

Efficacy of SGLT2-inhibitors across different definitions of heart failure with preserved ejection fraction

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Aims Sodium-glucose cotransporter 2 inhibitors (SGLT2i) have been evaluated in phase 3 randomized-controlled trials (RCTs) that enrolled individuals with heart failure and preserved ejection fraction (HFpEF) based on detailed clinical, biochemical, and echocardiographic criteria (hereafter HF-RCTs), and in cardiovascular outcomes trials (CVOTs) in diabetic patients, in which the diagnosis of HFpEF relied on medical history.

Methods and results We performed a study-level meta-analysis of the efficacy of SGLT2i across different definitions of HFpEF. Three HF-RCTs (EMPEROR-Preserved, DELIVER, and SOLOIST-WHF) and four CVOTs (EMPA-REG OUTCOME, DECLARE-TIMI 58, VERTIS-CV, and SCORED) were included, for a total of 14 034 patients. SGLT2i reduced the risk of cardiovascular death or heart failure hospitalization (HFH) in all RCTs pooled together [risk ratio 0.75, 95% confidence interval (95% CI) 0.63–0.89, NNT 19], in HF-RCTs (risk ratio 0.71, 95% CI 0.52–0.97, NNT 13), and in CVOTs (risk ratio 0.78, 95% CI 0.60–0.99, NNT 26). SGLT2i also decreased the risk of HFH in all RCTs (risk ratio 0.81, 95% CI 0.73–0.90, NNT 45), in HF-RCTs (risk ratio 0.81, 95% CI 0.72–0.93, NNT 37), and in CVOTs (risk ratio 0.78, 95% CI 0.61–0.99, NNT 46). By contrast, SGLT2i were not superior to placebo for cardiovascular death or all-cause death in all RCTs,

HF-RCTs, or CVOTs. Results were comparable after excluding one RCT at a time. Meta-regression analysis confirmed that the type of RCT (HF-RCT vs. CVOT) did not influence the SGLT2i effect.

Conclusions In RCTs, SGLT2i improved the outcomes of patients with HFpEF regardless of how the latter was diagnosed.

Graphical abstract <http://links.lww.com/JCM/A541>

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Introduction

Heart failure with preserved ejection fraction (HFpEF) is characterized by left ventricular ejection fraction (LVEF) at least 50% in addition to suggestive symptoms and signs, elevated concentrations of natriuretic peptides, and evidence of cardiac abnormalities consistent with left ventricular diastolic dysfunction/raised left ventricular filling pressures, most often obtained by transthoracic echocardiography.¹ Two recent phase 3 randomized-controlled trials (RCTs) have demonstrated that the sodium-glucose cotransporter 2 inhibitors (SGLT2i), empagliflozin and dapagliflozin, improve morbidity and mortality in patients with all the above-mentioned features of HFpEF.^{2,3} Furthermore, the Effect of Sotagliflozin on Cardiovascular Events in Patients with Type 2 Diabetes Post Worsening Heart Failure (SOLOIST-WHF) trial showed that the SGLT2i/sodium-glucose cotransporter

1 (SGLT1) inhibitor, sotagliflozin, reduced the total number of cardiovascular deaths, heart failure hospitalizations (HFH), and urgent visits for heart failure in individuals with type 2 diabetes mellitus (T2D) hospitalized for heart failure, as diagnosed based on clinical presentation, B-type natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) thresholds, and need for intravenous diuretic therapy.⁴

A benefit from SGLT2i was also found in HFpEF subgroups enrolled in earlier cardiovascular outcomes RCTs (CVOTs), assessing the effects of SGLT2i in T2D with heightened risk for or established atherosclerotic cardiovascular disease.^{5–8} However, in these studies, HFpEF was simply diagnosed according to medical history.^{5,9–11} Similarly, sotagliflozin was associated with a lower rate of

cardiovascular death, HFH, and urgent visits for heart failure than placebo in patients with T2D, chronic kidney disease, and risk for cardiovascular disease, some of whom had a history of heart failure and LVEF at least 50%.⁵

We conducted a systematic review and meta-analysis of the RCTs with different definitions of HFpEF, with the goal of making a comprehensive synthesis of the efficacy of SGLT2i in this syndrome.

