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Original Article

SGLT2 inhibitors and cardiovascular outcomes in heart failure with mildly reduced and preserved ejection fraction: A systematic review and meta-analysis

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ABSTRACT

Aim: To provide a pooled effect of sodium-glucose cotransporter-2 inhibitors (SGLT2i) on cardiovascular outcomes in patients with heart failure with preserved ejection fraction (HFpEF: ≥50%) or/and mildly reduced EF (HFmrEF: 41–49%) regardless of baseline diabetes.

Methods: We systemically searched PubMed/MEDLINE, Embase, Web of Science databases and clinical trial registries using appropriate keywords till August 28, 2022, to identify randomized controlled trials (RCTs) or post-hoc analysis of RCTs, reporting cardiovascular death (CVD) and/or urgent visits/hospitalization for heart failure(HHF) in patients with HFmrEF/HFpEF receiving SGLTi vs. placebo. Hazard ratios (HR) with 95% confidence intervals (CI) for outcomes were pooled together using generic inverse variance method with fixed-effects model.

Results: We identified six RCTs, pooling data retrieved from 15,769 patients with HFmrEF/HFpEF. Pooled analysis showed that compared to placebo, SGLT2i use was significantly associated with improved CVD/HHF outcomes in HFmrEF/HFpEF (pooled HR 0.80, 95% CI: 0.74, 0.86, $p < 0.001$, $I^2 = 0\%$). When separately analyzed, benefits of SGLT2i remained significant across HFpEF (N = 8891, HR 0.79, 95% CI: 0.71, 0.87, $p < 0.001$, $I^2 = 0\%$) and HFmrEF (N = 4555, HR 0.77, 95% CI: 0.67, 0.89, $p < 0.001$, $I^2 = 40\%$). Consistent benefits were observed also in HFmrEF/HFpEF subgroup without baseline diabetes (N = 6507, HR 0.80, 95% CI: 0.70, 0.91, $p < 0.001$, $I^2 = 0\%$). Sensitivity analysis including the DELIVER and EMPEROR-Preserved trials found a trend towards significant beneficial effects on CV deaths with no heterogeneity (HR 0.90, 95% CI: 0.79, 1.02, p = 0.08, $I^2 = 0\%$).

Conclusions: This meta-analysis established the place of SGLT2i as a foundational therapy among patients with HF with preserved and mildly reduced EF regardless of diabetes.

1. Introduction

Heart failure with preserved ejection fraction (HFpEF), characterized by heart failure (HF) syndrome and a normal or near-normal left ventricular ejection fraction (EF), has become the predominant form of HF.[1] Various cut-offs of EF have been proposed previously to define HFpEF. Recent guidelines have reached consensus and clearly suggested to use EF ≥ 50% cut-off to define HFpEF.[2,3] HF with mid-range EF (40–49%) has been renamed as "HF with mildly reduced EF" (HFmrEF) due to its distinct similarities with HF with reduced EF (HFrEF).[2–4] Approximately 10–25% of patients with HF belong to this HFmrEF group, while nearly 50% have HFpEF.[4]

HFpEF is recognized as a heterogeneous syndrome of multiple discrete phenotypes, such as diabetes mellitus (DM), obesity and hypertension.[1] Given the rising aging population in many countries and increasing prevalence of DM/obesity or hypertension, the proportion of HFpEF is also rapidly rising in comparison to HFrEF.[1] Unlike HFrEF or HFmrEF, the evidence of clear benefits of standard of care HF therapy (angiotensin receptor blockers/ARBs, mineralocorticoid receptor agonists/MRA, beta blockers, angiotensin receptor neprilysin inhibitors/ARNi) have been debatable in HFpEF.[3] Hence, there was an unmet need for an optimal therapy for

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patients with HFpEF, especially for those not in the lower end of EF spectrum.

SGLT2i, developed initially as anti-hyperglycemic agents, offer a myriad of cardio-renal benefits beyond glucose control.[5] Several post-hoc or pre-specified analysis studies of various randomized controlled trials (RCTs) have pointed towards benefits of SGLT2i on cardiovascular outcomes across the spectrum of heart failure.[6–8] Furthermore, the EMPEROR-Preserved trial and recently published DELIVER trial clearly demonstrated that SGLT2i reduces the risk of cardiovascular death (CVD) or urgent visits/hospitalization for heart failure (HHF) in patients with HFmrEF/HFpEF regardless of diabetes.[9,10] Benefits of SGLT2i in patients with heart failure and reduced EF (HFrEF) has been well-established in previous meta-analysis,[11] thereby justifying a strong (class 1, benefit>>>risk) recommendation for their use in HFrEF as per 2022 guidelines.[3] Nonetheless, the strength of evidence for SGLT2i use in HFpEF has been rated as moderate (class 2a recommendation).[3] Moreover, cardiovascular effects of SGLT2i have also not been meta-analysed separately in HFmrEF and HFpEF groups, as defined by current EF cut-offs.[12] With regard to HFpEF subpopulation defined by EF>50%, a recently published meta-analysis might have overestimated their effects on pooling data from the SOLOIST-WHF/SCORED trials only.[13]

The present systematic review and meta-analysis aimed to provide a comprehensive summary and pooled effects of SGLT2i on cardiovascular outcomes in patients with HFmrEF and/or HFpEF.

