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Impact of SGLT2 inhibitors on major clinical events and safety outcomes in heart failure patients: a meta-analysis of randomized clinical trials

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ABSTRACT

BACKGROUND Sodium-glucose co-transporter-2 inhibitors (SGLT2i) significantly reduce the risk of cardiovascular (CV) and renal adverse events in patients with diabetes mellitus, heart failure (HF) and/or chronic kidney disease. We performed a meta-analysis to explore the impact of several different SGLT2i on all-cause mortality, CV mortality, HF hospitalizations and the combined outcome CV death/HF hospitalization in HF patients across the spectrum of left ventricular ejection fraction (LVEF) phenotypes.

METHODS A systematic search in MEDLINE database and Cochrane library through March 2021 was performed without limitations. Randomized clinical trials that provided data about the impact of SGLT2i on all-cause mortality, CV mortality, HF hospitalizations or the combined outcome of CV death/HF hospitalization in HF patients were included. A random effects model was used for calculating the effect estimates.

RESULTS Nine studies (n = 16,723 patients, mean age: 65.9 years, males: 70.7%) were included in the quantitative synthesis. Compared to placebo, SGLT2i use was associated with 14% lower risk of all-cause mortality [hazard ratio (HR) = 0.86, 95% CI: 0.78–0.94, I^2 = 0, P = 0.0008], 32% lower risk of HF hospitalizations (HR = 0.68, 95% CI: 0.62–0.74, I^2 = 0, P < 0.001), 14% lower risk of CV mortality (HR = 0.86, 95% CI: 0.77–0.95, I^2 = 0, P = 0.003) and 26% lower risk of CV death/HF hospitalization (HR = 0.74, 95% CI: 0.68–0.80, I^2 = 0, P < 0.001). Regarding the safety outcomes, our data revealed no significant differences between SGLT2i and placebo groups in drug related discontinuations, amputations, severe hypoglycemia, hypotension, volume depletion, ketoacidosis and genital infections. By contrast, a protective role of SGLT2i against placebo was found for serious adverse events and acute kidney injury.

CONCLUSIONS In patients with HF, regardless of LVEF phenotype, all SGLT2i had an excellent safety profile and significantly reduced the risk of all-cause mortality, CV mortality, HF hospitalizations and CV deaths/HF hospitalizations compared to placebo.

Sodium-glucose co-transporter-2 inhibitors (SGLT2i) is an antidiabetic class category that acts by blocking glucose resorption in the proximal tubule of the kidney promoting glucosuria.[1] Randomized clinical trials have shown the beneficial role of SGLT2i in cardiovascular (CV) and renal outcomes in patients with or without diabetes mellitus (DM), including patients with heart failure (HF) and/or chronic kidney disease (CKD).[2–8] According to current guidelines, empagliflozin,

canagliflozin and dapagliflozin are recommended in patients with type 2 DM (T2DM) and CV disease, or at very high/high CV risk to reduce CV events, while empagliflozin is also recommended in patients with T2DM and CV disease to reduce the risk of death.[9] The protective role of SGLT2i on CV events is mainly driven by the reduction in HF hospitalizations.[4] For that reason, SGLT2i (empagliflozin, canagliflozin and dapagliflozin) are also recommended to lower risk of HF hospitalization in patients with DM.[9] Recent studies and meta-analyses have shown that empagliflozin and dapagliflozin can further improve CV and renal outcomes in HF patients with reduced left ventricular ejection fraction [LVEF, especially HF with reduced ejection fraction (HFrEF)], regardless of the presence of DM.[8,10,11] In addition, the American College of Cardiology has already recommended SGLT2i for the treatment of HFrEF.[12] However, there are still unanswered questions as to whether the observed favorable outcomes in efficacy and safety constitute a class effect of SGLT2i or an effect confined to specific agents and whether the benefit also extends to HF with preserved LVEF [especially HF with preserved ejection fraction (HFpEF)]. The aim of this meta-analysis is to shed some light on these open issues by pooling data from randomized controlled trials (RCTs) on all clinically available SGLT2i, while examining the effects of SGLT2i across the spectrum of LVEF phenotypes.

METHODS

This meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA Statement).[13]

Search Strategy

Two independent investigators performed a systematic search in MEDLINE database and Cochrane library through to March 2021 without any limitations. The reference lists of the relevant research studies as well as the relevant review studies and meta-analyses were also searched. We used the following algorithm to retrieve all relevant studies: "sodium-glucose transporter-2 inhibitors" (Pharmacological Action) OR "sodium-glucose transporter-2 inhibitors" (MeSH Terms) OR "sodium-glucose transporter-2 inhibitors" (All Fields) OR ["SGLT2" (All Fields) AND "inhibitor" (All Fields)] OR ["SGLT2 inhibitor" (All Fields) AND "heart failure" (MeSH Terms)] OR ["heart" (All Fields) AND "failure" (All Fields)] OR "heart failure" (All Fields)".

We first screened the titles and abstracts of each study and in case of considering a study as relevant then we went through the full text. Disagreements were resolved by a third investigator.

Eligibility Criteria

We considered eligible placebo RCTs that enrolled patients > 18 years with HF of ischemic or non-ischemic etiology and also provided data about the impact of SGLT2i on all-cause mortality, CV mortality, HF hospitalizations and the combined outcome of CV death/HF hospitalizations. We excluded studies that did not provide data about the HF status, observational studies and studies written in a different language than English.

Data Collection

The following data were extracted for each included study: first author, journal of publication, trial acronym, year of publication, number of patients in each group, duration of follow-up, gender, age, mean ejection fraction, comorbidities (DM, hypertension), HF etiology, safety outcomes and the point estimate and confidence intervals for the outcomes of interest (all-cause mortality, CV mortality, HF hospitalizations and the combined outcome of CV death/HF hospitalizations). The data extraction was performed by two independent investigators.

Statistical Analysis

Data analysis was conducted using RevMan 5.4 (Cochrane Training, London, United Kingdom). Separate analyses for the primary outcomes (all-cause mortality, CV mortality, HF hospitalizations and CV deaths/HF hospitalizations) and safety outcomes [drug related discontinuations, amputations, severe hypoglycaemia, serious adverse events and acute kidney injury (AKI)] were performed. Hazard ratio (HR) estimates were pooled from different studies for the primary outcomes, while risk ratio (RR) was pooled from crude event rates for safety

outcomes. The extent of statistical heterogeneity was assessed using the I^2 index, with values of 25% (I^2 = 25), 50% (I^2 = 50) and 75% (I^2 = 75) representing low, medium and high level of heterogeneity, respectively.[14] Funnel plots were used to assess publication bias. Cochrane collaboration's tool was used for assessing risk of bias.[15] A random effects model was used for the analyses. Two-sided *P*-value < 0.05 were considered statistically significant.