Materials and methods

This meta-analysis was done according to the Cochrane Collaboration and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines¹² (Table S1, <http://links.lww.com/JCM/A540>) and was registered with PROSPERO (CRD42022359925).

Search strategy

We systematically searched the MEDLINE, Embase, Scopus, and Cochrane Library databases for English-language, peer-reviewed publications of RCTs in HFpEF from inception to August 31, 2022, using the following keywords: “sodium glucose cotransporter 2 inhibitor”, every specific SGLT2i (e.g. “dapagliflozin” or “empagliflozin”), “sotagliflozin”, “SGLT2i”, “heart failure with preserved ejection fraction”, “HFpEF”, and “heart failure”. The references of the selected articles were also thoroughly screened to retrieve additional potentially eligible publications.

Eligibility criteria and data extraction

All phase 3 RCTs evaluating SGLT2i vs. placebo in individuals with heart failure and LVEF at least 50% were selected. Three investigators (V.D.M., G.S., and P.A.) independently reviewed the retrieved articles and extracted the information on baseline characteristics of the enrolled populations, follow-up duration, total numbers of patients, and outcome events.

RCTs were categorized as HF-RCTs if heart failure was defined at least on the basis of NYHA-graded symptoms and BNP/NT-proBNP concentrations. We decided to use the expression HF-RCTs, rather than HFpEF-RCTs, because these studies also enrolled patients with heart failure and mildly reduced LVEF. Conversely, in CVOTs, a check box in the electronic case record form was sufficient to define heart failure.

Disagreements were solved by involvement of the other investigators (M.M. and I.P.).

Analysis outcomes

The primary outcome was a composite of cardiovascular death or HFH. The secondary outcomes cardiovascular

death, HFH, and all-cause death were also evaluated for those RCTs with data available.

Quality of evidence

The quality of evidence was examined according to the Grading of Recommendations, Assessment, Development, and Evaluation tool and was categorized as high, low, or unclear.¹³

Assessment of risk of bias

We used the Cochrane Collaboration's tool to assess the risk of bias in six prespecified domains: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias.¹⁴ Comparison-adjusted funnel plots were employed to visualize publication bias, as previously described.^{15–17}

Data analysis

Risk ratios with 95% confidence intervals (95% CIs) were calculated with R 4.2.1 (The R Project for Statistical Computing, Vienna). The Cochran's Q test and Higgins and Thompsons' I^2 statistics were used to estimate heterogeneity among studies, with I^2 less than 25% indicating low, I^2 25–50% moderate, and I^2 more than 50% high heterogeneity.¹⁴ For moderate-to-high heterogeneity, a random-effects model with inverse variance weighting was run, or a fixed-effects model if it was more parsimonious than the random-effects one. The Mantel-Haenszel fixed-effect model was chosen for low heterogeneity.

The number needed to treat (NNT) was calculated according to the absolute risk differences.¹⁸

A leave-one-out analysis was performed by sequentially excluding each study. Furthermore, meta-regression analyses were carried out to determine the impact of the type of HFpEF definition (i.e. HF-RCTs vs. CVOTs), the year of the publication of the RCTs, and the length of follow-up on the end points of interest.

P-values less than 0.05 were considered significant.

Results

The PRISMA flowchart depicting the search and selection of references is provided in Figure S1, <http://links.lww.com/JCM/A540>, while the references of the RCTs included in the meta-analysis are listed in Table S2, <http://links.lww.com/JCM/A540>.

