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ORIGINAL ARTICLE

Sodium-glucose cotransporter-2 inhibitors in heart failure: an updated meta-analysis

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Abstract

Aims We aimed to examine efficacy and safety outcomes of sodium-glucose cotransporter-2 inhibitor (SGLT2i) for the treatment of heart failure (HF), especially in patients with heart failure with preserved ejection fraction (HFpEF).

Methods and results PubMed, Web of Science, and Cochrane Library were searched to identify randomized controlled trials comparing SGLT2i vs. placebo in HF patients. A total of 10 studies with 23 852 HF patients were eventually included. Compared with placebo, SGLT2i is associated with a lower incidence of composite of first hospitalization for heart failure (HHF) or cardiovascular death (CV death) [hazard ratio (HR) = 0.76 95% confidence interval (CI) = 0.71–0.81], which is consistent regardless of the diabetes status, type of gliflozines used, and follow-up duration. SGLT2i can reduce the risk of total HHF or CV death (HR = 0.74, 95%CI = 0.68–0.81), first HHF (HR = 0.69, 95%CI = 0.64–0.75), CV death (HR = 0.88, 95%CI = 0.80–0.96), any death (HR = 0.90, 95%CI = 0.83–0.97), and any serious events (HR = 0.90, 95%CI = 0.87–0.93) in HF patients, at the cost of increased risk of urinary tract infections (risk ratio = 1.17, 95%CI = 1.03–1.33). In HFpEF patients, SGLT2i is associated with a significant reduction of composite of first HHF or CV death (HR = 0.81, 95%CI = 0.73–0.91), first HHF (HR = 0.71, 95%CI = 0.62–0.82), and total HHF or CV death (HR = 0.61, 95%CI = 0.43–0.86).

Conclusions Sodium-glucose cotransporter-2 inhibitor contributed to better efficacy outcomes in overall HF patients and showed an inspiring breakthrough in the treatment of HFpEF.

Keywords Heart failure; Sodium-glucose cotransporter-2 inhibitors; Heart failure with preserved ejection fraction; Meta-analysis

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Introduction

Heart failure (HF), as the end-stage manifestation of most heart diseases, is an increasing public health concern worldwide.[1] Among studies[2–4] using standardized criteria and reporting long-term data, the mortality after the incidence of HF is almost 50% in 5 years. Meanwhile, diabetes mellitus and HF interact and coexist frequently. HF accounts for 14.1% of the first cardiovascular events in patients with diabetes mellitus, and 49.4% of hospitalized patients with acute HF have known or previously undiagnosed diabetes.[5,6] Therefore, hypoglycaemic drugs that can improve cardiovascular prognosis need to be developed urgently. Of note, HFpEF, which accounts for approximately 50% of all HF patients, tends to have more comorbidities than HFrEF, and no convincing treatment is available to reduce mortality and morbidity currently.[7,8]

Sodium-glucose cotransporter-2 inhibitor (SGLT2i), as new robustly effective hypoglycaemic therapy, unexpectedly showed profound cardiovascular benefits in cardiovascular outcomes trials mandated by the US Food and Drug Administration. In several large-scale randomized controlled trials (RCTs),[9–18] SGLT2i significantly improved prognosis in HF patients with or without diabetes. However, previous RCTs and meta-analyses[19–22] of SGLT2i did not specifically distinguish first hospitalization for heart failure (HHF) and total HHF and still had controversies on efficacy and safety outcomes such as cardiovascular death, any death, and acute

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kidney injury. The therapeutic role of SGLT2i in HFpEF also remains unclear. The recently published EMPEROR-Preserved study showed a breakthrough that may change the current treatment of HFpEF. Herein, we present an updated meta-analysis of SGLT2i focusing on new data on HF patients with left ventricular ejection fraction (LVEF) $>$ 40% and systematically review and synthesize these data in two ways: (i) all HF patients without LVEF restriction and (ii) HF patients with restricting only to HFpEF.

Methods

This meta-analysis was completed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[23]

Data sources and search strategy

A comprehensive search was conducted in PubMed, Web of Science, and Cochrane Library on 29 August 2021. The following keywords and their MeSH terms were used for the search: (sodium-glucose cotransporter-2 inhibitor OR SGLT2 inhibitor OR canagliflozin OR dapagliflozin OR empagliflozin OR ertugliflozin OR sotagliflozin OR ipragliflozin OR remogliflozin OR sergliflozin OR tofogliflozin) AND (heart failure OR cardiac failure OR HF). The detailed search strategy is presented in the supporting information. Additional studies were selected by manually screening the references of articles identified by the search. No restrictions were placed on the publication date or language.

Study selection and eligibility criteria

After duplicates were removed, the titles and abstracts of retrieved literature were reviewed to exclude uncorrelated studies and the full texts of the remaining articles.

