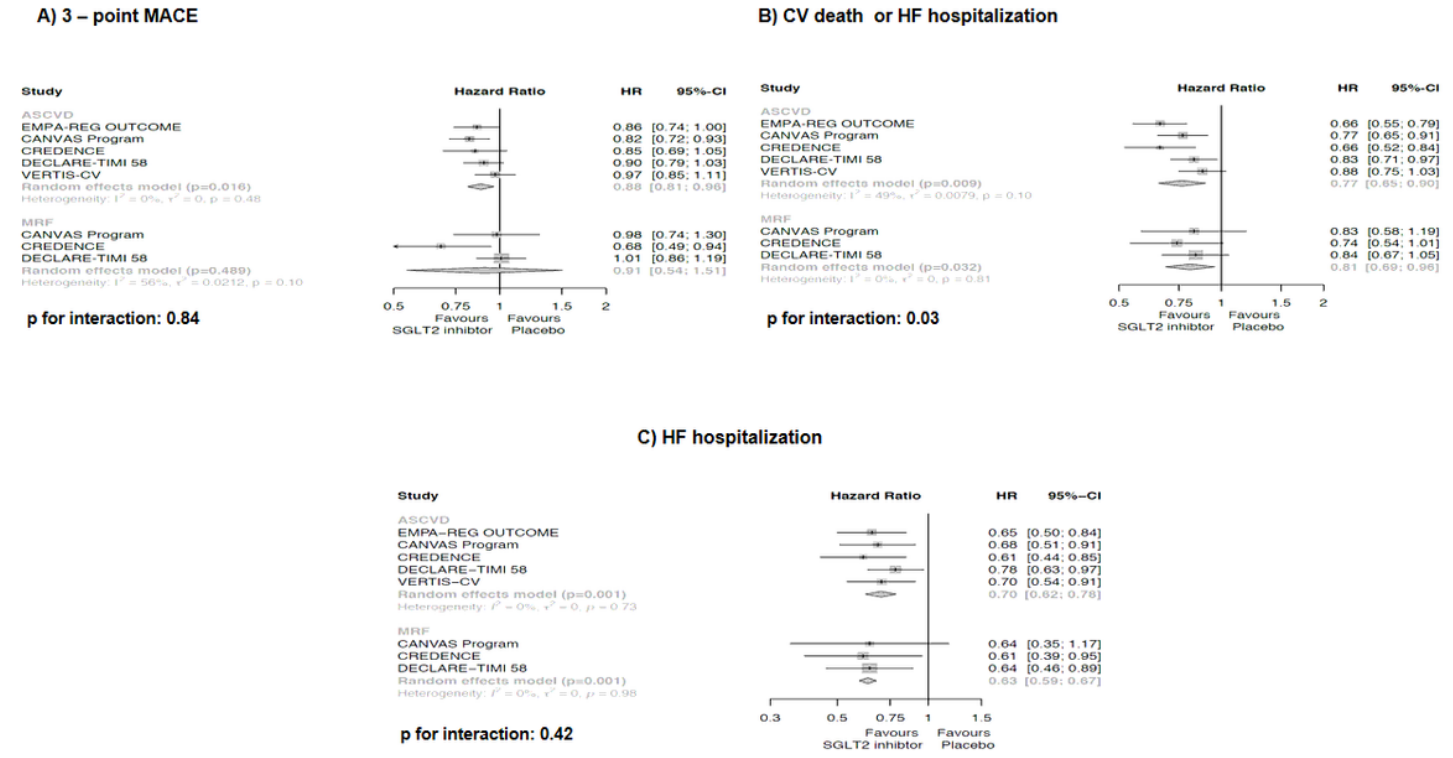

Figure 3

3-point MACE (A), CV death or HF hospitalization (B) and HF hospitalization (C) by ASCVD status. MACE: major adverse cardiovascular events; CV: cardiovascular; HF: heart failure; ASCVD: atherosclerotic CV disease; MRF: multiple risk factors.

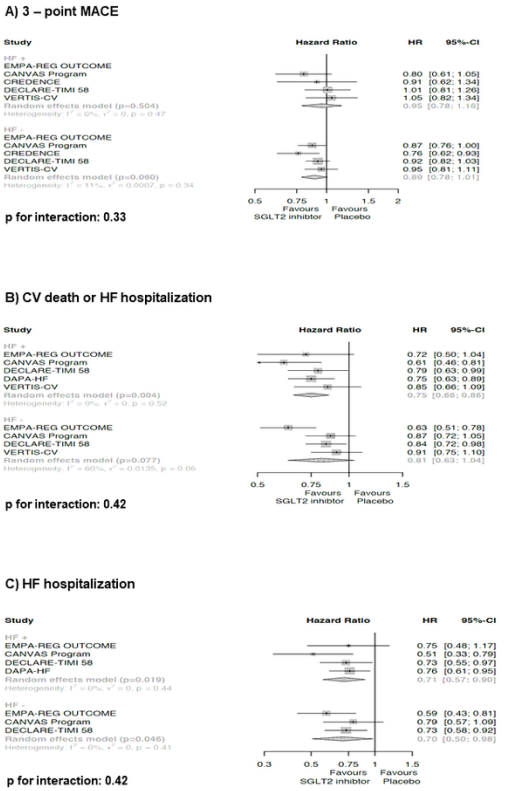

Figure 4

3-point MACE (A), CV death or HF hospitalization (B), and HF hospitalization by HF at baseline. MACE: major adverse cardiovascular events; CV: cardiovascular; HF: heart failure.

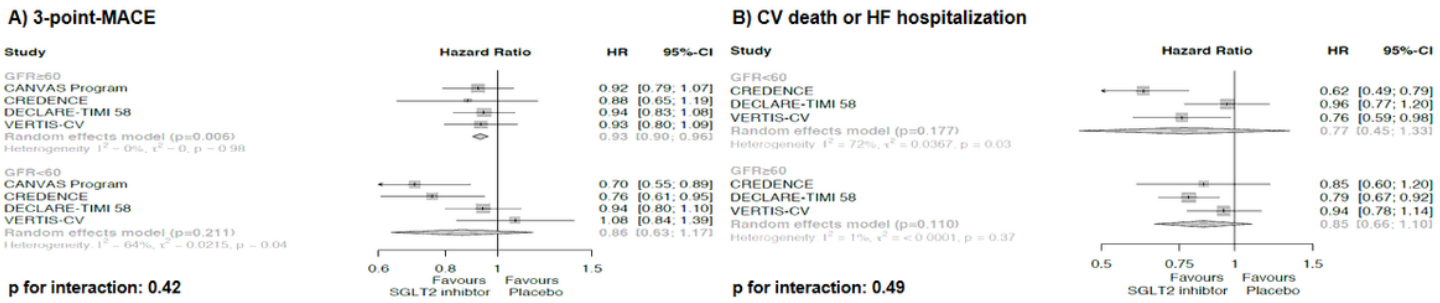

Figure 5

3-point MACE (A) and CV death or HF hospitalization (B), stratified by eGFR. MACE: major adverse cardiovascular events; CV: cardiovascular; HF: heart failure; eGFR: estimated glomerular filtration rate.

Supplementary Files

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