Study and patient characteristics

Seven RCTs out of 417 760 potentially relevant screened articles were included in the meta-analysis for the composite end point of cardiovascular death or HFH: three HF-

RCTs [Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction (EMPEROR-Preserved),² Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure (DELIVER) trial,³ and SOLOIST-WHF trial⁴] and four CVOTs [Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes trial (EMPA-REG OUTCOME),⁸ Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58 (DECLARE–TIMI 58) trial,⁷ Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes Trial (VERTIS-CV),⁶ and Effect of Sotagliflozin on Cardiovascular and Renal Events in Patients with Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk (SCORED) trial].⁵

For the dapagliflozin vs. placebo in HF-RCTs trial, we used the aggregated data from a patient-level, pooled meta-analysis¹⁹ of the DELIVER and Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction (DAPA-HF)²⁰ trials, in which LVEF was post-hoc re-adjudicated.

The overall population included 41 310 patients, and the mean follow-up was 29.8 ± 14.5 months (range: 9.0–50.4 months). As some of the participants in HF-RCTs had LVEF between 40 and 49% and CVOTs were conducted in patients with T2D with only a subset having heart failure, the proportion of individuals with HFpEF varied from 3.0% in EMPA-REG OUTCOME to 66.8% in EMPEROR-Preserved. The mean was $31.4 \pm 28.6\%$, and in total, 14 034 patients with HFpEF were included in the RCTs examined (Table 1).

The overall quality of evidence was high and the overall risk of bias was low (Table S3, <http://links.lww.com/JCM/A540>), whereas visual inspection suggested some degree of publication bias for the primary composite end point (Figure S2, <http://links.lww.com/JCM/A540>).

Meta-analysis results

The number of events for the end points of interest in each RCT are presented in Table 1.

Pooling the data of all RCTs together, the risk of cardiovascular death or HFH was significantly decreased by SGLT2i as compared with placebo (risk ratio 0.75, 95% CI 0.63–0.89, $P=0.001$, $I^2=59.7\%$) (Fig. 1a). When considering only HF-RCTs, the benefit was numerically greater (risk ratio 0.71, 95% CI 0.52–0.97, $P=0.030$, $I^2=75.7\%$). The reduction in cardiovascular death or HFH was confirmed in CVOTs (risk ratio 0.78, 95% CI 0.60–0.99, $P=0.047$, $I^2=56.9\%$) (Fig. 1a). The NNT was 19 for all RCTs, 13 for HF-RCTs, and 26 for CVOTs.

The secondary end points could not be evaluated in the SOLOIST-WHF and SCORED trials due to the lack of published data.

The risk of HFH was lower with SGLT2i than with placebo (risk ratio 0.81, 95% CI 0.73–0.90, $P<0.001$, $I^2=18.1\%$) and the benefit on this outcome was retained in both HF-RCTs (risk ratio 0.81, 95% CI 0.72–0.93, $P<0.001$, $I^2=18.1\%$) and CVOTs (risk ratio 0.78, 95% CI 0.61–0.99, $P=0.043$, $I^2=0.0\%$) (Fig. 1b). The NNT was 45, 37, and 46 for all RCTs, HF-RCTs, and CVOTs, respectively.

By contrast, SGLT2i were not superior to placebo for cardiovascular death or all-cause death, either when RCTs were analyzed in aggregate or when HF-RCTs and CVOTs were considered separately (Fig. 2).