RESULTS

Quality Assessment of Studies and Patients

The search strategy identified 810 studies (Figure 1). Of these studies, 756 studies were excluded at the title/abstract level while 45 studies were excluded at the full-text level. As a result, nine studies[8,11,16–22] (*n* = 16,723 patients, mean age: 65.9 years, males: 70.7%) were included for further analysis (Table 1). The SGLT2i that were used in the analyses included: canagliflozin (two studies),[16,22] dapagliflozin (two studies),[20,21] empagliflozin (three studies),[8,11,17] ertugliflozin (one study),[18] and sotagliflozin (one study).[19] Regarding the quality assessment, all studies were rated as having low quality in all assessed domains (Figure 2).

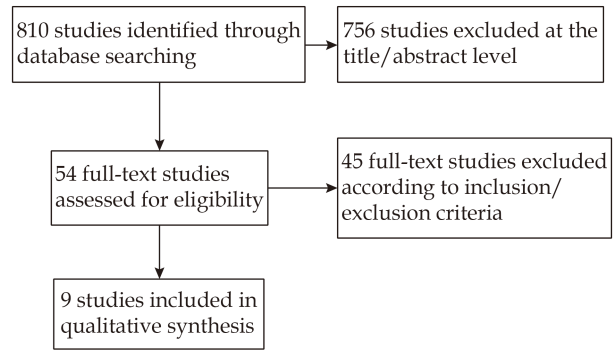

Figure 1 Flow diagram of the search strategy.

Impact of SGLT2i on All-cause Mortality in HF Patients

Eight studies[8,11,16–20,22] provided data about the impact of SGLT2i on all-cause mortality. The quantitative synthesis showed that SGLT2i are related with 14% lower risk of all-cause mortality compared to placebo (12% *vs.* 13.8%, HR = 0.86, 95% CI: 0.78–0.94, I^2 = 0, *P* = 0.000 8) (Figure 3). We found only two studies[18,20] that provided data regarding the impact of SGLT2i on all-cause mortality according to LVEF status. Compared to placebo, the quantitative synthesis showed a non-significant association of SGLT2i with all-cause mortality in both the LVEF ≤ 45% subgroup (16.7% *vs.* 20.4%, HR = 0.74, 95% CI: 0.46–1.19, I^2 = 61%, *P* = 0.22) and >

Table 1 Baseline characteristics and major outcomes of the included studies.

Authors	Trial	Year	SGLT2i	*n*	SGLT2i group	Placebo group	Age, yrs	Males, %	Diabetes mellitus, %	All-cause mortality events		Heart failure hospitalizations events		Cardiovascular deaths events	
										SGLT2i group	Placebo group	SGLT2i group	Placebo group	SGLT2i group	Placebo group
Rådholm K, *et al.*[16]	CANVAS	2018	Canagliflozin	1,461	803	658	63.8	56	100	84	92	41	67	70	75
Fitchett D, *et al.*[17]	EMPAREG	2016	Empagliflozin	706	462	244	64.5	70	100	56	35	48	30	38	27
Packer M, *et al.*[11]	EMPEROR reduced	2020	Empagliflozin	3,730	1,863	1,867	66.9	76	49.8	249	266	246	342	187	202
McMurray JJV, *et al.*[8]	DAPA-HF	2019	Dapagliflozin	4,744	2,373	2,371	66.4	77	41.8	276	329	231	318	227	273
Cosentino F, *et al.*[18]	VERTIS CV	2020	Ertugliflozin	1,958	1,286	672	64.4	68	100	150	81	69	55	116	64
Bhatt DL, *et al.*[19]	SOLOIST WHF	2021	Sotagliflozzin	1,222	608	614	69.5	66	100	65	76	194	297	51	58
Kato ET, *et al.*[20]	DECLARE TIMI-58	2019	Dapagliflozin	1,987	980	1,007	64.0	71	100	122	149	92	130	79	85
Nassif ME, *et al.*[21]	DEFINE-HF	2019	Dapagliflozin	263	131	132	61.3	73	63.1	1	1	10	8	1	1
Sarraju A, *et al.*[22]	CREDENCE	2021	Canagliflozin	652	329	323	65.2	61	100	45	44	34	36	–	–

SGLT2i: sodium-glucose co-transporter-2 inhibitors.

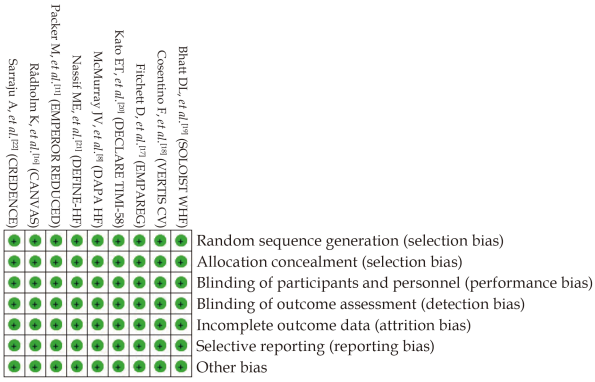

Figure 2 Quality assessment of the included studies.

45% subgroup (10.4% *vs.* 10.5%, HR = 1.04, 95% CI: 0.77–1.39, I^2 = 0, P = 0.81) (Figure 4). However, these data should be interpreted with caution because of the small number of included studies.

Impact of SGLT2i on HF Hospitalizations in HF Patients

We found nine studies[8,11,16–22] that provided data about the impact of SGLT2i on HF hospitalizations. The quantitative synthesis showed that SGLT2i are related with 32% lower risk of HF hospitalizations compared to placebo (10.9% *vs.* 16.3%, HR = 0.68, 95% CI: 0.62–0.74, I^2 = 0, P < 0.001) (Figure 5). Only two studies[18,20] provided data on the impact of SGLT2i on HF hospitalizations according to LVEF status. Compared to placebo, the quantitative synthesis showed that SGLT2i have a beneficial role in reducing HF hospitalizations in both LVEF ≤ 45% subgroup (HR = 0.62, 95% CI: 0.46–0.85, I^2 = 0, P = 0.003) and > 45% subgroup (HR = 0.71, 95% CI: 0.52–0.97, I^2 = 0, P = 0.03) and there is no statistically significant difference between the two subgroups (P = 0.55) (Figure 6).

Impact of SGLT2i on CV Mortality in HF Patients

Seven studies[8,11,16–20] provided data about the impact of SGLT2i on CV mortality. The quantitative synthesis showed that SGLT2i are related with 14% lower risk of CV mortality compared to placebo (9.2% *vs.* 10.6%, HR = 0.86, 95% CI: 0.77–0.95, I^2 = 0, P = 0.003) (Figure 7). Compared to placebo, the quantitative synthesis of the two studies[18,20] that provided separate data according to LVEF status showed a non-significant association of SGLT2i with CV mortality in both the LVEF ≤ 45% subgroup (12.4% *vs.* 15.1%, HR = 0.72, 95% CI: 0.42–1.24, I^2 = 58%, P = 0.24) and > 45% subgroup (7.2% *vs.* 5.8%, HR = 1.24, 95% CI: 0.85–1.81, I^2 = 0, P = 0.27) (Figure 8).