2. Methods

The meta-analysis was conducted and reported according to the Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) statement.[14] The study protocol was prospectively registered in PROSPERO database (CRD42022356582).

2.1. Search strategy

"PubMed/MEDLINE", "Embase", and "Web of Science" databases and clinical trial registries were systematically searched from inception till August 28, 2022 by two independent investigators. The search was conducted using appropriate keywords or MeSH terms or Emtree terms **(sMEthod-1)**. The search was restricted only to English language. For potentially eligible articles, the investigators also screened the references of pertinent reviews and retrieved articles. Wherever possible, for missing data, the investigators contacted the corresponding authors of the potentially eligible articles.

2.2. Eligibility and exclusion criteria

Eligibility criteria were set as follows.

1. Given the scarcity of literature, we planned to select randomized controlled trials (RCTs), post hoc analysis of RCTs that included subjects with HFmrEF (EF 41–49%) and/or HFpEF (EF $\geq$ 50%)
2. Studies should include these patients with HFmrEF/HFpEF, a proportion of who should be taking SGLT2i and the rest should be taking placebo.
3. Studies reporting clinical outcomes in terms of HHF (total events or analyzed as time-to-first event or urgent visits) and/or CVD and all-cause death as one of the end-points were included.
4. The clinical outcomes should be reported as adjusted hazard ratio (HR) in patients with HFmrEF/HFpEF taking SGLT2i compared to those who were taking placebo.

Exclusion criteria were set as follows.

1. Clinical case series, comments, editorials, reviews, study protocols, letters to the editor.
2. Studies not reporting clinical outcomes in terms of HHF, CVD, or all-cause death.
3. Non-peer reviewed manuscripts published as preprints.
4. Incomplete data.

2.3. Data extraction

Titles and/or abstracts were scanned independently by two investigators to exclude duplicate studies; besides, studies that did not meet the aforementioned eligibility criteria were also excluded. Thereafter, the full text of potentially eligible studies was assessed. Any discrepancies between MB and RP were solved by discussions with a third senior investigator. Finally, the studies that were selected were thoroughly reviewed.

The following data were extracted for further assessment: the study characteristics, the total study population, the population of interest (HFmrEF and/or HFpEF), the type and dose of SGLT2i used, the median follow-up period, the number of those patients taking SGLT2i vs. placebo, the reported outcome of interest as the number of events or events per 100 patient-years or absolute number of events and the HR in those treated with SGLT2i vs. those who received placebo.

2.4. Assessment of risk of bias of studies

The risk of bias for the included RCTs was assessed using the revised Cochrane Collaboration's tool; it consists of the five domains: randomization process, deviations from the intended interventions, missing outcome data, measurement of the outcome and selection of the reported results.[15] Each of these domains was rated as "low", "unclear", or "high" risk of bias. A study with presence of adequate procedures in all the domains was rated as being of low risk of bias; on the other hand, an inadequate procedure in at least one domain rated a study as high risk of bias. In any other case, a study was labeled as an unclear risk of bias.

The risk of bias was independently assessed by two investigators (MB and KN). Any discrepancy was solved by discussion with a third senior investigator (SM).

2.5. Statistical analysis

Hazard ratios (HR) for the outcome of interest and the 95% confidence intervals (CI) from each study were extracted. Data were pooled together using the generic inverse variance method after implementation of the fixed-effects model. Analysis with random effects model and sensitivity analysis was planned in case of significant heterogeneity in pooled effects. Subgroup analyses was performed with respect to presence of baseline diabetes.

I^2 statistics was used to assess statistical heterogeneity among studies. Based on the upper limit of I^2, statistical heterogeneity was categorized as "low" (25%), "moderate" (50%), and "high" (75%).[16] For the present meta-analysis, an I^2 value was $\geq$50%, with a corresponding p value < 0.05 was used to define significant heterogeneity. Sensitivity analysis using leave-one-out method was planned in case of heterogeneity in pooled effects of SGLT2i on outcomes in HFmrEF/HFpEF.

A $p < 0.05$ was considered to be statistically significant for pooled results. The meta-analysis was performed using the RevMan

5.4 software (Cochrane Collaboration). Analysis of publication bias was conducted using Stata software version 15.1 (STATA Corp., College Station, TX, USA).

3. Results

3.1. Characteristics of the included studies

Following a meticulous search, six RCTs were included,[6–10] pooling data were retrieved from 15,769 patients with HFmrEF/HFpEF. The PRISMA flow-chart describing the study selection process has been given in sFig. 1.