Leave-one-out and meta-regression analyses

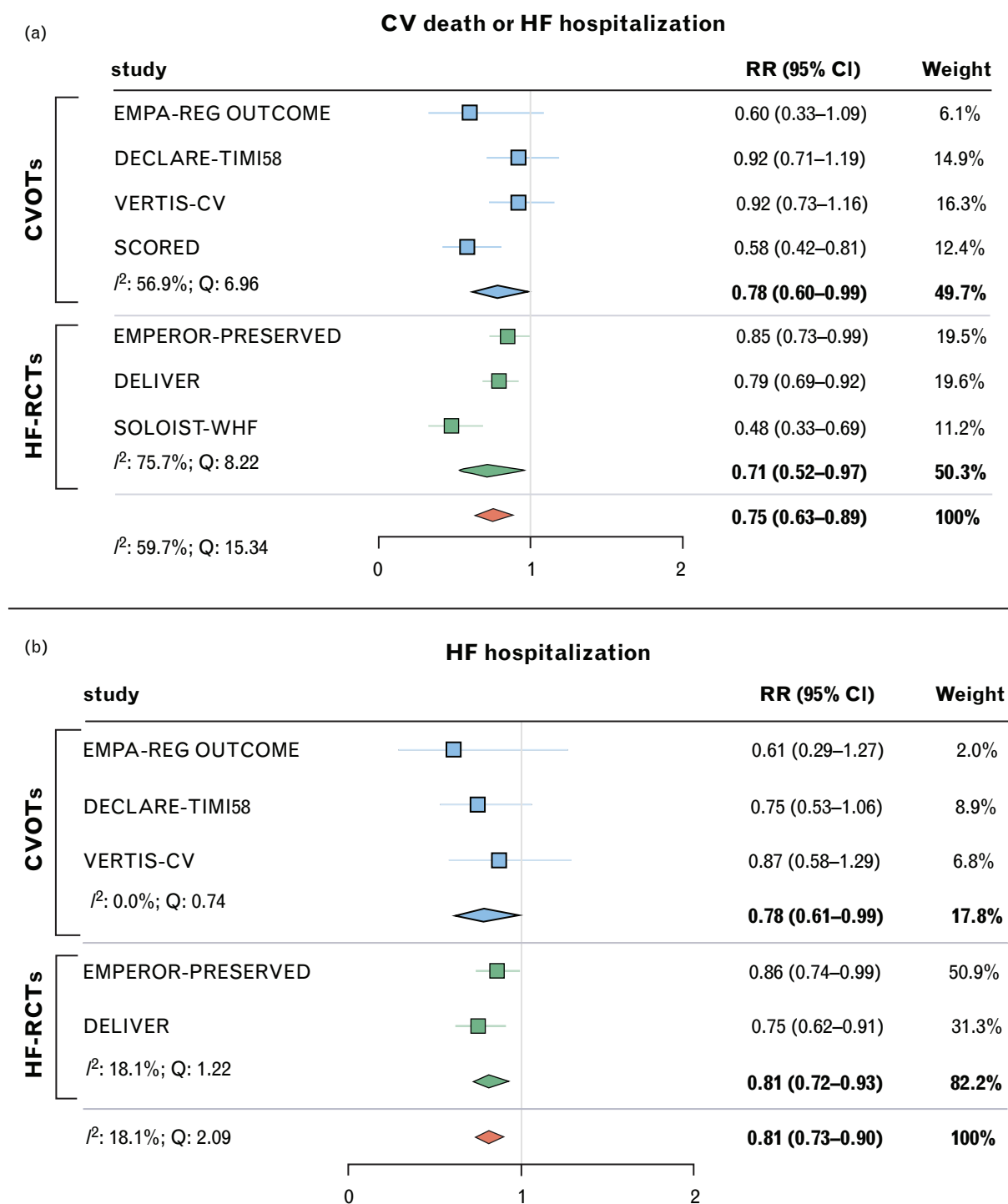
The exclusion of one study at a time from the pooled effect estimates did not change the results (Fig. S3, <http://links.lww.com/JCM/A540>).

Table 1 Number of patients and events in the phase 3 randomized–controlled trials included in the meta-analysis

RCT	Year of publication	Follow-up (months)	% of patients with HFpEF (n/N)	Intervention	Patients (n)	CV death or HFH (n)	HFH (n)	CV death (n)	All-cause death (n)
HF-RCTs									
SOLOIST-WHF ⁴	2021	9.0	20.9 (256/1222)	Sotagliflozin Placebo	128 128	29 61	NA	NA	NA
EMPEROR-Preserved ²	2021	26.2	66.9 (4005/5988)	Empagliflozin Placebo	2002 2003	270 318	285 332	186 213	422 427
DELIVER ³	2022	27.6	56.5 (3537/6263)	Dapagliflozin Placebo	1765 1772	267 338	173 231	260 273	273 260
CVOTs									
EMPA-REG OUTCOME ⁸	2015	37.1	3.0 (208/7020)	Empagliflozin Placebo	133 75	18 17	13 12	7 8	15 12
DECLARE-TIMI 58 ⁷	2019	50.4	7.7 (1316/17160)	Dapagliflozin Placebo	662 654	92 99	51 67	54 38	84 81
VERTIS-CV ⁶	2020	42.0	49.1 (4047/8246)	Ertugliflozin Placebo	2724 1323	197 104	66 37	142 76	206 107
SCORED ⁵	2021	16.0	6.3 (665/10584)	Sotagliflozin Placebo	333 332	46 79	NA	NA	NA

CV, cardiovascular; HFH, heart failure hospitalization; HFpEF, heart failure with preserved ejection fraction; RCT, randomized–controlled trial.