Inclusion criteria included the following: (i) compared SGLT2i vs. placebo in HF patients regardless of the LVEF, diabetes status, and follow-up duration; (ii) RCTs or their subgroup analyses and post hoc analyses; and (iii) reported at least one of the predefined efficacy and safety outcomes. Exclusion criteria included the following: (i) observational or nonrandomized studies and (ii) studies that did not provide enough data to analyse the outcomes of interest.

Outcomes of interest, data extraction, and quality assessment

The predefined primary efficacy outcome was composite of first hospitalization for HF (HHF) or cardiovascular death (CV death). Other efficacy outcomes were (i) composite of total (first and recurrent) HHF and CV death; (ii) first HHF; (iii) CV death; (iv) any death; (v) major adverse cardiovascular events defined as composite of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke; and (vi) Kansas City Cardiomyopathy Questionnaire (KCCQ). The primary safety outcome was any serious adverse events (SAE). Other safety outcomes included acute kidney injury (AKI), urinary tract infections, hypoglycaemia, amputation, volume depletion, and bone fracture.

The characteristics, baseline demographics, outcome data, and safety data of eligible studies were extracted onto a predesigned excel spreadsheet. Quality assessment of included RCTs was conducted using Cochrane Handbook for Systematic Reviews of Interventions (version 5.1.0).[24]

All the processes of study selection, data extraction, and quality assessment were carried out by two reviewers (Y. Cao and P. Li) independently, and discrepancies were identified by the third reviewer (Y. Li).

Statistical analysis

Pooled hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated for estimates of efficacy outcomes using the generic inverse-variance method. Total HHF was reported as a rate ratio among the including studies. Safety outcomes were usually reported as dichotomous data, which would be used to calculate risk ratios (RRs) by Mantel–Haenszel fixed effects model. The heterogeneity between studies was assessed using I^2 statistic. Studies with an I^2 statistic $>$ 50% were considered to have substantial heterogeneity, and the random effects model would be used to analyse. Otherwise, the fixed effects model would be used. Considering the heterogeneity of the follow-up duration, we further calculated the incidence rate ratios (IRR) and incidence rate differences (IRD) to verify the robustness of the results.[25]The results were considered statistically significant when P value $<$ 0.05. Publication bias was examined using a funnel graph. Subgroup analyses were conducted based on the diabetes status, type of gliflozines used, and follow-up duration. Sensitivity analyses were performed by sequential trials removal. Review Manager 5.3 and Stata 16.0 were used for all statistical analyses.

Results

Literature search and characteristics of identified studies

Ten RCTs were finally included in our meta-analysis. Of these, four trials (DAPA-HF, EMPEROR-Reduced, SOLOIST-WHF, and EMPEROR-Preserved) were HF-specific, and five trials (CAN-

VAS, EMPA-REG OUTCOME, CREDENCE, DECLARE-TIMI 58, and VERTIS-CV) reported cardiovascular outcomes in subgroup analyses or post hoc analyses. The authors of the SCROED trial presented a pooled analysis of the SOLOIST-WHF and SCORED trials at the American Heart Association 2020 conference. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart summarized the search and study selection process and was shown in *Figure 1*.

A total of 23 825 HF patients were eventually included in our meta-analysis. The median follow-up time ranges from 0.75 to 4.2 years. The EMPA-REG OUTCOME, CREDENCE, CANVAS, DECLARE-TIMI 58, VERTIS-CV, and SCORED trials included only DM patients. The DAPA-HF, EMPEROR-Reduced, SOLOIST-WHF, and EMPEROR-Preserved trials included only HF patients. *Table 1* showed the baseline characteristics of the included studies.

Cardiovascular outcomes for the overall heart failure patients

Compared with placebo, SGLT2i can significantly reduce the risk of composite of first HHF or CV death (HR = 0.76, 95%CI = 0.71–0.81, $P < 0.01$; *Figure 2A*), composite of total HHF or CV death (RR = 0.74, 95%CI = 0.68–0.81, $P < 0.01$; *Figure 2B*), first HHF (HR = 0.69, 95%CI = 0.64–0.75, $P < 0.01$; *Figure 2C*), CV death (HR = 0.88, 95%CI = 0.80–0.96, $P < 0.01$; *Figure 2D*), and any death (HR = 0.90, 95%CI = 0.83–0.97, $P < 0.01$; *Figure 2E*). However, no significant difference in major adverse cardiovascular event (HR = 0.95, 95%CI = 0.83–1.09, $P = 0.48$; *Figure 2F*) was observed between placebo and SGLT2i. It should be noted that the improvement of KCCQ (mean difference = 1.62, 95%CI = 1.28–1.97, $P < 0.01$; *Figure 2G*) was also statistically significant. The result of primary outcome was consistent regardless of the diabetes status, type of gliflozines used, and follow-up duration (Supporting Information, *Figure S1*). For CV death or first HHF and CV death, IRR and IRD methods gave similar estimates of effect in favour of the intervention (*Figure S2* and *Table S1*). IRR suggested a 25% reduction in the incidence of the CV death or first HHF (IRR = 0.75, 95%CI = 0.70-0.80, $P < 0.01$), while IRD implied that the intervention reduced the risk of CV death or first HHF by 3% per patient-year (IRD −0.03/patient-year, 95%CI −0.04 to −0.03, $P < 0.01$). Sensitivity analyses also showed consistent results.