Impact of SGLT2i on CV Deaths/HF Hospitalizations in HF Patients

We found eight studies[8,11,16–20,22] that provided data about the impact of SGLT2i on the combined outcome CV deaths/HF hospitalizations. The quantitative synthesis showed that SGLT2i are related with 26% lower risk of CV deaths/HF hospitalizations compared to placebo (17.7% *vs.* 23.8%, HR = 0.74, 95% CI: 0.68–0.80, I^2 = 0, P < 0.001) (Figure 9). We found four studies[8,11,18,20] that provided data regarding the impact of SGLT2i on CV deaths/HF hospitalizations according to LVEF status. Compared to placebo, the quantitative synthesis showed a beneficial role of SGLT2i in reducing the combined outcome in the LVEF ≤ 45% subgroup (four studies: 18% *vs.* 23.1%, HR = 0.74, 95% CI: 0.67–0.81, I^2 = 0, P < 0.001) without reaching a statistical significance in the LVEF > 45% subgroup (two studies: 11.5% *vs.* 14.1%, HR = 0.84, 95% CI: 0.65–1.10, I^2 = 0, P = 0.20), and there is no statistically signif-

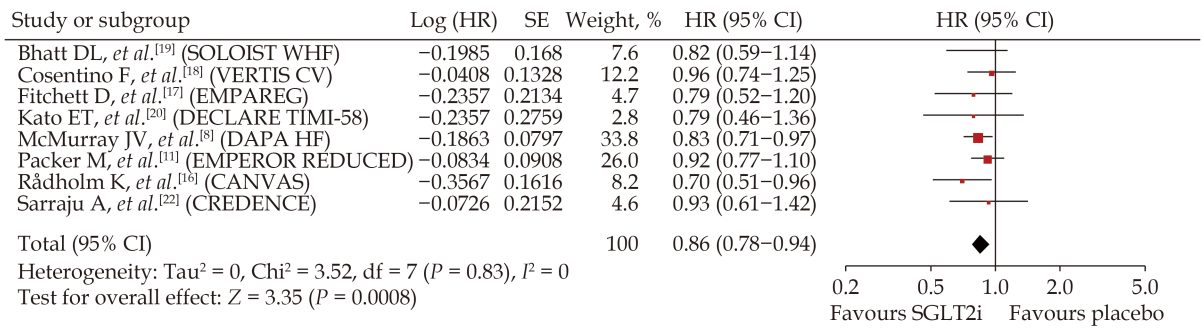

Figure 3 Impact of SGLT2i on all-cause mortality in heart failure patients. HR: hazard ratio; SGLT2i: sodium-glucose co-transporter-2 inhibitors.

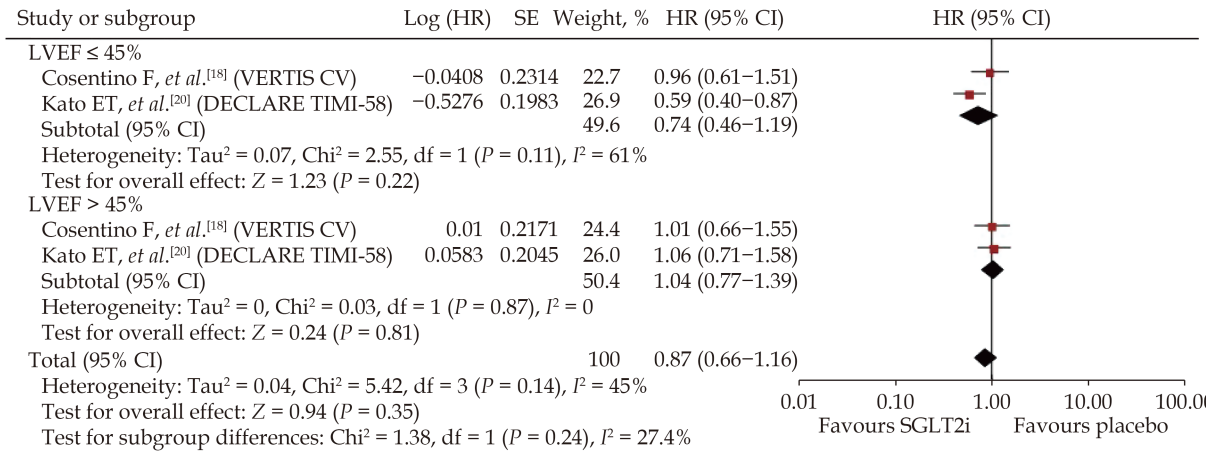

Figure 4 Impact of SGLT2i on all-cause mortality according to LVEF status. HR: hazard ratio; LVEF: left ventricular ejection fraction; SGLT2i: sodium-glucose co-transporter-2 inhibitors.

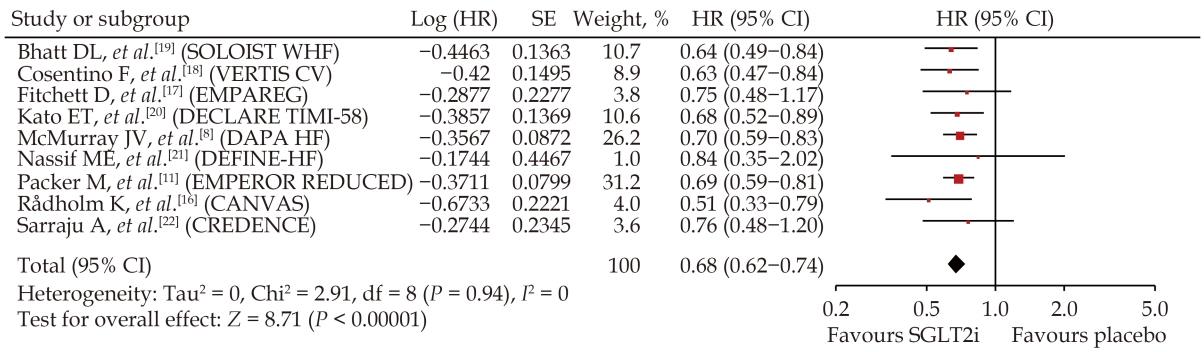

Figure 5 Impact of SGLT2i on heart failure hospitalizations in heart failure patients. HR: hazard ratio; SGLT2i: sodium-glucose co-transporter-2 inhibitors.