Relevant data from two related cardiovascular outcome trials on dual SGLT-1/2 inhibitor sotagliflozin, namely the SOLOIST-WHF[17] and SCORED trial,[18] were extracted for the pooled analysis by Bhatt et al.[6] Of note, the SOLOIST-WHF trial was conducted on T2DM patients with worsening HF,[17] whereas the SCORED trial had included T2DM patients with moderate renal impairment.[18] Two studies were post-hoc analyses[7,8] on data derived from DECLARE-TIMI 58 and VERTIS-CV trials respectively.[19,20] Finally. EMPEROR-Preserved and DELIVER trials were cardiovascular outcome trials specifically designed to evaluate effects of empagliflozin and dapagliflozin in patients with HFpEF or HFmrEF.[9,10] Amongst them, 3 studies were identified,[6,9,10] which separately provided data of patients with HFpEF (N = 8891) and HFmrEF (N = 4555).

Baseline characteristics of the study population of interest and outcomes with the reported hazard ratios have been described in Table 1. The risk of bias for the RCTs has been depicted in sTable 1. **All the RCTs were found to have a low risk of bias**.

3.2. Quantitative synthesis

Primary outcome of cardiovascular death (CVD) and hospitalization or urgent visits for heart failure (HHF) were reported by all 5 studies. Pooled analysis showed that compared to placebo, SGLT2i use was significantly associated with reduced risk of CVD/HHF outcomes in HFmrEF/HFpEF (pooled HR 0.80, 95% CI: 0.74, 0.86, $p < 0.001$, $I^2 = 0\%$) (Fig. 1A).

The effects of SGLT2i were also separately analyzed in HFpEF and HFmrEF. Randomization to SGLT2i versus placebo significantly

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

Studies (references)	Bhatt et al[6] SOLOIST-WHF and SCORED trials[15,16]	Kato et al[7] analysis of DECLARE-TIMI 58 trial[17]	Cosentino et al[8] analysis of VERTIS-CV trial[18]	Anker et al. EMPEROR-Preserved trial[9]	Solomon et al. DELIVER trial[10]
Study type	Pre-specified analysis of 2 RCTs	Post-hoc analysis of RCT	Post-hoc analysis of RCT	RCT	RCT
Population	T2DM, age 18–85 years, recent worsening HF (SOLOIST-WHF) T2DM, age ≥18 years, HbA1c ≥ 7%, eGFR 25–60 ml/min per 1.73 m^2 & CVD risk (SCORED) HF and EF ≥ 50% (N = 739) or EF 40-<50% (N = 456)	T2DM, age ≥40 years, HbA1c 6.5–12%, creatinine clearance> 60 ml/min, ASCVD risk factors (no ASCVD, n = 10,186) HF and EF ≥ 45% (N = 1316)	T2DM, age ≥40 years, HbA1c 7–10.5%, established ASCVD, eGFR> 30 ml/min/1.73 m^2 HF and EF>45% (N = 1007)	Age ≥18 years, with or without T2DM NYHA class II–IV chronic HF and EF >40% (N = 5988; T2DM, n = 2938)	Age ≥40 years, with or without T2DM; stabilized HF and EF >40% (N = 6263; T2DM, n = 2806)
Baseline parameters					
Mean age (yrs)	69 (both RCTs)	65	64	71.8	71.7
Female (%)	–	42.8%	36%	44.6%	43.9%
Race (%)	–	94% whites, 5% Asians	95% whites, 2% Asians	76% whites, 13% Asians	71% whites, 20% Asians
Mean BMI (kg/m2)	–	33.1	32.7	29.8	29.8
eGFR(ml/min/1.7m2)	–	86	81	60	61
HF therapy use (%)	–	Loop diuretic (35%), ACEI/ARB (85%), beta blocker (77%), MRA (13.8%)	Loop diuretic (23%), ACEI/ARB (85%), beta blocker (78%), MRA (11%)	ACEI or ARB or ARNI (81%), MRA (37%)	Loop diuretic (73%), ACEI/ARB (76%), beta blocker (82%), ARNI (4%), MRA (42%)
Cardiovascular outcomes reported	CV Death (CVD), urgent visits or hospitalization for HF (HHF)	CVD or HHF, analyzed as time to first event	CVD or HHF, time to first event (secondary endpoint)	CVD or HHF, analyzed as time to first event	CVD or HHF, analyzed as time to event
Intervention versus placebo	Sotagliflozin 200–400 mg OD vs placebo	Dapagliflozin 10 mg OD vs placebo	Ertugliflozin 5–15 mg OD vs placebo	Empagliflozin 10 mg OD vs placebo	Dapagliflozin 10 mg OD vs placebo
Median follow-up duration	2 years	4.2 years	3.5 years	2.1 years	2.3 years
Results in HF with mrEF/pEF	mrEF: 45.2 vs 71 events per 100 py (HR 0.61; 95% CI: 0.40, 0.94)	92/662 vs 99/654 (HR 0.88; 95% CI: 0.66, 1.17)	68/680 vs 35/327 (HR 0.92; 95% C.I. 0.61–1.39)	415/2997 vs 511/2991[a] (HR 0.79; 95% CI: 0.69, 0.90)	512/3131 vs 610/3132[b] (HR 0.82; 95% CI: 0.73, 0.92)
CVD/HHF		54/662 vs 38/654 (HR 1.41; 95% CI: 0.93, 2.13)	47/680 vs 21/327 (HR 1.08; 95% C.I. 0.64–1.80)	219/2997 vs 244/2991 (HR 0.91; 95% CI: 0.76, 1.09)	231/3131 vs 261/3132 (HR 0.88; 95% CI: 0.74, 1.05)
CVD	pEF: 37.5 vs 59 events per 100 py (HR 0.63; 95% CI: 0.45, 0.88)	84/662 vs 81/654 (HR 1.02; 95% CI: 0.75, 1.38)	63/680 vs 30/327 (HR 1.01; 95% C.I. 0.66–1.56)	422/2997 vs 427/2991 (HR 1.00; 95% CI: 0.87, 0.)	497/3131 vs 526/3132 (HR 0.94; 95% CI: 0.83, 1.07)
All-cause mortality	–				
	–				