Figure 1 Study flowchart of the article identification, inclusion, and exclusion.

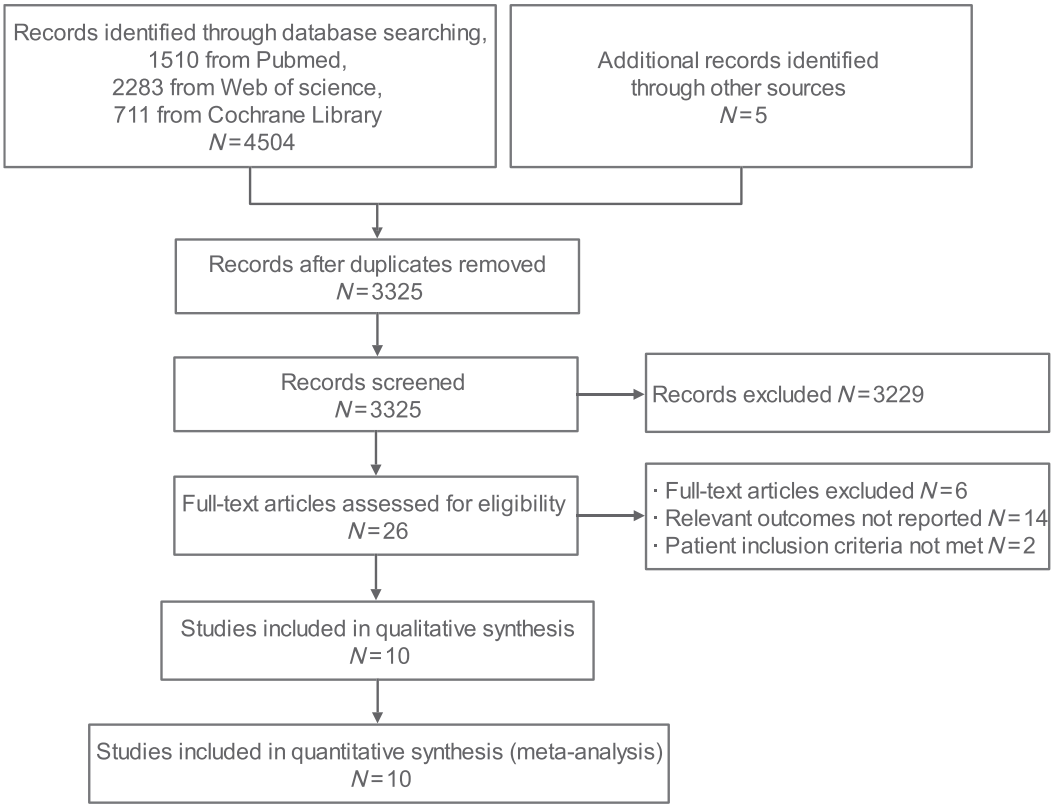

Table 1 Characteristics of studies included in the meta-analysis

	EMPA-REG OUTCOME 2015		CANVAS 2017		CREDENCE 2019		DECLARE-TIMI 58 2019		DAPA-HF 2019	
Drug	Empagliflozin	Placebo	Canagliflozin	Placebo	Canagliflozin	Placebo	Dapagliflozin	Placebo	Dapagliflozin	Placebo
Total number	462	244	803	658	329	323	852	872	2373	2371
Age, years	64.5 (8.8)	64.5 (8.9)	64.1 (8.3)	63.4 (8.3)	64.8 (8.1)	65.5 (8.1)	NA	NA	66.2 (11.0)	66.5 (10.8)
Female, %	142 (30.7)	69 (28.3)	346 (43.1)	302 (45.9)	124 (37.7)	133 (41.2)	NA	NA	564 (23.8)	545 (23.0)
BMI, kg/m^2	31.9 (5.6)	32.3 (5.4)	33.1 (5.9)	33.2 (5.9)	32.9 (6.2)	32.5 (6.1)	NA	NA	28.2 (6.0)	28.1 (5.9)
DM, %	462 (100)	244 (100)	803 (100)	658 (100)	329 (100)	323 (100)	NA	NA	993 (41.8)	990 (41.8)
HbA1c, %	8.11 (0.87)	8.01 (0.82)	8.4 (1.0)	8.4(1.0)	8.4(1.3)	8.4 (1.4)	NA	NA	NA	NA
NT-proBNP, pg/mL	NA	NA	NA	NA	NA	NA	NA	NA	1428 (857–2655)	1446 (857–2641)
eGFR, mL/min/1.73 m^2	68.4 (20.2)	69.3 (20.7)	72.7 (19.5)	73.3 (19.8)	56.7 (18.8)	57.3 (19.1)	NA	NA	66.0 (19.6)	65.5 (19.3)
Follow up (years)	3.1		3.6		2.6		4.2		1.5	
NYHA										
II	NA	NA	NA	NA	NA	NA	NA	NA	1606 (67.7)	1597 (67.4)
III	NA	NA	NA	NA	NA	NA	NA	NA	747 (31.5)	751 (31.7)
IV	NA	NA	NA	NA	NA	NA	NA	NA	20 (0.8)	23 (1.0)

BMI, body mass index; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HbA1c, haemoglobin A1c; NA, not available; NT-proBNP, NT-proB-type natriuretic peptide. Data are reported as *n* (%), mean (SD), or median (interquartile range).