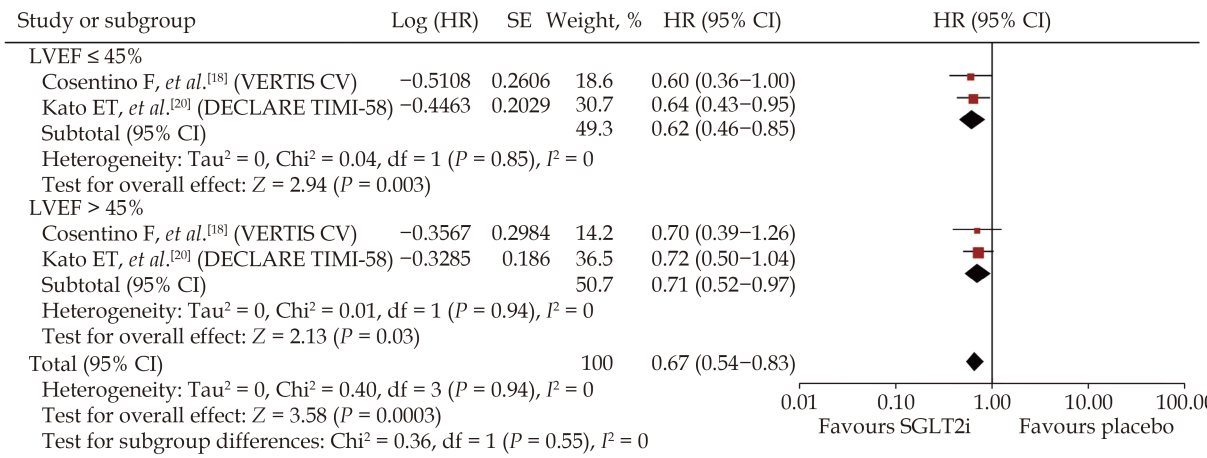

Figure 6 Impact of SGLT2i on heart failure hospitalizations according to LVEF status. HR: hazard ratio; LVEF: left ventricular ejection fraction; SGLT2i: sodium-glucose co-transporter-2 inhibitors.

icant difference between the two subgroups ($P = 0.36$) (Figure 10). Subgroup analysis according to the DM status was provided in eight studies.[8,11,16–20,22] Compared to placebo, the quantitative synthesis showed a beneficial role of SGLT2i in reducing the combined outcome in both diabetic patients (eight studies: 18.7% *vs.* 25.9%, HR = 0.73, 95% CI: 0.67−0.80, $I^2 = 0$, $P < 0.001$) and non-diabetic patients (two studies: 14.9% *vs.* 19.1%, HR = 0.75, 95% CI: 0.66−0.87, $I^2 = 0$, $P < 0.001$), and there is no statistically signi-

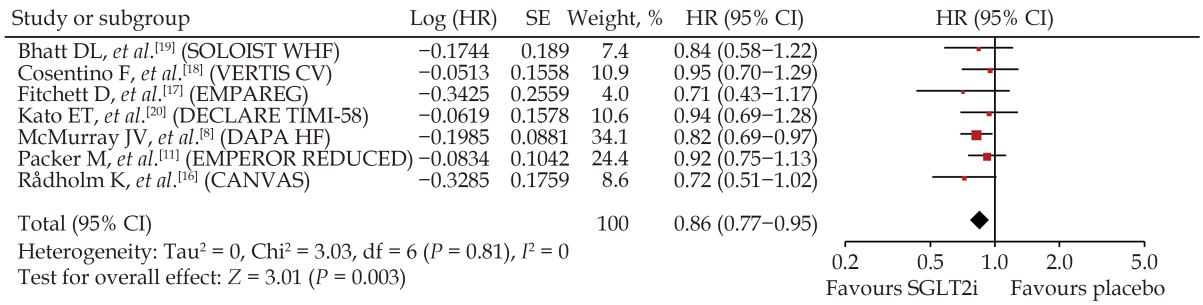

Figure 7 Impact of SGLT2i on cardiovascular mortality in heart failure patients. HR: hazard ratio; SGLT2i: sodium-glucose co-transporter-2 inhibitors.

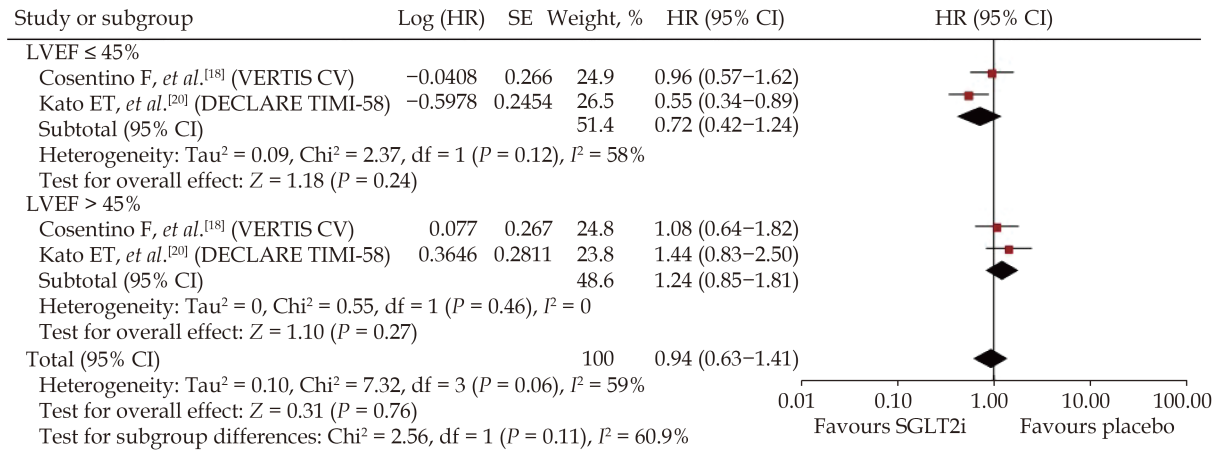

Figure 8 Impact of SGLT2i on cardiovascular mortality according to LVEF status. HR: hazard ratio; LVEF: left ventricular ejection fraction; SGLT2i: sodium-glucose co-transporter-2 inhibitors.

