

# Sodium-glucose cotransporter 2 inhibitors in heart failure with reduced or preserved ejection fraction: a meta-analysis

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## Abstract

**Aims** Sodium-glucose cotransporter 2 (SGLT2) inhibitors have been shown to be an effective therapy in improving heart failure outcomes. We conducted a meta-analysis of randomized controlled trials to evaluate the efficacy of SGLT2 inhibitors in heart failure patients with either a reduced or preserved ejection fraction.

**Methods and results** We searched MEDLINE and EMBASE for large ( $\geq 1000$  patients) randomized controlled trials evaluating the effects of SGLT2 inhibitors compared with placebo in the setting of heart failure until September 2021. Our primary outcome was the composite of heart failure hospitalization and cardiovascular death, and secondary outcomes included all-cause mortality and total heart failure hospitalizations. We pooled hazard ratios and risk ratios and evaluated risk of bias with the Cochrane Collaboration tool. Four randomized controlled trials (DAPA HF, EMPEROR-Preserved, EMPEROR-Reduced, and SOLOIST-WHF) were included ( $n = 15\,684$ ); two of which evaluated patients with a reduced LVEF, one of which evaluated patients with a preserved LVEF, and one of which included both. Treatment with SGLT2 inhibitors resulted in a significant reduction in the composite of CV death and heart failure hospitalization (HR: 0.76, 95% CI: 0.70, 0.82,  $I^2$ : 0%,  $P < 0.00001$ ). This was consistent in sub-groups of patients with LVEF  $\leq 40\%$  ( $n = 9199$ , HR: 0.74, 95% CI: 0.68, 0.81,  $I^2$ : 0%) and LVEF  $> 40\%$  ( $n = 6482$ , HR: 0.78, 95% CI: 0.68, 0.89,  $I^2$ : 0%,  $P$ -for-interaction: 0.57), as well as in sub-groups of patients with and without diabetes mellitus at baseline ( $P$ -for-interaction: 0.81). SGLT2 inhibitors were associated with a significant reduction in cardiovascular death (HR: 0.87, 95% CI: 0.79, 0.97,  $I^2$ : 0%,  $P < 0.00001$ ) and total heart failure hospitalization (RR: 0.71, 95% CI: 0.67, 0.76,  $I^2$ : 0%,  $P < 0.00001$ ); although a potential trend towards reduced all-cause mortality was noted with SGLT2 inhibitors, no statistically significant difference was observed (HR: 0.91, 95% CI: 0.83, 1.00,  $I^2$ : 14%,  $P = 0.05$ ).

**Conclusions** Sodium-glucose cotransporter 2 inhibitors reduce cardiovascular death and heart failure hospitalization among patients with heart failure, regardless of LVEF status.

**Keywords** SGLT2i; Diabetes; HFrEF; HFpEF

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## Background

There are limited evidence-based therapeutic options for patients with heart failure (HF) with a preserved left ventricular ejection fraction (LVEF).<sup>1,2</sup> Sodium-glucose cotransporter 2 (SGLT2) inhibitors have been demonstrated to be an effective

therapy for reducing HF outcomes across a broad spectrum of patients, including those at a high cardiovascular (CV) risk, renal impairment, and HF patients with a reduced LVEF.<sup>3–8</sup> Recent randomized controlled trials (RCTs) have evaluated the effects of SGLT2 inhibitors in HF patients with a preserved LVEF.<sup>9,10</sup>

## Aims

We performed a systematic review and meta-analysis of large randomized controlled trials to assess whether SGLT2 inhibitors improved outcomes in all HF patients, including non-diabetics and those with a preserved LVEF.

## Methods

### Registration

The protocol for this systematic review and meta-analysis was not registered. The data underlying this article are available in the article and in its online supplementary material.

### Search strategy and selection criteria

We searched MEDLINE and EMBASE from inception until September 2021 using groups of keywords for SGLT2 inhibitors and a validated filter to exclude reports that were not RCTs.<sup>11</sup> A copy of the search strategy can be found in Supporting Information, *Table S1*. We screened references of eligible papers and consulted experts to identify additional trials. All studies were screened independently and in duplicate by A. K. P., N. K. D., and M. H. We only included large RCTs ( $\geq 1000$  patients) evaluating SGLT2 or dual SGLT1/2 inhibitors in the setting of HF (regardless of ejection fraction or other co-morbidities such as diabetes mellitus).