Table 1 (continued)

	EMPEROR-Reduced 2020		SCORED 2020		VERTIS-CV 2020		SOLOIST-WHF 2021		EMPEROR-Preserved 2021	
Drug	Empagliflozin	Placebo	Sotagliflozin	Placebo	Ertugliflozin	Placebo	Sotagliflozin	Placebo	Empagliflozin	Placebo
Total number	1863	1867	NA	NA	1286	672	608	614	2997	2991
Age, years	67.2 (10.8)	66.5 (11.2)	NA	NA	64.2 (7.9)	64.7 (7.8)	69 (63–76)	70 (64–76)	71.8 (9.3)	71.9 (9.6)
Female, %	437 (23.5)	456 (24.4)	NA	NA	395 (30.7)	229 (34.1)	198 (32.6)	214 (34.9)	1338 (44.6)	1338 (44.7)
BMI, kg/m^2	28.0 (5.5)	27.8 (5.3)	NA	NA	32.5 (5.5)	32.7 (5.2)	30.4 (26.3–34.3)	31.1 (27.3–34.5)	29.77 (5.8)	29.90 (5.9)
DM, %	927 (49.8)	929 (49.8)	NA	NA	1286 (100)	672 (100)	608 (100)	614 (100)	1466 (48.9)	1472 (49.2)
HbA1c, %	NA	NA	NA	NA	8.3 (0.9)	8.3 (0.9)	7.1 (6.4–8.3)	7.2 (6.4–8.2)	NA	NA
NT-proBNP, pg/mL	1887 (1077–3429)	1926 (1153–3525)	NA	NA	NA	NA	1816.8 (854.7–3658.5)	1741.0 (842.5–3582.2)	994 (501–1740)	946 (498–1725)
eGFR, mL/min/1.73 m^2	61.8 (21.7)	62.2 (21.5)	NA	NA	NA	NA	49.2 (39.5–61.2)	50.5 (40.5–64.6)	60.6 (19.8)	60.6 (19.9)
Follow up (years)	1.3		1.3		3.5		0.7		2.2	
NYHA										
II	1399 (75.1)	1401 (75.0)	NA	NA	838 (65.2)	451 (67.1)	NA	NA	2432 (81.1)	2451 (81.9)
III	455 (24.4)	455 (24.4)	NA	NA	102 (7.9)	37 (5.5)	NA	NA	552 (18.4)	531 (17.8)
IV	9 (0.5)	11 (0.6)	NA	NA	1 (0.1)	0	NA	NA	10 (0.3)	8 (0.3)

BMI, body mass index; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HbA1c, haemoglobin A1c; NA, not available; NT-proBNP, NT-proB-type natriuretic peptide. Data are reported as *n* (%), mean (SD), or median (interquartile range).