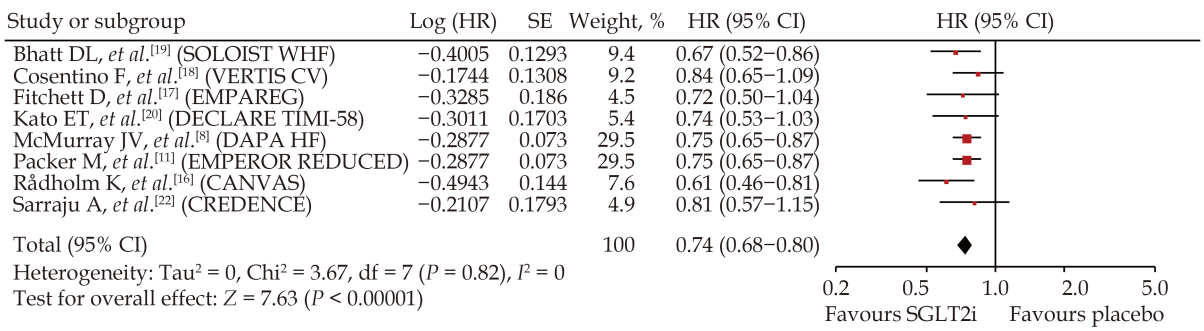

Figure 9 Impact of SGLT2i on cardiovascular deaths/heart failure hospitalizations in HF patients. HR: hazard ratio; SGLT2i: sodium-glucose co-transporter-2 inhibitors.

ficant difference between the two subgroups (P = 0.69) (Figure 11).

Safety Outcomes

Regarding safety outcomes, events on drug related discontinuations, amputations, severe hypoglycemia, serious adverse events and AKI were extracted from the different studies. Specifically, our data revealed no significant differences between SGLT2i and placebo groups in drug related discontinuations (six studies: RR = 0.94, 95% CI: 0.83−1.07, I^2 = 0, P = 0.36) (Figure 12), amputations (six studies: RR = 1.42, 95% CI: 1.00−2.03, I^2 = 0, P = 0.05) (Figure 13), severe hypoglycemia (six studies: RR = 0.93, 95% CI: 0.75−1.16, I^2 = 0, P = 0.53) (Figure 14), hypotension (three studies: RR = 1.09, 95% CI: 0.90−1.31, I^2 = 0, P = 0.37) (Figure 15), diabetic ketoacidosis (two studies: RR = 1.40, 95% CI: 0.11−17.30, I^2 = 56%, P = 0.79) (Figure 16), volume depletion (six studies: RR = 1.09, 95% CI: 0.96−1.24, I^2 = 0,

P = 0.16) (Figure 17) and genitalia infection (four studies: RR = 1.90, 95% CI: 0.34–10.45, I^2 = 43%, P = 0.46) (Figure 18). On the other hand, a protective role of SGLT2i against placebo was found for serious adverse events (seven studies: RR = 0.89, 95% CI: 0.86–0.93, I^2 = 0, P < 0.001) (Figure 19) and AKI (four studies: RR = 0.67, 95% CI: 0.52–0.87, I^2 = 0, P = 0.003) (Figure 20).

Publication Bias

Funnel plots revealed no significant publication bias in any of the performed analyses (data not shown).

DISCUSSION

The initiation of SGLT2i has been associated with a lower risk of CV events across a broad range of outcomes and patient characteristics.[23,24] The present meta-analysis showed that in patients with HF, SGLT2i significantly reduce all-cause mortality, CV mortality, HF hospitalizations and the combined outcome of CV deaths/HF hospitalizations compared to placebo, regardless of the presence of DM, while having an excellent safety profile. Important strengths of this analysis compared to previous meta-analyses[10,25–27] include the fact that it addressed outcomes of all clinically available SGLT2i

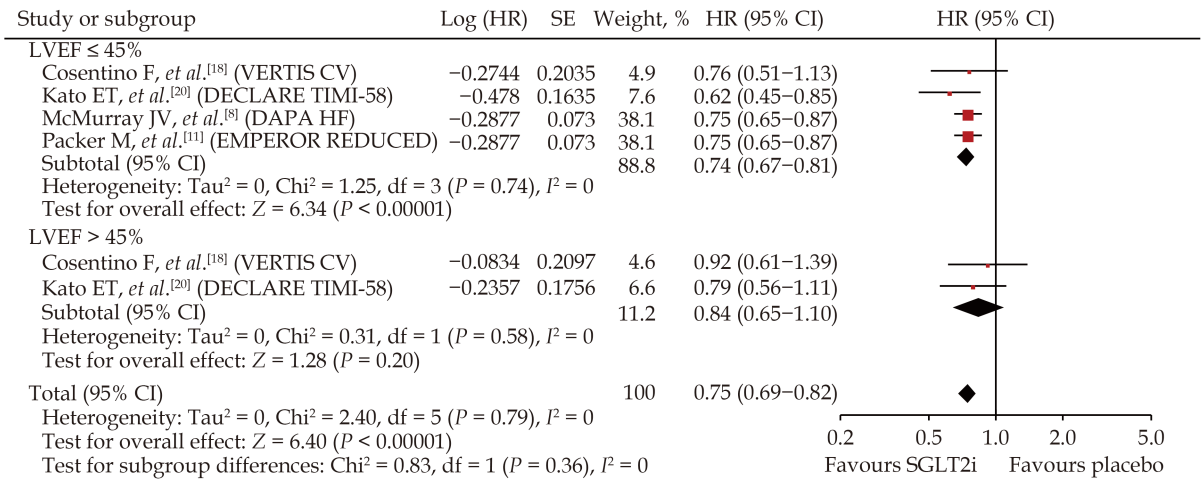

Figure 10 Impact of SGLT2i on cardiovascular deaths/heart failure hospitalizations according to LVEF status. HR: hazard ratio; LVEF: left ventricular ejection fraction; SGLT2i: sodium-glucose co-transporter-2 inhibitors.

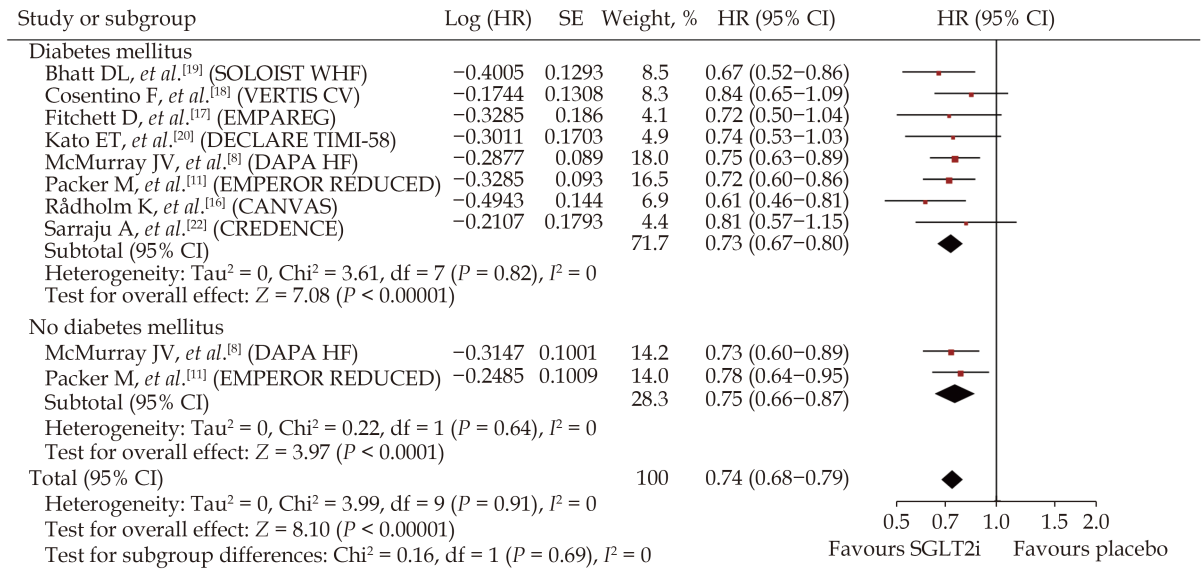

Figure 11 Impact of SGLT2i on cardiovascular deaths/heart failure hospitalizations according to diabetes mellitus status. HR: hazard ratio; SGLT2i: sodium-glucose co-transporter-2 inhibitors.