### Outcomes

The primary outcome was the composite of HF hospitalization and cardiovascular death. Secondary outcomes included total HF hospitalizations, all-cause mortality, and cardiovascular death.

### Data extraction and quality assessment

Two reviewers independently extracted data on study characteristics, baseline patient demographics, intervention, and outcomes. Risk of bias was assessed using the Cochrane Collaboration Tool independently and in duplicate.<sup>12</sup> The following domains were evaluated: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, and selective reporting. For analysis and presentation purposes, risk of bias was dichotomized as high (or likely high) or low (or likely low). Reviewers compared results and resolved disagreements by discussion with a third party.

## Data synthesis

We used hazard ratios to report effect estimates for the composite of HF hospitalization and cardiovascular death, all-cause mortality, and cardiovascular death. We used risk ratios to report effect estimates for total HF hospitalizations. All analyses followed the intention-to-treat principle.

We assessed clinical and methodological heterogeneity based on study characteristics. We assessed heterogeneity qualitatively by evaluating overlapping of CIs and quantitatively by using the  $I^2$  statistic.<sup>12</sup> We pooled hazard ratios using the generic inverse variance method.<sup>12</sup> We pooled risk ratios using the random-effects models with Mantel–Haenszel weighting because we expected comparisons to show heterogeneity. HR for the composite of HF hospitalization or cardiovascular death were pooled using the generic inverse-variance method. All analyses were conducted using RevMan 5.4.1. We considered a  $P$ -value of  $<0.05$  (two-sided) to be statistically significant.

### Subgroups (a priori)

We performed pre-specified subgroups analysis to compare the effects of SGLT2 inhibitors on the primary outcome (HF hospitalization and cardiovascular death) among patients with reduced vs. preserved LVEF as well as in diabetics vs. non-diabetics. We performed a standard test for heterogeneity to examine interaction between subgroups.

## Results

The electronic search identified 5916 references. After removal of duplicate records as well as title/abstract and full-text screening, four met eligibility criteria (Supporting Information, *Figure S1*).<sup>7–10</sup> Details on included studies are presented in *Table 1*.

### Risk of bias assessment

All of the trials were randomized, double-blinded placebo controlled trials. All studies were judged to be at a low/likely low risk of bias in all domains of the Cochrane Risk of Bias tool, except for SOLOIST-WHF study which was judged to be at a likely high risk of both Selective Reporting bias due to endpoint switching, as well as Blinding of Outcome/Assessment bias due to a failure to adjudicate events; both were due to a result of loss of sponsor funding.<sup>10</sup>

**Table 1** Baseline demographics of patients enrolled in landmark SGLT2 heart failure trials

	DAPA-HF (n = 4744)	EMPEROR-Preserved (n = 5988)	EMPEROR-Reduced (n = 3730)	SOLOIST-WHF (n = 1222)
<b>Demographics</b>				
Age, years	66	72	67	69
Female sex	23%	45%	24%	34%
White	70%	76%	70%	93%
Black	5%	4%	7%	4%
Asian	24%	14%	18%	1%
Other/unknown	1%	6%	5%	2%
<b>Co-morbidities/Clinical Characteristics</b>				
Diabetes mellitus	42%	49%	50%	100%
NYHA class III/IV	32%	18%	25%	50%
Mean/median LVEF, %	31%	54%	27%	35%
LVEF ≤40%	100%	0%	100%	59%
Mean/median BMI, kg/m <sup>2</sup>	28.1	29.8	27.9	~31
<b>Heart failure medications</b>				
RAAS Inhibitor	94%	81%	89%	91%
Beta-Blocker	96%	86%	95%	92%
MRA	71%	37%	71%	64%
ARNI	11%	2%	19%	17%

Abbreviations: ARNI, angiotensin receptor-neprolysin inhibitor; BMI, body mass index; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonists; NYHA, New York Heart Association; RAAS, renin-angiotensin-aldosterone system.

**Outcomes**

Outcomes for the entire cohort analysed in the present meta-analysis are presented in *Figure 1*. Pooled data from DAPA HF, EMPEROR-Preserved, EMPEROR-Reduced, and SOLOIST-WHF (n = 15 864) demonstrated a significant reduction in the primary composite outcome of CV death and first HF hospitalization (HR: 0.76, 95% CI: 0.70, 0.82, I<sup>2</sup>: 0%, P < 0.00001). A sensitivity analysis excluding SOLOIST-WHF yielded similar results (HR: 0.76, 95% CI: 0.71, 0.82, I<sup>2</sup>: 0%, P < 0.00001).