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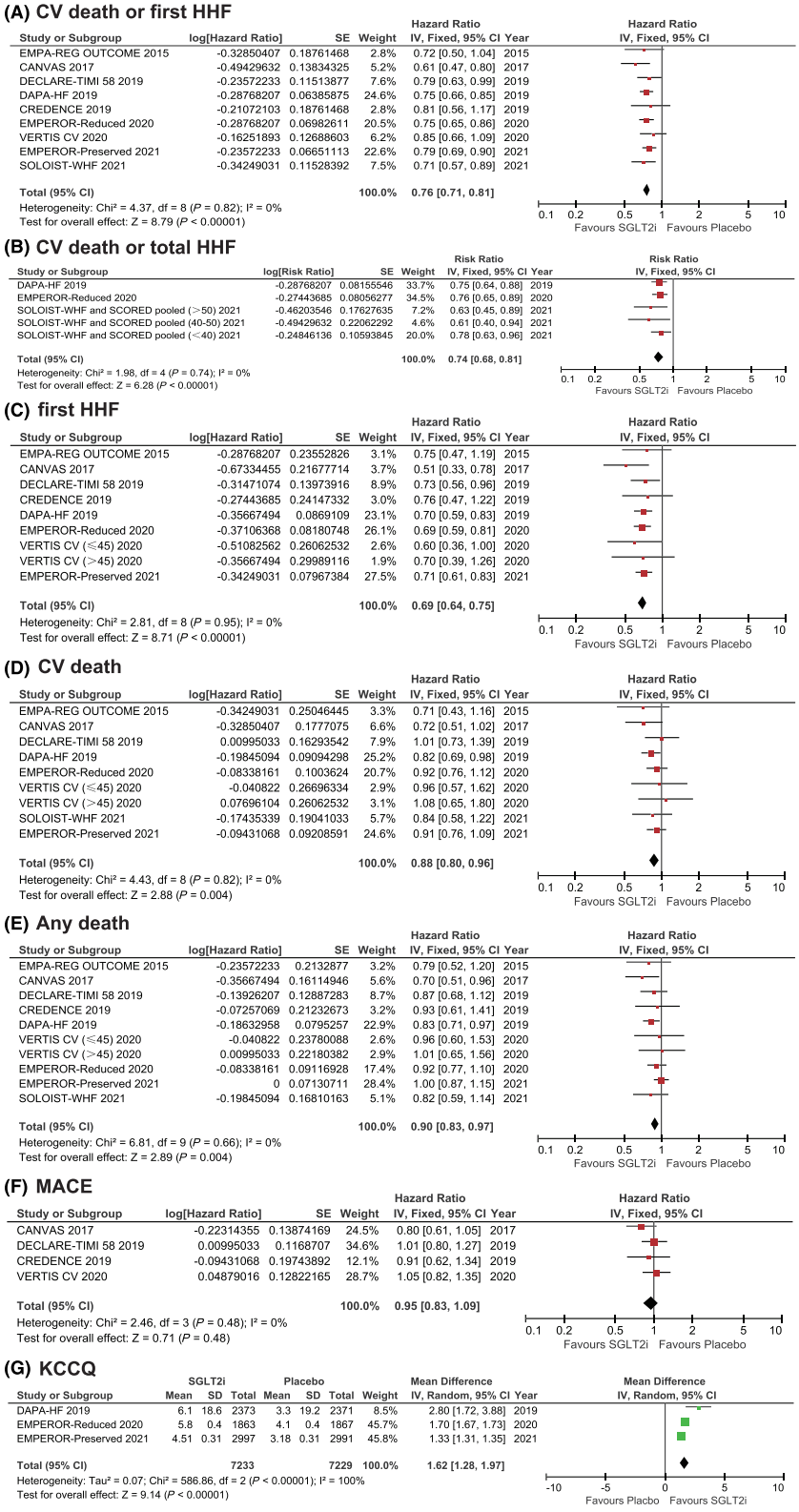
Figure 2 Forest plot of efficacy outcomes of sodium-glucose cotransporter-2 inhibitor vs. placebo in overall heart failure patients. CI, confidence interval; CV death, cardiovascular death; HHF, hospitalization for heart failure; KCCQ, Kansas City Cardiomyopathy Questionnaire; MACE, major adverse cardiovascular events; SGLT2i, sodium-glucose cotransporter-2 inhibitor.



Safety outcomes for the overall heart failure patients

The results showed that SGLT2i use was associated with a reduction of SAE (RR = 0.90, 95%CI = 0.87–0.93, $P < 0.01$; *Figure 3A*) and an increase of urinary tract infections (RR = 1.17, 95%CI = 1.03–1.33, $P = 0.02$; *Figure 3C*). Other safety outcomes were not statistically significant between placebo and SGLT2i including AKI (RR = 0.89, 95%CI = 0.78–1.01, $P = 0.07$; *Figure 3B*), hypoglycaemia (RR = 0.95, 95%CI = 0.80–1.14, $P = 0.58$; *Figure 3D*), amputation (RR = 1.27, 95%CI = 0.79–2.03, $P = 0.32$; *Figure 3E*), volume depletion (RR = 1.08, 95%C I = 0.95–1.23, $P = 0.23$; *Figure 3F*), and bone fracture (RR = 1.04, 95%C I = 0.88–1.23, $P = 0.64$; *Figure 3G*).

Efficacy and safety outcomes for heart failure with preserved ejection fraction patients

The recently published EMPEROR-Preserved study[18] showed exhilarating results in HFpEF patients. We combined data from the DECLARE-TIMI 58, VERTIS-CV, SCORED, SOLOIST-WHF, and EMPEROR-Preserved studies to estimate efficacy and safety outcomes. HFpEF patients were predefined as having an EF cut point of >45% in the first two studies, >40% in the last study, and >50% in SCORED and SOLOIST-WHF studies. The results showed a significant reduction in the composite of first HHF or CV death (HR = 0.81, 95%CI = 0.73–0.91, $P < 0.01$; *Figure 4A*), first HHF (HR = 0.71, 95%CI = 0.62–0.82, $P < 0.01$; *Figure 4B*), and total HHF or CV death (HR = 0.61, 95%CI = 0.43–0.86, $P < 0.01$; *Figure 4E*) with SGLT2i use. However, there was no statistical significance in CV death (HR = 0.99, 95%CI = 0.84–1.15, $P = 0.86$; *Figure 4C*) and any death (HR = 1.00, 95%CI = 0.89–1.13, $P = 0.95$; *Figure 4D*).