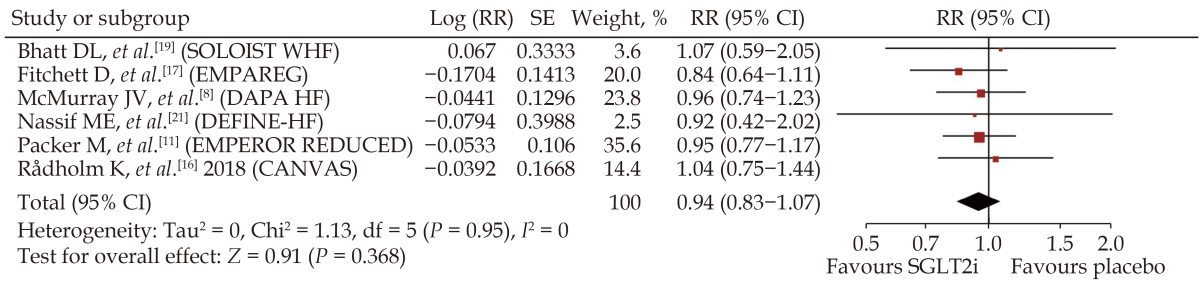

Figure 12 Impact of SGLT2i on drug-related discontinuations. RR: risk ratio; SGLT2i: sodium-glucose co-transporter-2 inhibitors.

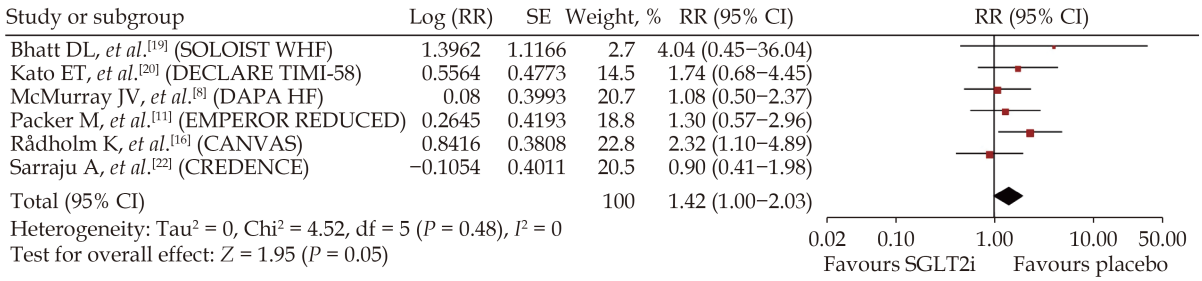

Figure 13 Impact of SGLT2i on amputations. RR: risk ratio; SGLT2i: sodium-glucose co-transporter-2 inhibitors.

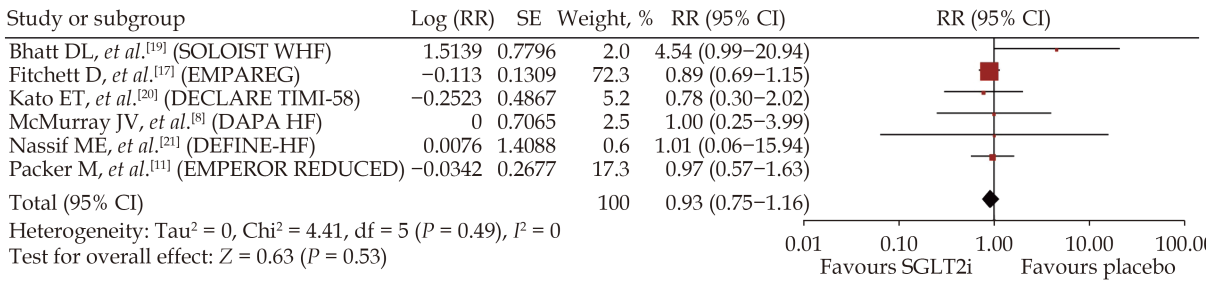

Figure 14 Impact of SGLT2i on severe hypoglycemia. RR: risk ratio; SGLT2i: sodium-glucose co-transporter-2 inhibitors.

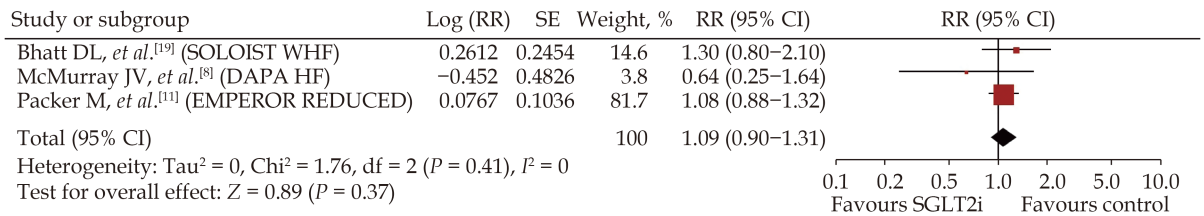

Figure 15 Impact of SGLT2i on hypotension. RR: risk ratio; SGLT2i: sodium-glucose co-transporter-2 inhibitors.

showing consistent results across the whole drug category, thus indicating a class effect of SGLT2i in HF. Furthermore, it addressed the effects of SGLT2i across the spectrum of LVEF phenotypes, an important aspect, given the lack of effective therapies in HFpEF and the long-expected results of RCTs on empagliflozin/dapagliflozin in these patients. Finally, it assessed important safety concerns, including volume depletion, hypotension, severe hypoglycemia, diabetic ketoacidosis and genital infections.