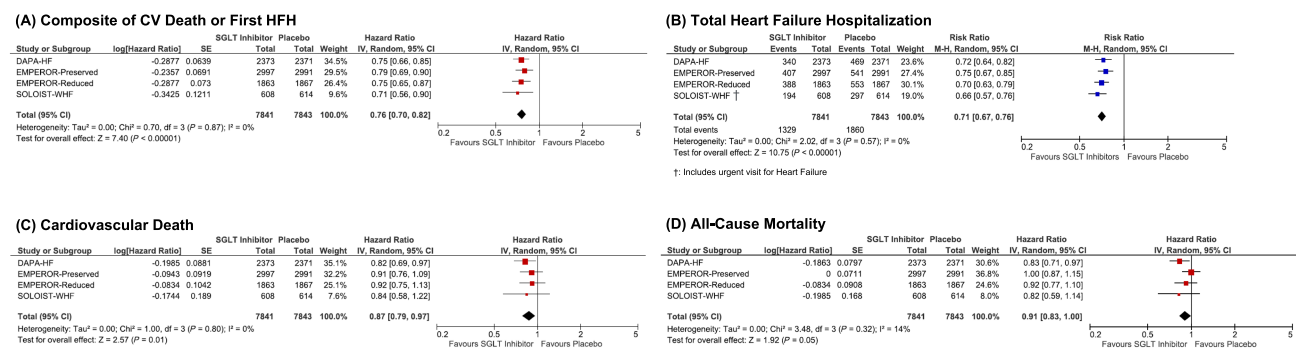
Reductions in both components of the composite outcome were observed as well. SGLT2 inhibitors significantly reduced the hazard of cardiovascular death (1461 events, HR: 0.87, 95% CI: 0.79, 0.97, I<sup>2</sup>: 0%, P = 0.01) and the risk of total HF hos-

pitalizations (3189 events, RR: 0.71, 95% CI: 0.67, 0.76, I<sup>2</sup>: 0%, P < 0.00001). Potential trends towards reductions in all-cause mortality (HR: 0.91, 95% CI: 0.83, 1.00, I<sup>2</sup>: 14%, P = 0.05) and composite renal outcomes, which included chronic dialysis, renal transplantation and sustained decline in estimated glomerular filtration rate, among other renal endpoints (HR: 0.72, 95% CI: 0.48, 1.07, I<sup>2</sup>: 67%, P = 0.10, Supporting Information, *Figure S2*) were noted with SGLT2 inhibitors, although no statistically significant differences were observed.

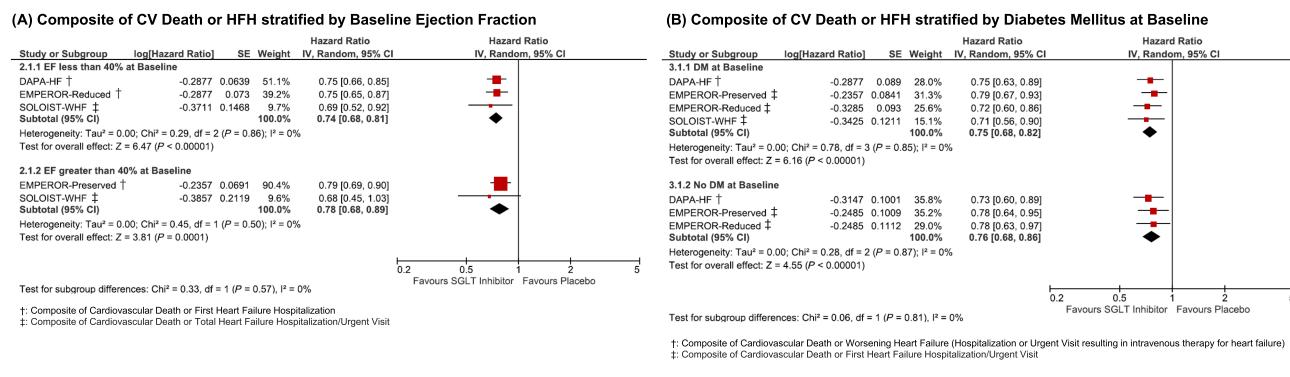
**Subgroup analyses**

Results of the prespecified subgroup analyses are presented in *Figure 2*. Two trials included only patients with a reduced

**Figure 1** Forest plot demonstrating clinical outcomes between patients on SGLT2 inhibitors vs. placebo in randomized controlled trials in the setting of heart failure. Square markers represent point estimate of HR for individual studies, with square size representing proportional weight given to each study in the meta-analysis. Horizontal lines indicate 95% CIs. The solid diamonds represent the estimated 95% CI for effect size of all meta-analysed data. Abbreviations: CI, confidence interval; CV, cardiovascular; HFH, heart failure hospitalization; HR, hazard ratio; RR, risk ratio; SGLT, sodium glucose cotransporter.