Quality assessment and publication bias

Of these included RCTs, four trials (CREDENCE, EMPA-REG OUTCOME, EMPEROR-Reduced, and VERTIS-CV) did not explicitly elucidate the blinding of outcomes assessment in their predesign plans and were considered as unclear risk. The data that produced primary efficacy or safety outcomes were not analysed in accordance with a prespecified analysis plan in three trials (DECLARE-TIMI 58, VERTIS CV, and SCORED) due to loss of funding or change of outcomes. However, these changes were made without knowledge of any blinded or unblinded comparative data, and the statistical method has also changed accordingly. So we tend to determine the three trials as low risk in other bias (*Figure S3*). Visual analyses of funnel plots did not suggest any risk of publication bias (*Figure S4*).

Discussion

In this updated meta-analysis, we included a total of 10 RCT studies with 23 825 patients. In the overall HF cohort, SGLT2i significantly reduced the risk of composite of first HHF or CV death, composite of total HHF or CV death, first HHF, CV death, and any death by 24%, 26%, 31%, 12%, and 10%, respectively. In several recently published results of large-scale clinical trials,[10,11,14] cardiovascular death and all-cause death tended not to be statistically significant. Nonetheless, our meta-analysis suggests the improvement effect to be statistically significant after combining them. As we all know, HF is characterized by repeated hospitalizations, and the risk of death and successive rehospitalization rises sharply when a patient is firstly admitted to the hospital for decompensated HF.[26] Therefore, distinguishing the first and total rehospitalization for HF is essential for evaluating the effect of new therapy and the prognosis of HF patients clinically. Fortunately, SGLT2i performed well in both outcomes. This is one of the main points highlighted in this article. Symptom control is considered as one of important characteristics of HF management programme, greatly affecting the long-term compliance of chronic HF patients to certain drugs.[8] The effect of SGLT2i on the benefit of quality of life represented by KCCQ in HF patients is inspiring, which indicated that SGLT2i improved not only the long-term prognosis but also clinical symptoms and activity ability. Although the benefit is affirmative, it is noteworthy that the extent of the benefit in our conclusion is exploratory because of the different follow-up durations in various studies. The result of PRESERVED-HF study recently released at the Heart Failure Society of America Annual Scientific Meeting 2021 showed that SGLT2i can improve KCCQ clinical summary score at 12 weeks in HF patients with LVEF $\geq$ 45%, which further validated our conclusion.

In terms of safety outcomes, the SGLT2i group was able to reduce the risk of SAE by 10% and increase the risk of urinary tract infections by 17%. Given that the unique mechanism of SGLT2i is the inhibition of filtered glucose reabsorption in renal proximal convoluted tubule,[27] the increased occurrence of urinary tract infections may be an inevitable result, and this is a risk that we must be aware of in our clinical practice. The remaining safety outcomes were not statistically significant. Although the improvement effect of SGLT2i on AKI was not statistically significant, several studies showed its protective effects on chronic kidney disease by glycaemic control, slowing down the decline of eGFR and other underlying mechanisms.[9,15,18,28] This suggests that SGLT2i can be recommended more often for HF patients in combination with chronic kidney disease or diabetes.

This meta-analysis was the first to include the EMPEROR-Preserved study, which has made a groundbreaking contribution to promoting the use of SGLT2 inhibitors in patients with HFpEF. Our results showed that the risk

Figure 3 Forest plot of safety outcomes of sodium-glucose cotransporter-2 inhibitor vs. placebo in overall heart failure patients. AKI, acute kidney injury; SAE, serious adverse events.