Abbreviations: HR, hazard ratio; HF, heart failure; EF, ejection fraction; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; NYHA: New York Heart Association; BMI, body mass index; eGFR, effective glomerular filtration rate; ASCVD, atherosclerotic cardiovascular disease; CVD, cardiovascular death; HHF, hospitalization for heart failure; ACEI, angiotensinogen converting enzyme inhibitor; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor.

[a] HRs according to baseline EF: 1) HFmrEF (40-<50%): 145/995 vs 193/988 (HR 0.71; 95% CI: 0.57, 0.88); 2) HFpEF (50-<60%): 138/1028 vs 173/1030 (HR 0.80; 95% CI: 0.64, 0.99); 3) HFpEF (≥60%): 132/974 vs 145/973 (HR 0.87; 95% CI: 0.69, 1.10).

[b] HRs according to baseline EF: 1) HFmrEF (40-<50%): 207/1067 vs 229/1049 (HR 0.87; 95% CI: 0.72, 1.07); 2) HFpEF (50-<60%): 174/1133 vs 211/1123 (HR 0.79; 95% CI: 0.65, 0.97); 3) HFpEF (≥60%): 131/931 vs 170/960 (HR 0.78; 95% CI: 0.62, 0.98).

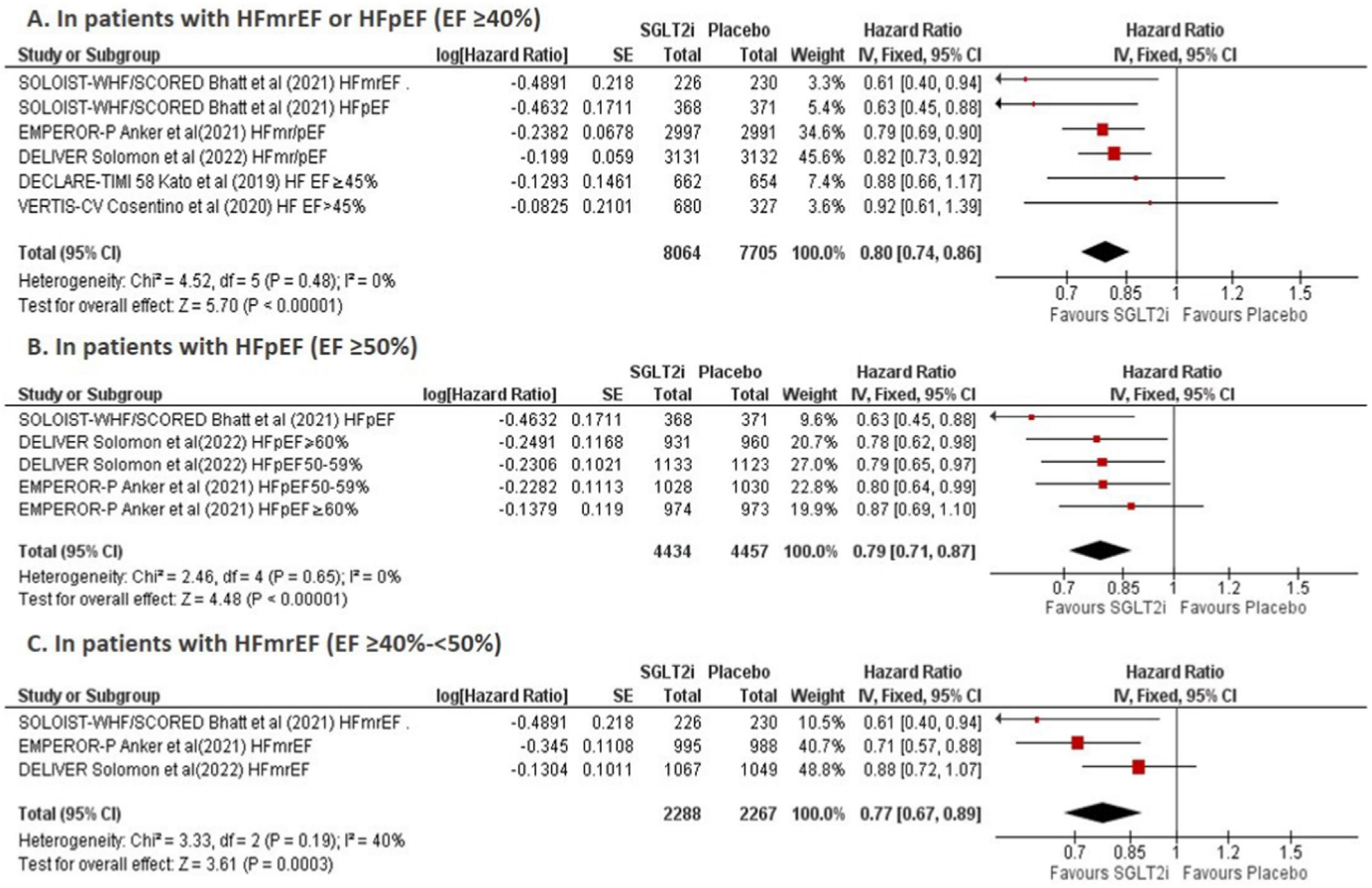

Fig. 1. Risk of composite cardiovascular outcomes of CVD/HHF in patients with HFpEF and/or HFmrEF receiving SGLT2 inhibitors versus placebo Abbreviations: CVD, cardiovascular death; HHF, hospitalization for heart failure; HFpEF, Heart failure with preserved ejection fraction; HFmrEF, Heart failure with mildly reduced ejection fraction.

improved CVD/HHF in patients with HFpEF (N = 8891, HR 0.79, 95% CI: 0.71, 0.87, $p < 0.001$, $I^2 = 0\%$) (Fig. 1B). These benefits were also significant in patients with HFmrEF (N = 4555, HR 0.77, 95% CI: 0.67, 0.89, $p < 0.001$, $I^2 = 40\%$) (Fig. 1C).

In particular, improvement in the composite cardiovascular outcomes appeared to be largely driven by significant benefits of SGLT2i on HHF (HR 0.76, 95% CI: 0.68, 0.84, p < 0.001, $I^2 = 0\%$) (sFig. 2). SGLT2i use was not associated with significant risk reduction in CVD events in patients with HFrEF/HFmrEF (HR 0.94, 95% CI: 0.83, 1.05, p = 0.2, $I^2 = 34\%$) (sFig. 3A). Likewise, no significant beneficial effects of SGLT2i on risk of all-cause death was noted (sFig. 4).