**Figure 2** Forest plot demonstrating composite of heart failure hospitalization or cardiovascular death between patients on SGLT2 inhibitors vs. placebo/control in randomized controlled trials stratified by (A) LVEF at baseline and (B) DM status at baseline. Square markers represent point estimate of HR for individual studies, with square size representing proportional weight given to each study in the meta-analysis. Horizontal lines indicate 95% CIs. The solid diamonds represent the estimated 95% CI for effect size of all meta-analysed data. Abbreviations: CI, confidence interval; CV, cardiovascular; DM, diabetes mellitus; EF, ejection fraction; HFH, heart failure hospitalization; HR, hazard ratio; RR, risk ratio; SGLT, sodium glucose cotransporter.



LVEF, one trial included only patients with a preserved LVEF, and one trial included both. Similar reductions in the composite outcome of HF hospitalization and CV death were observed in sub-groups of patients with LVEF  $\leq 40\%$  ( $n = 9199$ , HR: 0.74, 95% CI: 0.68, 0.81,  $I^2$ : 0%,  $P < 0.00001$ ) and LVEF  $> 40\%$  ( $n = 6482$ , HR: 0.78, 95% CI: 0.68, 0.89,  $I^2$ : 0%,  $P = 0.0001$ ;  $P$ -for-interaction: 0.57).

Three trials included patients with and without diabetes mellitus, and one trial only included diabetic patients. A similar reduction in the composite outcome of HF hospitalization and CV death was also noted in both diabetics ( $n = 8155$ , HR: 0.75, 95% CI: 0.68, 0.82,  $I^2$ : 0%,  $P < 0.00001$ ) and non-diabetics ( $n = 7529$ , HR: 0.76, 95% CI: 0.68, 0.86,  $I^2$ : 0%,  $P < 0.00001$ ;  $P$ -for-interaction: 0.81).

## Conclusions

In this meta-analysis of large RCTs in the setting of HF, treatment with SGLT2 inhibitors resulted in a significant reduction in cardiovascular death and HF hospitalizations, as well as a potential trend towards a reduction in all-cause mortality. SGLT2 inhibitors reduced the composite of CV death and HF hospitalizations to a similar degree in patients with a reduced and preserved LVEF, as well as in people with and without diabetes. These data support the notion that SGLT2 inhibitors should be considered broadly in the treatment of HF, irrespective of baseline ejection fraction, glycaemic status or background therapies. The exact molecular mechanisms that underlie the broad benefit observed across ejection fraction remain unclear but may include increased natriuresis, diuresis, EPO release and improved myocardial metabolism, cardio-renal signalling and changes in cardiac ion-channels.<sup>13–16</sup> In patients with and without HF or

diabetes, SGLT2 inhibitors have been shown to promote reverse cardiac remodelling.<sup>13–16</sup> There are several important limitations of this analysis including minor differences in the definition of composite outcomes across studies as well as lack of subgroup data for individual components of the composite outcome. Nevertheless, this investigation represents the most updated analysis to-date demonstrating the efficacy of SGLT2 inhibitors across the spectrum of HF patients.

## Conflict of interest

Arjun K. Pandey, Nitish K. Dhingra, Makoto Hibino, and Vijay Gupta have no conflict of interest. Subodh Verma holds a Tier 1 Canada Research Chair in Cardiovascular Surgery. He has also received grants and personal fees for speaker honoraria and advisory board participation from AstraZeneca, Bayer, Boehringer Ingelheim, Janssen, Amgen, HLS, Merck, Novartis, Sun Pharmaceuticals, Toronto Knowledge Translation Working Group, Phase Bio. He also serves as President of the Canadian Medical and Surgical Knowledge Translation Research Group, a federally incorporated not-for-profit physician organization.

## Supporting information

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

**Table S1.** Search Strategy for MEDLINE Database.

**Figure S1.** PRISMA Flow Diagram.

**Figure S2.** Forest plot demonstrating composite renal outcomes between patients on SGLT2 inhibitors versus placebo/control in randomized controlled trials.

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