The results of this meta-analysis confirms the results of individual studies. DAPA-HF trial assigned 4,744 patients with NYHA II-IV and LVEF ≤ 40% regardless of the presence of DM that were randomized to receive either dapagliflozin or placebo.[8] Dapagliflozin was related with a 26% reduction in the risk of the composite outcome consisted of worsening HF or CV death.[8] Similarly, EMPEROR-Reduced trial recruited 3,730 patients with NYHA II-IV and LVEF ≤ 40% with or without DM.[11] The authors found that the empagliflozin group had a lower risk of CV death/HF hospitalization compared to the placebo group, regardless of DM status.[11] A

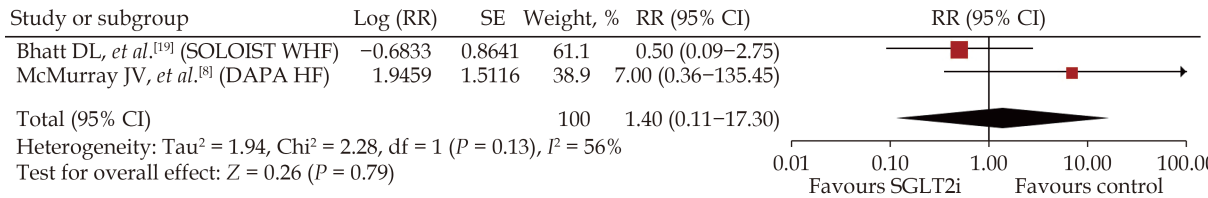

Figure 16 Impact of SGLT2i on ketoacidosis. RR: risk ratio; SGLT2i: sodium-glucose co-transporter-2 inhibitors.

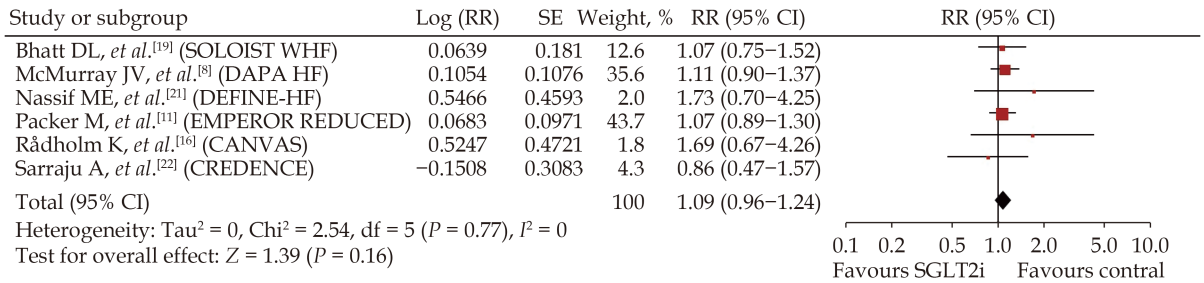

Figure 17 Impact of SGLT2i on volume depletion. RR: risk ratio; SGLT2i: sodium-glucose co-transporter-2 inhibitors.

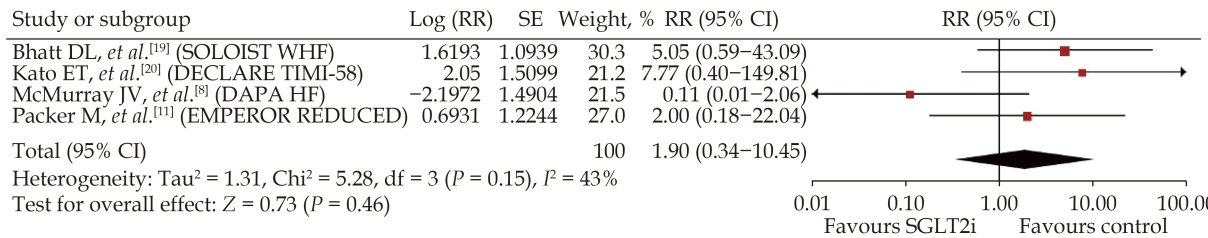

Figure 18 Impact of SGLT2i on genitalia infections. RR: risk ratio; SGLT2i: sodium-glucose co-transporter-2 inhibitors.

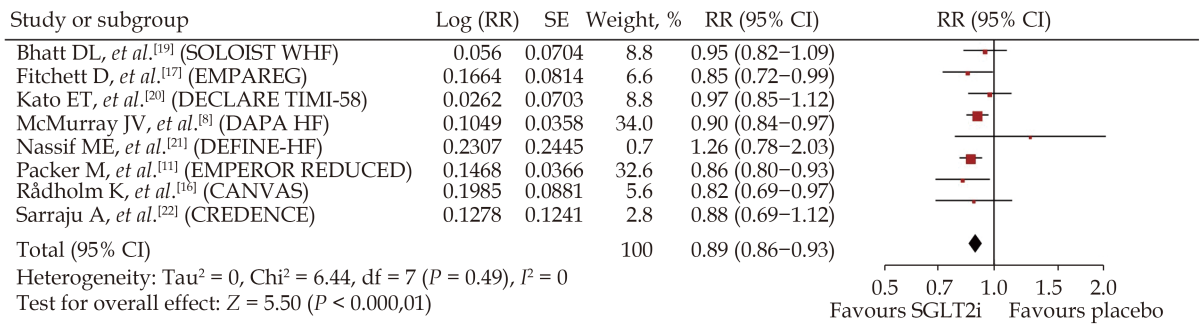

Figure 19 Impact of SGLT2i on severe adverse events. RR: risk ratio; SGLT2i: sodium-glucose co-transporter-2 inhibitors.

recent meta-analysis of DAPA-HF and EMPEROR-Reduced trials showed that SGLT2i were associated with a 13% reduction in all-cause death and 14% reduction in CV death compared to placebo group.[10] SOLOIST-WHF trial recruited 1,222 patients with recent worsening HF who were randomized to receive sotagliflozin or placebo.[19] This study showed that sotagliflozin therapy if initiated shortly after an episode of worsening HF, resulted in a significantly lower total number of CV deaths and HF hospitalizations and urgent visits compared to placebo.[19] These findings were consistent in patients with mid-range and reduced ejection fraction and in patients with preserved ejection fraction. However, the results of DECLARE TIMI-58 trial showed that dapagliflozin reduced the risk of CV death or HF hospitalization to a greater extent in patients with HFrEF than in those without.[20] Similarly, dapagliflozin significantly reduced all-cause mortality in patients with HFrEF but not in those without.[20] In the clinical setting of acute decompensated HF, a pilot multi-center study showed that treatment with empagliflozin was safe, increased urinary output and reduced a combined end-