Fig. 1



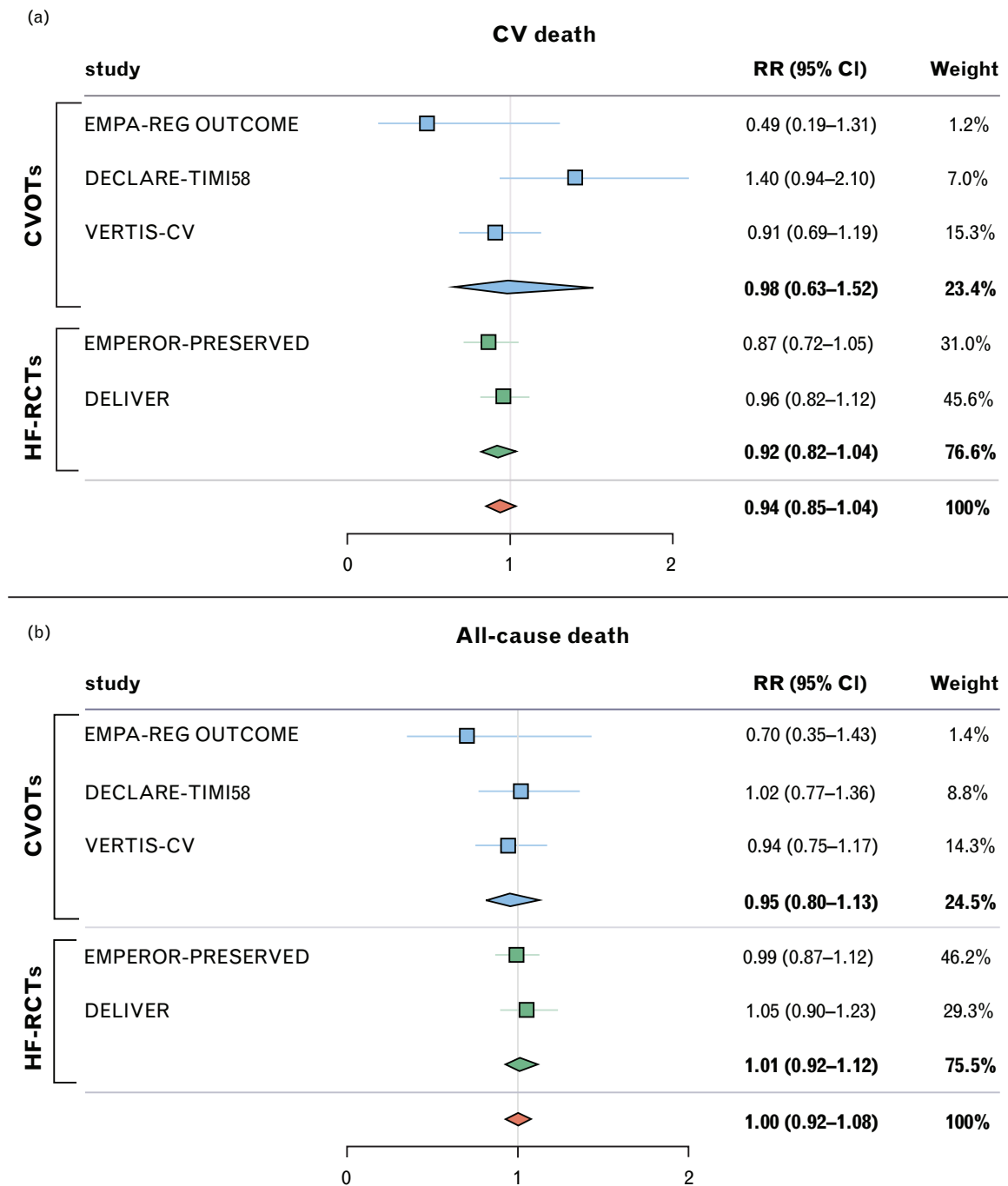
Forest plot for the effect of SGLT2i vs. placebo on the composite outcome of cardiovascular death or HFH (a), and on HFH (b).