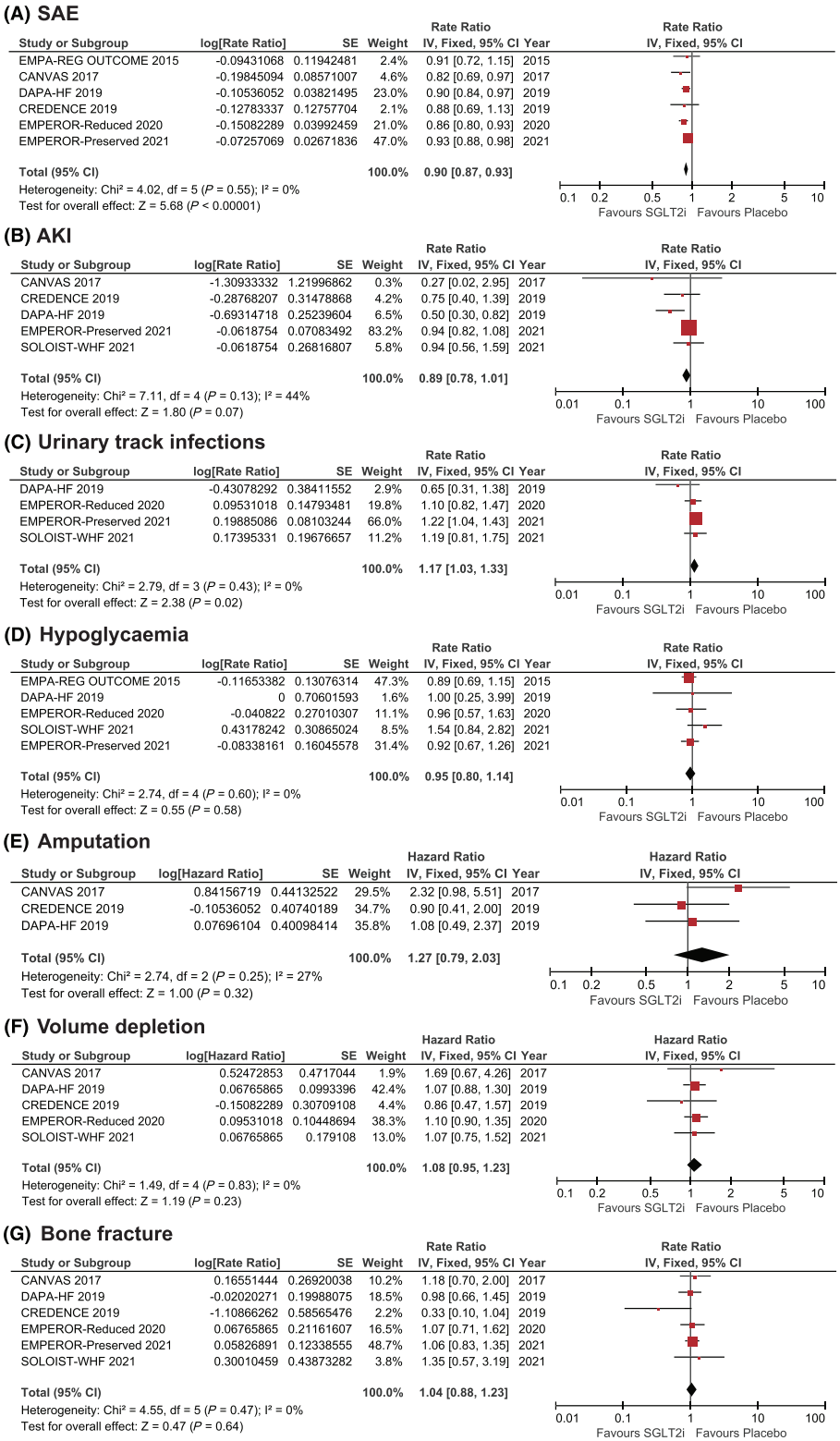


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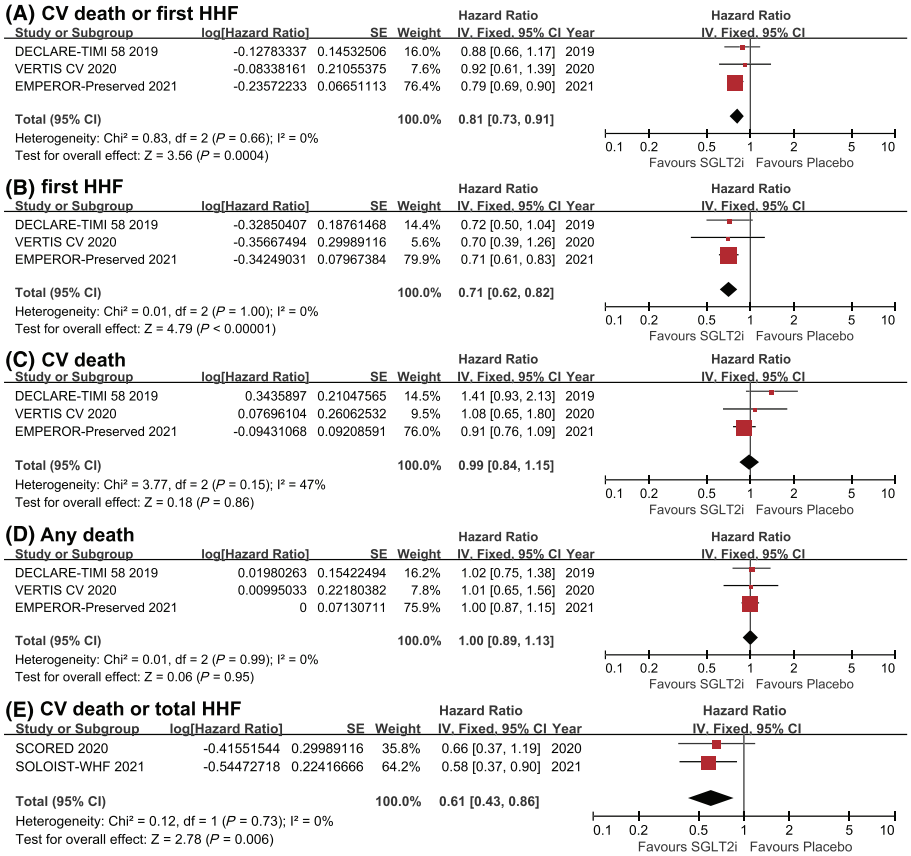
Figure 4 Forest plot of efficacy outcomes of sodium-glucose cotransporter-2 inhibitor vs. placebo in patients with heart failure with preserved ejection fraction. CI, confidence interval; CV death, cardiovascular death; HHF, hospitalization for heart failure; SGLT2i, sodium-glucose cotransporter-2 inhibitor.