Sensitivity analysis using leave-one-out method was performed in view of heterogeneity of pooled effects of SGLT2i on CV deaths in HFmrEF/HFpEF. Pooled analysis of DELIVER and EMPEROR-Preserved trials eliminated this heterogeneity in SGLT2i treatment effects, and a trend towards significant beneficial effects was observed on CV deaths (HR 0.90, 95% CI: 0.79, 1.02, p = 0.08, $I^2 = 0\%$) (sFig. 3B).

3.3. Subgroup analyses

Subgroup analysis found no significant effect of baseline diabetes on effects of SGLT2i on CVD/HHF in HFpEF/HFmrEF. Consistent benefits were observed in HFmrEF/HFpEF subgroup with diabetes (N = 9262, HR 0.79, 95% CI: 0.72, 0.88, $p < 0.001$, $I^2 = 0\%$) and those without baseline diabetes (N = 6507, HR 0.80, 95% CI: 0.70, 0.91, $p < 0.001$, $I^2 = 0\%$) (p value > 0.3 for subgroup comparison) (Fig. 2).

3.4. Publication bias

The funnel plots and Egger's test for asymmetry conducted for all reported outcomes showed no evidence of publication bias (sFig. 4).

4. Discussion

In a meta-analysis of trials in HFrEF population, SGLT2 inhibition led to a 26% relative reduction in the CVD/HHF (HR = 0·74; 95% CI, 0·68–0·82).[21] The present systematic review and meta-analysis showed that SGLT2i use was associated with similar benefits on HHF/CVD in patients with HFmrEF (HR = 0.77) and/or HFpEF (HR = 0.79). The beneficial effects appeared to be largely driven by their effects on HHF. As opposed to the conclusions of previous meta-analysis involving HFmrEF/HFpEF population,[13] sensitivity analysis suggested a trend towards significant effects of SGLT2i in preventing CV death in present study. HR for CV death in HFmrEF/HFpEF (HR = 0.90; 95%CI 0.79–1.02) was comparable to that shown in HFrEF (HR = 0·86; 95%CI 0·76–0·98).[21]

It has increasingly been clear that HFrEF and HFpEF are two distinct clinical entities, and rate of transformation of HFpEF into HFrEF in long-term survivors is not frequent.[22] HFmrEF is intermediate between the two entities, but largely considered to be similar to HFrEF for majority of aspects, particularly with regard to