Meta-regression analysis revealed a positive association between the magnitude of risk reduction in the composite outcome of cardiovascular death or HFH and the duration of follow-up ($P=0.001$). Conversely, there was no interaction between the risk reduction attained with SGLT2i and the

type of study (HF-RCTs vs. CVOTs, $P=0.72$) or the year of publication of the RCTs ($P=0.11$).

Meta-regression analysis for the secondary outcomes showed no significant influence of follow-up length, type

Fig. 2



Forest plot for the effect of SGLT2i vs. placebo on cardiovascular death (a) and on all-cause death (b).

of RCT, or year of publication on the effect of SGLT2i (all $P > 0.05$).

Discussion

In sharp contrast with the success of RCTs in heart failure with reduced LVEF (HFrEF), an effective treatment for HFpEF has historically been missing,

with no consistent benefit observed with beta blockers, angiotensin-receptor converting enzyme inhibitors, angiotensin-receptor blockers, mineralocorticoid receptor antagonists, and sacubitril-valsartan. This lack of successful therapy is at least in part the consequence of greater phenotypic heterogeneity in HFpEF than in HFrEF.^{1,21–23}

Very recently, however, SGLT2i have been shown to improve the outcomes of patients with HFpEF across a wide range of LVEF values above the 50% cut-off and in clinically relevant subgroups.^{2,3}

Here, we show that SGLT2i reduced the risk of the composite end point of cardiovascular death and HFH, as well as of HFH, regardless of how HFpEF was diagnosed in RCTs. By summarizing the data on SGLT2i across RCTs with different definitions of HFpEF, our work confirms and extends other meta-analyses.^{24,25}

HF-RCTs were specifically designed to verify the signal for a protective effect of SGLT2i against HFH noted in CVOTs, and remain the strongest evidence regarding SGLT2i in HFpEF. Paradoxically, however, characterization of HFpEF in clinical practice may not be as precise as in HF-RCTs.

In real life, HFpEF is primarily encountered and managed by noncardiologists, who are more likely to replicate the scenario of CVOTs with the diagnosis of HFpEF relying on medical records, rather than on the measurement of BNP or NT-proBNP and the echocardiographic assessment of left ventricular dimensions, left ventricular diastolic function, and left atrial size.

Among 9134 patients enrolled in the Heart Failure Long-Term Registry of the European Society of Cardiology, only 16% had HFpEF.²⁶ In Sweden, the proportion of HFpEF among all HFH decreased from 2000 to 2016, while the proportion of HFpEF increased, and this occurred especially in noncardiology wards in which HFpEF cases almost doubled.²⁷ Remarkably, echocardiography during the index hospitalization was less commonly performed in noncardiology than in cardiology units, and heart failure was mainly classified based on historical information.²⁸ A low prevalence of HFpEF was also described in community-based studies conducted in the cardiology setting.²³

In view of these considerations, it is notable that this meta-analysis highlighted a similar risk reduction with SGLT2i in HF-RCTs and CVOTs, indicating that different ways of diagnosing HFpEF do not have an impact on the efficacy of SGLT2i.

Clearly, we do not imply that assessment of natriuretic peptides and echocardiography are dispensable to diagnose HFpEF. In fact, additional examinations up to cardiac catheterization may be required. To date, the scientific background upon which SGLT2i can be proposed for treatment of HFpEF remains one of the HF-RCTs with detailed definitions of HFpEF.