of composite of first HHF or CV death, first HHF, and total HHF or CV death were reduced by 19%, 29%, and 39%, respectively, suggesting the effects of SGLT2i on HF events do not vary meaningfully with the HF phenotype. At present, the treatment of HFpEF is mainly to use diuretics to reduce symptoms of congestion.[8] From this point of view, SGLT2i, which has a milder natriuretic effect and will not bring related side effects due to the activation of the sympathetic nervous system or renin-angiotensin system compared with traditional loop diuretics,[29,30] may become a good additional choice for HFpEF patients in the future. It should be noted that the therapeutic effect is different between HFpEF patients with LVEF $>$ 60% and HFrEF patients, which has been demonstrated by the results of PARAGON-HF study and EMPEROR-Preserved study.[18,31] This may be partly due to the apparently lower incidence of cardiovascular events (e.g. hospitalization for HF and cardiovascular death) in HFpEF patients (e.g. EMPEROR-Preserved) than in HFrEF patients (e.g. EMPEROR-Reduced and DAPA-HF). Meanwhile, the difference in drug response to SGLT2i in patients with HF is relatively smaller than that of ARNI. Compared with the latter's no beneficial effect in the PARAGON-HF study, SGLT2i could reduce the risk of first HF hospitalization even in patients with LVEF $>$ 62.5%, although there was no statistical difference. This broad-spectrum effect may be explained by the multiple mechanisms of SGLT2i, which can reduce cardiac overload by osmotic diuresis, suppress inflammation by activation of adenosine monophosphate-activated protein kinase, and ameliorate myocardial energy metabolism by hypoglycaemic effect. As we know, hypertension, diabetes, and chronic inflammation are all major risk factors for HFpEF.[32] We still need more studies focusing on specific subpopulations of HF to provide evidence for the use of SGLT2i. In addition to the ongoing DELIVER study (NCT01297257), several smaller RCTs are evaluating the effects of SGLT-2i on left ventricular systolic and diastolic function, pulmonary capillary wedge pressure, haemodynamics, biomarkers, and health status in HFpEF patients (NCT04739215, NCT04475042, NCT04730947, NCT03030222,

and NCT03416270). We hope that future research can bring more evidence.

In the recently published ESC guidelines for the treatment of acute and chronic HF,[8] SGLT2i was recommended as a new pillar of management of patients with HFrEF (I, A) on the basis of the previous triple therapy (ACEI/ARNI, β-blockers, and MRA). Meanwhile, the US Food and Drug Administration also approved SGLT2i as a treatment for patients with HFrEF. We believe that SGLT2i will also be used in HFpEF patients in near future. But as a new hypoglycaemic drug, the widespread clinical use of SGLT2i in the treatment of HF patients still needs more collaboration between cardiologists and endocrinologists.

It is important to recognize that our study has some limitations. Firstly, the target population, dosage of SGLT2i used, and duration of follow up exist differences between the 10 included RCTs. Although the primary efficacy outcome remained consistent in the subgroup analysis, this difference could still affect the study's evidence level to some extent. Secondly, baseline information was not available in the DECLARE-TIMI 58 and SCORED trials, which makes it difficult to determine whether the ameliorative effect of SGLT2i on HF is influenced by the background therapy or severity of HF. Finally, the sample size of the HFpEF population is relatively small for pooling data, and more evidence focusing on HFpEF patients is needed.

Conclusion

Sodium-glucose cotransporter-2 inhibitor is associated with lower risk of hospitalization for HF and mortality in patients with HF compared with placebo, regardless of the diabetes status, types of gliflozines used, and follow-up duration. The effect of SGLT2i in HFpEF patients tended to be beneficial in terms of the composite of first HHF or CV death, first HHF, and total HHF or CV death, at a cost of increased risk of urinary tract infections. In a nutshell, its story continues to unfold, and its safety needs further validation.

Conflict of interest

All authors declare that they have no conflict of interest.

Funding

No funding was received to assist with the preparation of this manuscript.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Subgroup analysis based on diabetes status, type of gliflozines used, and follow-up duration.
Figure S2. Forest plot of efficacy outcomes calculated by IRD and IRR IRR, the incidence rate ratio obtained using Mantel–-Haenszel procedure to estimate a fixed effects model; IRD, the incidence rate difference obtained using a Mantel–-Haenszel procedure to estimate a fixed-effects model and an inverse-variance method to estimate a random-effects model; CV death, cardiovascular death; HHF, hospitalization for heart failure.
Figure S3. Quality assessment of the enrolled trials.
Figure S4. Funnel plots in the meta-analysis. SAE, serious adverse events; HHF, hospitalization for heart failure.
Table S1. Summary outcomes by different measures.

References

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