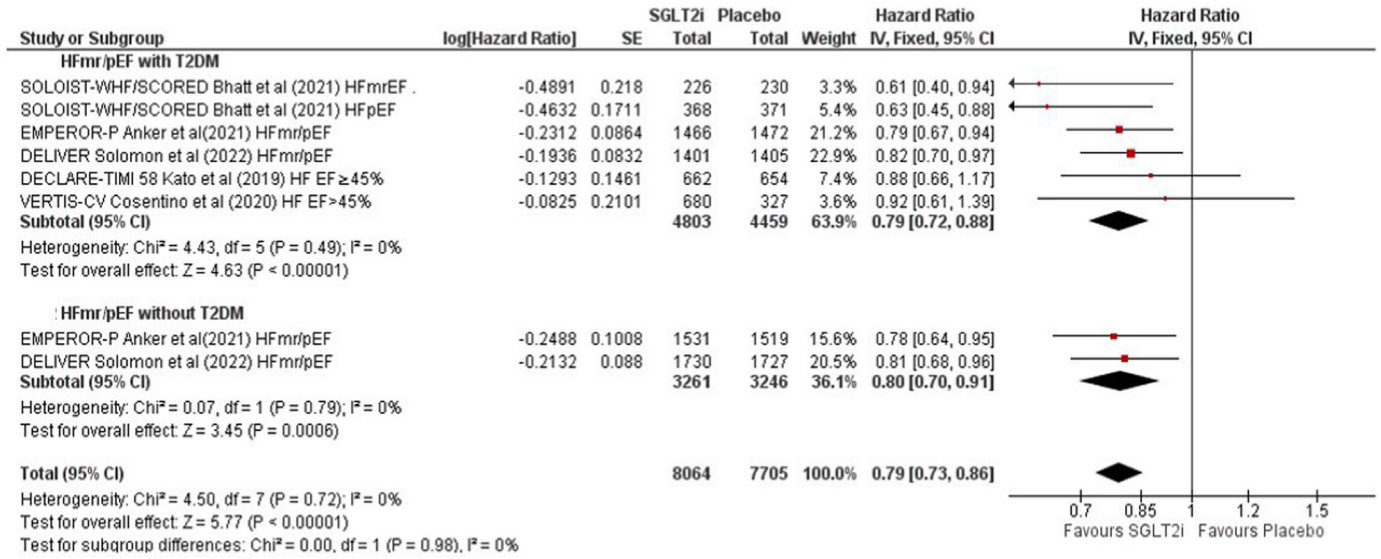

Fig. 2. Subgroup analysis showing impact of baseline diabetes on risk of composite cardiovascular outcomes of CVD/HHF in patients with HFpEF and/or HFmrEF receiving SGLT2 inhibitors versus placebo Abbreviations: CVD, cardiovascular death; HHF, hospitalization for heart failure; HFpEF, Heart failure with preserved ejection fraction; HFmrEF, Heart failure with mildly reduced ejection fraction.

the high prevalence of ischemic heart disease.[4] HFpEF is considered as a heterogeneous clinical syndrome of discrete phenotypes, such as aging, diabetes mellitus (DM), obesity, hypertension, pulmonary hypertension (PH) and coronary artery disease (CAD).[23] DM is known to cause up-regulation of the SGLT2, which in turn leads to increased proximal renal tubular reabsorption of sodium, volume expansion, and decreased diuretic responsiveness.[24] Obesity adversely affects chronic pulmonary vascular remodeling, leading to PH and exercise intolerance in patients with HFpEF.[23] All these comorbid conditions combine to produce a sustained low-grade pro-inflammatory state, that causes cardiomyofibrosis, adversely affects coronary microvascular regulation and atrial or ventricular remodeling, thereby leading to diastolic dysfunction and risk of cardiac arrhythmias.[23]

SGLT2i can reinstate diuresis and natriuresis without any risk of sympathetic activation.[25] Other mechanisms for their benefits include blood pressure reduction, epicardial fat reduction, inhibition of the Na/H-exchanger, improved cardiac energy metabolism, increasing erythropoietin levels, increasing circulating pro-vascular progenitor cells.[26] In particular, SGLT2i in individuals with HFpEF may shift cardiac metabolism towards ketone bodies (the superfuel hypothesis); thereby reducing oxygen consumption and subsequent free radical generation.[25] SGLT2i can target the pro-inflammatory pathways to reverse endothelial dysfunction and decelerate cardiac muscle remodeling. SGLT2i also protects kidneys via activation of tubuloglomerular feedback and reducing the risk of hyperfiltration injury.[26] This is even more relevant for patients with moderate chronic kidney disease, which also happens to be an important phenotype of HFpEF.[23]