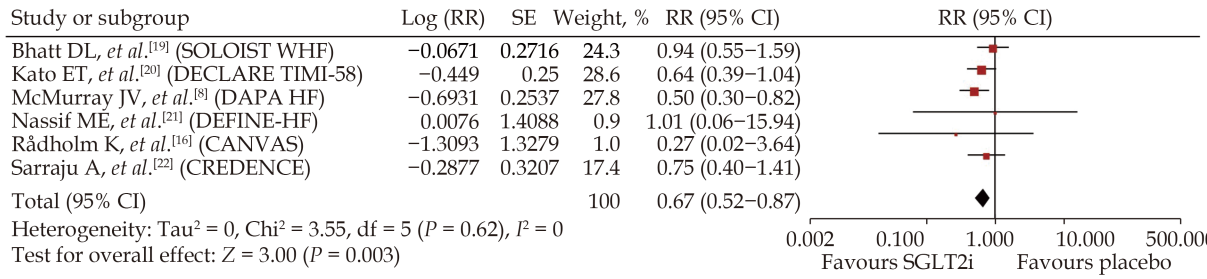

Figure 20 Impact of SGLT2i on acute kidney injury. RR: risk ratio; SGLT2i: sodium-glucose co-transporter-2 inhibitors.

point of worsening HF, HF rehospitalization or death at 60 days.[28] However, larger studies are needed to further explore the role of SGLT2i in acute HF patients. Our findings showed a beneficial role of SGLT2i compared to placebo in reducing the combined outcome of CV deaths/HF hospitalizations without a significant interaction between patients with reduced and preserved LVEF. This later finding is consistent with the results of the SOLOIST-WHF trial on sotagliflozin,[19] while the ongoing EMPEROR-Preserved[29] and DELIVER (NCT 03619213) trials on empagliflozin and dapagliflozin, respectively, will provide more solid evidence on the role of SGLT2i in the HFpEF patients. Our meta-analysis did not assess the impact of SGLT2i on clinical outcomes according to the etiology of HF due to the lack of data. However, EMPEROR-Reduced trial showed that SGLT2i significantly reduced the composite outcome of CV death/HF hospitalization in patients with either ischemic or non-ischemic cause of HF.[11] VERTIS CV (Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes) trial assigned 8,246 patients with T2DM and atherosclerotic CV disease that were randomized to receive ertugliflozin or placebo.[18] The results showed that ertugliflozin significantly reduced the risk for HF hospitalization while did not significantly reduce the risk for first CV death/HF hospitalization, while previous HF status did not modify the risk of first HF hospitalization.[18] Subgroup analyses from VERTIS-CV trial on risk for first composite of CV death/HF hospitalization, CV mortality, or all-cause mortality based on pretrial LVEF showed no significant interactions.[18] In a recent meta-analysis of six trials, SGLT2i were associated with a reduced risk of major adverse CV events in patients with T2DM while the largest benefit across the class was for an associated reduction in risk for HF hospitalizations and kidney outcomes.[30]

Regarding the potential mechanisms that explain the beneficial role of SGLT2i in HF patients, several mechanisms have been proposed including diuresis/natriuresis, blood pressure reduction, erythropoiesis, improved cardiac energy metabolism, inflammation reduction and prevention of ischemia/reperfusion injury among others.[31] A recent study showed that empagliflozin significantly improves left ventricular volumes, mass and systolic function independently of the glycemic status.[32,33] Other small mechanistic clinical trials or preclinical studies have pointed towards diverse mechanisms but no solid evidence is yet available.

The role of SGLT2i in kidney outcomes has been well studied. In this regard, this meta-analysis showed that a protective role of SGLT2i against placebo in AKI. Data from the EMPAREG OUTCOME trial showed that in patients with T2DM at high CV risk, empagliflozin as compared to placebo was associated with slower progression of kidney disease and lower rates of clinically relevant renal events.[34] Furthermore, the CREDENCE trial showed that in patients with T2DM and CKD, the risk of kidney failure and CV events was lower in the canagliflozin group than in the placebo group.[5] The DAPA-CKD trial enrolled patients with CKD.[6] The authors found that the risk of the composite outcome consisted of sustained decline in the estimated glomerular filtration rate of at least 50%, end-stage kidney disease, or death from renal or CV causes was significantly lower with dapagliflozin than with placebo independently of the diabetes status.[6] A recent meta-analysis showed that in patients with T2DM, SGLT2i reduced the risk of dialysis, transplantation, or death due to kidney disease while provided protection against AKI.[35] In addition, another recent meta-analysis showed that SGLT2i reduced the risk of progression of renal disease by 45%.[36] This association remained consistent regardless the history of

atherosclerotic CV disease while the magnitude of benefit of SGLT2i varied with baseline renal function, with lesser reductions in progression of renal disease in patients with more severe kidney disease at baseline.[36] Results of a meta-analysis that included RCTs and observational studies showed that SGLT2i reduced the odds of suffering AKI with and without hospitalization in randomized trials and the real-world setting.[37] Moreover, it has been found that in patients with HF and T2DM, empagliflozin in combination with diuretics caused a significant increase in urine volume compared with placebo, as well as a significant increase in electrolyte free water clearance.[38] All these data highlights the role of this drug category in the management of patients with HF and CKD, two clinical entities that often coexist. These findings are in accordance with our secondary analysis which showed a protective role of SGLT2i compared to placebo in reducing the risk of AKI in HF patients.

LIMITATIONS

A subgroup analysis according to DM status and etiology of HF (ischemic and non-ischemic) could not be performed for all-cause mortality, CV mortality and HF hospitalizations outcomes due to lack of data. Only two studies[18,20] provided data about the impact of SGLT2i on the primary outcomes of interest according to LVEF status. Furthermore, in one study, LVEF status was retrieved from medical records and not from measurements at the patient enrollment.[18] This consist a major limitation for this analysis and as a result, more data are needed to elucidate the role of SGLT2i in different LVEF categories. Furthermore, in the analysis of regarding the combined CV death/HF hospitalization outcome, in the reduced ejection fraction subgroup defined as ≤ 45%, we also included two studies[8,11] that provided data from patients with LVEF ≤ 40% which consists a limitation of this analysis. However, by removing these two studies, the results did not significantly change [LVEF ≤ 45% (two studies: HR = 0.67, 95% CI: 0.52–0.86, I^2 = 0, P = 0.002) and LVEF > 45% (two studies: HR = 0.84, 95% CI: 0.65–1.10, I^2 = 0, P = 0.20)], and there is no statistically significant difference between the two subgroups (P = 0.22). Regarding the safety outcome analysis of genital infections, one of the included studies provided data about genital mycotic infections[19] while another one provided data about epididymitis and Fournier gangrene.[8]

CONCLUSIONS

In patients with HF, SGLT2i showed an excellent safety profile and significantly reduced all-cause mortality, CV mortality, HF hospitalizations and CV deaths/HF hospitalizations compared to placebo. These beneficial effects are independent of the presence of DM, while they seem to extent to the whole SGLT2i class and to patients with HFpEF.

DISCLOSURE

Dr. Dimitrios Farmakis reports speaker honoraria and/or consultation fees from Abbott Laboratories, Bayer, Boehringer-Ingelheim, Leo, Menarini, Novartis, Orion and Roche Diagnostics, outside this work. The rest of the authors had no conflicts of interest to disclose.

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