It is also noteworthy that some patients receiving SGLT2i in CVOTs were asymptomatic, while NYHA I class was a

reason for exclusion from HF-RCTs. This difference in the study populations might explain why the outcome risk reduction was numerically greater in HF-RCTs than in CVOTs in our meta-analysis. Although the exact distribution of NYHA classes is not published, more than 30% of individuals in the DECLARE-TIMI58 trial⁷ and around 25% in VERTIS-CV⁶ had NYHA I. Nonetheless, it has yet to be proven that SGLT2i are beneficial in asymptomatic HFpEF and, thereby, expand the indication to initiate these drugs.

In the examined RCTs, SGLT2i decreased the risk of HFH, which can be attributed to multiple mechanisms of action, including decongestion, improvement in metabolic asset, and positive changes in the adipose tissue and circulating adipokines.²⁹

Conversely, cardiovascular death was not significantly less frequent with SGLT2i than with placebo. This is not surprising, as non-cardiovascular death is predominant in HFpEF³⁰ and the influence of SGLT2i on mortality is limited.³¹ Interestingly, it has recently been suggested that SGLT2i may affect the risk of sudden cardiac death in HFpEF.³² As this meta-analysis was based on aggregate data with no distinction of the modes of death, we cannot address this observation.

We acknowledge that our study has limitations. First, it is based on study-level and not patient-level data. Second, several sources of heterogeneity were present in the selected RCTs, such as the variability in the proportion of patients with HFpEF and chronic kidney disease, who have higher risk of events (e.g. the DECLARE-TIMI58 trial included individuals with a creatinine clearance of ≥ 60 ml/min, whereas the mean estimated glomerular filtration rate in EMPEROR-Preserved and DELIVER was 60.6 and 61 ml/min/1.73 m², respectively), in the duration of follow-up (e.g. 9 months in SOLOIST-WHF vs. 50.4 months in DECLARE-TIMI58), and in outcome rates (e.g. the rate of cardiovascular death/HFH was 35.2% in SOLOIST-WHF vs. 14.7–17.1% in the other HF-RCTs; and it was 7.4% in VERTIS-CV vs. 14.5–18.8% in the other CVOTs). Third, the SOLOIST-WHF trial⁴ enrolled patients with acute decompensated heart failure who may differ from those with ambulatory heart failure, thus introducing a potential source of bias, and investigated a dual SGLT2/SGLT1 inhibitor. Yet, the leave-one-out analysis confirmed the benefit of SGLT2i independently of SOLOIST-WHF. Fourth, no data about key subpopulations (e.g. distinguishing by race and sex) were available for analysis.

In conclusion, SGLT2i ameliorated the outcomes of patients with HFpEF in RCTs irrespective of the criteria adopted to define HFpEF. This finding provides an additional argumentation in favor of the use of SGLT2i to treat HFpEF.

Conflicts of interest

V.D.M. received consultant or speaker fees from Astra Zeneca, Daiichi-Sankyo, Bristol-Myers Squibb, and Bayer not related to this work.

G.S. received grants and personal fees from Vifor, AstraZeneca, Novartis, Cytokinetics, and Pharmacosmos; personal fees from Roche, Servier, and Medtronic; grants and nonfinancial support from Boehringer Ingelheim; and grants from Boston Scientific, Merck, and Bayer, all outside the submitted work.

I.P. received personal fees as speaker and/or adviser from AstraZeneca, Daiichi-Sankyo, Terumo Corporation, Biotronik, Bayer, and Amgen, all outside the submitted work.

M.M. received personal fees as Executive Committee member from Vifor Pharma, Amgen, LivaNova, and Windtree Therapeutics; personal fees as DMC Member from Actelion; and personal fees as speaker and/or adviser from AstraZeneca, Abbott Vascular, Bayer, Servier, and Edwards Therapeutics, all outside the submitted work.

P.A. received personal fees as speaker and/or adviser from AstraZeneca, Boehringer Ingelheim, Bayer, Novartis, Vifor, Daiichi-Sankyo, Janssen, MSD, and Amgen, all outside the submitted work.

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