Essential characteristics of the three RCTs on patients with baseline HF must be borne in mind. The EMPEROR-Preserved trial enrolled patients with NYHA functional class II-IV chronic HF and LVEF >40% regardless of DM. The inclusion criteria required study participants to have an N-terminal pro—B-type natriuretic peptide (NT-proBNP) level >300 pg/m, or for patients with atrial fibrillation at baseline, an NT-proBNP >900 pg/ml.[9] The SOLOIST-WHF trial included patients with T2DM who had been hospitalized because of heart failure and received treatment with intravenous diuretic therapy. The NT-proBNP thresholds for patient inclusion in this trial were higher, i.e., at least 600 pg/ml (≥1800 pg/ml for patients with atrial fibrillation).[17] Participants in the SOLOIST-WHF trial were at a higher risk for CV events, as indicated by the placebo event rate (48%) for CVD/HHF, compared to 17.2% in EMPEROR-Preserved and 19.5% in DELIVER trial. These comparative data could suggest the potential of sotagliflozin to reduce cardiovascular outcomes in a population with very high risk of HF, which might have not been adequately represented in other SGLT2i trials. Sotagliflozin differs from other SGLT2i given its additional SGLT1 inhibiting properties. Unlike SGLT2, SGLT1 receptors are expressed in heart. Hence, inhibition of these SGLT1 receptors in heart might have the potential to decrease hyperglycemia-induced oxidative stress.[23] However, it is unlikely that the benefits of other SGLT2i can be explained by any secondary effect on SGLT1 inhibition.[23] Future RCTs with a direct comparison of dual SGLT inhibitors versus SGLT2i in HFpEF can address this hypothesis.

The recently published DELIVER trial has significant differences in the inclusion criteria as compared to EMPEROR-Preserved trial. This trial includes both ambulatory and hospitalized participants stable on oral therapy for at least 24 h (at least 7 days for EMPEROR-Preserved) and participants with symptomatic HF for at least 6 weeks (at least 3 months for EMPEROR-Preserved).[10] The significant cardiovascular benefits seen with earlier initiation of SGLT2i in the DELIVER trial, that includes hospitalized patients as well, adds significant clinical and economic implications for patients with HFrEF/HFmrEF via reduction of hospital stay.[27] Moreover, cardiovascular benefits of SGLT2i were demonstrated on top of background HF therapies in DELIVER trial, where use of beta blockers, angiotensin-converting enzyme inhibitors (ACEI)/angiotensin receptor blockers (ARB) and loop diuretics ranged from 73 to 82% in study population.[10]

The present study does have certain limitations. Subgroup analysis could not be done with regard to use of background HF medication use, which could provide additional insights to present findings. None of the studies were adequately powered to address mortality in this population; hence, limited sample size can explain the lack of statistical benefits on CV death. Nonetheless, the consistency of benefits on cardiovascular outcomes with use of various SGLT2i across studies adds to the robustness of present data.

In conclusion, this comprehensive meta-analysis summarizes the available literature and reinforces the significant beneficial effects of SGLT2i use on reducing hospitalizations for HF or CV deaths in patients with HF and mildly reduced or preserved ejection fraction regardless of presence of diabetes at baseline.

Declarations

Funding

None.

Conflicts of interest/Competing interests

None to declare.

Ethics approval

Not applicable.

Availability of data and material

Not applicable.

Code availability

Not applicable.

Authors' contributions

MB is the primary author and the guarantor of work done. MB and RP had performed literature search and data extraction. Formal analysis was performed by MB. KN assessed publication bias. SM edited the manuscript. All the authors approved the final version of the manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ihj.2023.03.003.

References

1. Borlaug BA. Evaluation and management of heart failure with preserved ejection fraction. *Nat Rev Cardiol*. 2020;17:559–573. https://doi.org/10.1038/s41569-020-0363-2.
2. McDonagh TA, Metra M, Adamo M, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2021;2021(42):3599–3726. https://doi.org/10.1093/eurheartj/ehab368.
3. Heidenreich PA, Bozkurt B, Aguilar D, et al. AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of cardiology/American heart association joint committee on clinical practice guidelines. *Circulation*. 2022;145. https://doi.org/10.1161/CIR.0000000000001063, 2022.
4. Savarese G, Stolfo D, Sinagra G, Lund LH. Heart failure with mid-range or mildly reduced ejection fraction. *Nat Rev Cardiol*. 2022;19:100–116. https://doi.org/10.1038/s41569-021-00605-5.
5. Zelniker TA, Braunwald E. Mechanisms of cardiorenal effects of sodium-glucose cotransporter 2 inhibitors. *J Am Coll Cardiol*. 2020;75:422–434. https://doi.org/10.1016/j.jacc.2019.11.031.
6. Bhatt D, Szarek M, Steg P. Benefits of sodium glucose co-transporter-1/2 inhibition with sotagliflozin across the full spectrum of ejection fraction, including heart failure with preserved ejection fraction. In: *Presented at the American College of Cardiology 2021 Scientific Sessions*. 2021. May 17.
7. Kato ET, Silverman MG, Mosenzon O, et al. Effect of dapagliflozin on heart failure and mortality in type 2 diabetes mellitus. *Circulation*. 2019;139:2528–2536. https://doi.org/10.1161/CIRCULATIONAHA.119.040130.
8. Cosentino F, Cannon CP, Cherney DZI, et al. Efficacy of ertugliflozin on heart failure–related events in patients with type 2 diabetes mellitus and established atherosclerotic cardiovascular disease: results of the VERTIS CV trial. *Circulation*. 2020;142:2205–2215. https://doi.org/10.1161/CIRCULATIONAHA.120.050255.
9. Anker SD, Butler J, Filippatos G, et al. Empagliflozin in heart failure with a preserved ejection fraction. *N Engl J Med*. 2021, NEJMoa2107038. https://doi.org/10.1056/NEJMoa2107038.
10. Solomon SD, McMurray JJV, Claggett B, et al. Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction. *N Engl J Med*. 2022. https://doi.org/10.1056/NEJMoa2206286. NEJMoa2206286.
11. Aimo A, Pateras K, Stamatelopoulos K, et al. Relative efficacy of sacubitril-valsartan, vericiguat, and SGLT2 inhibitors in heart failure with reduced ejection fraction: a systematic review and network meta-analysis. *Cardiovasc Drugs Ther*. 2021;35:1067–1076. https://doi.org/10.1007/s10557-020-07099-2.
12. Tsampasian V, Elghazaly H, Chattopadhyay R, et al. Sodium glucose co-transporter 2 inhibitors in heart failure with preserved ejection fraction: a systematic review and meta-analysis. *Eur J Prev Cardiol*. 2022;29:e227–e229. https://doi.org/10.1093/eurjpc/zwab189.
13. Wang Y, Gao T, Meng C, et al. Sodium-glucose co-transporter 2 inhibitors in heart failure with mildly reduced or preserved ejection fraction: an updated systematic review and meta-analysis. *Eur J Med Res*. 2022;27:314. https://doi.org/10.1186/s40001-022-00945-z.
14. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ*. 2009;339:b2700. https://doi.org/10.1136/bmj.b2700. b2700.
15. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. 2019:l4898. https://doi.org/10.1136/bmj.l4898.
16. Higgins JPT. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327:557–560. https://doi.org/10.1136/bmj.327.7414.557.
17. Bhatt DL, Szarek M, Steg PG, et al. Sotagliflozin in patients with diabetes and recent worsening heart failure. *N Engl J Med*. 2021;384:117–128. https://doi.org/10.1056/NEJMoa2030183.
18. Bhatt DL, Szarek M, Pitt B, et al. Sotagliflozin in patients with diabetes and chronic kidney disease. *N Engl J Med*. 2021;384:129–139. https://doi.org/10.1056/NEJMoa2030186.
19. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2019;380:347–357. https://doi.org/10.1056/NEJMoa1812389.
20. Cannon CP, Pratley R, Dagogo-Jack S, et al. Cardiovascular outcomes with ertugliflozin in type 2 diabetes. *N Engl J Med*. 2020;383:1425–1435. https://doi.org/10.1056/NEJMoa2004967.
21. Zannad F, Ferreira JP, Pocock SJ, et al. SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: a meta-analysis of the EMPEROR-Reduced and DAPA-HF trials. *Lancet*. 2020;396:819–829. https://doi.org/10.1016/S0140-6736(20)31824-9.
22. Lupón J, Gavidia-Bovadilla G, Ferrer E, et al. Heart failure with preserved ejection fraction infrequently evolves toward a reduced phenotype in long-term survivors: a long-term prospective longitudinal study. *Circ Heart Fail*. 2019;12, e005652. https://doi.org/10.1161/CIRCHEARTFAILURE.118.005652.
23. Epidemiology and pathogenesis of heart failure with preserved ejection fraction. *Rev Cardiovasc Med*. 2020;21:531. https://doi.org/10.31083/j.rcm.2020.04.154.
24. Heerspink HJL, Perkins BA, Fitchett DH, Husain M, Cherney DZI. Sodium glucose cotransporter 2 inhibitors in the treatment of diabetes mellitus: cardiovascular and kidney effects, potential mechanisms, and clinical applications. *Circulation*. 2016;134:752–772. https://doi.org/10.1161/CIRCULATIONAHA.116.021887.
25. Butler J, Hamo CE, Filippatos G, et al. The potential role and rationale for treatment of heart failure with sodium-glucose co-transporter 2 inhibitors: SGLT2 inhibitors in heart failure. *Eur J Heart Fail*. 2017;19:1390–1400. https://doi.org/10.1002/ejhf.933.
26. Lopaschuk GD, Verma S. Mechanisms of cardiovascular benefits of sodium glucose Co-transporter 2 (SGLT2) inhibitors. *JACC Basic Transl Sci*. 2020;5:632–644. https://doi.org/10.1016/j.jacbts.2020.02.004.
27. Williams DM, Evans M. Dapagliflozin for heart failure with preserved ejection fraction: will the DELIVER study deliver? *Diabetes Ther*. 2020;11:2207–2219. https://doi.org/10.1007/s13300-020-00911-0.