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Published in:
The Lancet

DOI:
10.1016/S0140-6736(22)01429-5

SGLT-2 inhibitors in patients with heart failure: a comprehensive meta-analysis of five randomised controlled trials

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Summary

Background SGLT2 inhibitors are strongly recommended in guidelines to treat patients with heart failure with reduced ejection fraction, but their clinical benefits at higher ejection fractions are less well established. Two large-scale trials, DELIVER and EMPEROR-Preserved, in heart failure with mildly reduced or preserved ejection fraction have been done, providing power to examine therapeutic effects on cardiovascular mortality and in patient subgroups when combined with the earlier trials in reduced ejection fraction.

Methods We did a prespecified meta-analysis of DELIVER and EMPEROR-Preserved, and subsequently included trials that enrolled patients with reduced ejection fraction (DAPA-HF and EMPEROR-Reduced) and those admitted to hospital with worsening heart failure, irrespective of ejection fraction (SOLOIST-WHF). Using trial-level data with harmonised endpoint definitions, we did a fixed-effects meta-analysis to estimate the effect of SGLT2 inhibitors on various clinical endpoints in heart failure The primary endpoint for this meta-analysis was time from randomisation to the occurrence of the composite of cardiovascular death or hospitalisation for heart failure. We assessed heterogeneity in treatment effects for the primary endpoint across subgroups of interest. This study is registered with PROSPERO, CRD42022327527.

Findings Among 12 251 participants from DELIVER and EMPEROR-Preserved, SGLT2 inhibitors reduced composite cardiovascular death or first hospitalisation for heart failure (hazard ratio 0·80 [95% CI 0·73–0·87]) with consistent reductions in both components: cardiovascular death (0·88 [0·77–1·00]) and first hospitalisation for heart failure (0·74 [0·67–0·83]). In the broader context of the five trials of 21 947 participants, SGLT2 inhibitors reduced the risk of composite cardiovascular death or hospitalisation for heart failure (0·77 [0·72–0·82]), cardiovascular death (0·87 [0·79–0·95]), first hospitalisation for heart failure (0·72 [0·67–0·78]), and all-cause mortality (0·92 [0·86–0·99]). These treatment effects for each of the studied endpoints were consistently observed in both the trials of heart failure with mildly reduced or preserved ejection fraction and across all five trials. Treatment effects on the primary endpoint were generally consistent across the 14 subgroups examined, including ejection fraction.

Interpretation SGLT2 inhibitors reduced the risk of cardiovascular death and hospitalisations for heart failure in a broad range of patients with heart failure, supporting their role as a foundational therapy for heart failure, irrespective of ejection fraction or care setting.

Funding None.

Lancet 2022; 400: 757–67

Published Online August 27, 2022 https://doi.org/10.1016/S0140-6736(22)01429-5

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Introduction

SGLT2 inhibitors have been shown to have salutary cardioprotective and renoprotective effects in various diseases including type 2 diabetes, chronic kidney disease, and heart failure. In patients with heart failure, the clinical benefits of SGLT2 inhibitors were first established in those with reduced ejection fraction and are now strongly recommended as a key component of comprehensive disease management.[1,2] More recently, the EMPEROR-Preserved[3] and DELIVER trials[4] showed reductions in composite cardiovascular death or heart failure events in patients with heart failure with mildly reduced or preserved ejection fraction.

Clinical practice guidelines were updated after EMPEROR-Preserved was published, but recommendations for SGLT2 inhibitors in heart failure with mildly reduced and preserved ejection fraction remain either absent, because of timing of publications, or weaker (class II) than recommendations for these same therapies in heart failure with reduced ejection fraction (class I).[1,2] This difference might partly be due to uncertainty around the consistency of clinical benefits across the classes and therapeutic effects on individual endpoints that neither trial was specifically designed or powered to examine, particularly cardiovascular death. Similarly, whether the clinical benefits of SGLT2 inhibitors in heart failure extend to all subpopulations including those at the highest end of the ejection fraction spectrum[5] and those already treated with other therapies commonly used in heart failure[6] has not been established.

Research in context

Evidence before this study

Current clinical practice guidelines strongly recommend the use of SGLT2 inhibitors in the treatment of patients with heart failure with reduced ejection fraction (class I). However, guidelines make a weaker recommendation for their use in heart failure with mildly reduced or preserved ejection fraction (class II), potentially due to residual uncertainties related to therapeutic effects on mortality. Although two large-scale trials of heart failure with mildly reduced or preserved ejection fraction (DELIVER and EMPEROR-Preserved) have been done, neither was individually designed nor powered to address these issues.

Added value of this study

We did a prespecified meta-analysis examining the effects of SGLT2 inhibitors on fatal and non-fatal events overall and in subgroups of interest using data from DELIVER and EMPEROR-Preserved. For additional context, we aligned data from adjacent populations of heart failure with reduced ejection fraction (DAPA-HF and EMPEROR-Reduced) and those hospitalised for worsening heart failure (SOLOIST-WHF). This comprehensive meta-analysis of over 20 000 participants provides firm evidence that SGLT2 inhibitors reduce the risk of hospitalisation for heart failure, extend survival, and improve overall health status in patients with heart failure. Clinical benefits of SGLT2 inhibitors appeared consistent across broad clinical profiles and patient subgroups, and extend to patients with left ventricular ejection fraction graeter than 60% and those already treated with other common heart failure therapies.

Implications of all the available evidence

This comprehensive meta-analysis supports the role of the SGLT2 inhibitors as a foundational therapy in the management of heart failure, irrespective of ejection fraction or care setting.

In light of these uncertainties, we undertook a prespecified meta-analysis of the two largest trials of heart failure with mildly reduced or preserved ejection fraction. We also extended this meta-analysis to include trials in patients with reduced ejection fractions (DAPA-HF and EMPEROR-Reduced)[7,8] and those admitted to hospital with worsening heart failure who were enrolled with any ejection fraction (SOLOIST-WHF)[9] to increase power to assess various clinical endpoints, both overall and within subgroups of interest. In this comprehensive meta-analysis of five placebo-controlled trials, we estimated the effects of SGLT2 inhibitors on heart failure hospitalisations, mortality outcomes, and health status overall, and in 14 clinically relevant subgroups.

Methods

Search strategy and selection criteria

We did a prespecified meta-analysis of two trials of heart failure with mildly reduced or preserved ejection fraction (DELIVER and EMPEROR-Preserved), and further analysed these data together with two trials of heart failure with reduced ejection fraction (DAPA-HF and EMPEROR-Reduced) and a trial of patients with recent worsening heart failure (SOLOIST-WHF). To ensure other important trials were not missed, we did a systematic review of the literature via PubMed and MEDLINE of randomised, placebo-controlled trials with cardiovascular and kidney outcomes of SGLT2 inhibitors published between Jan 1, 2015, and July 1, 2022. To capture trials designed to examine clinical outcomes, we limited our selection to studies enrolling at least 1000 participants with heart failure. The pre-registered search query, which was run on July 1, 2022, is in the appendix (p 1). Despite systematic search, no additional trials were identified that met criteria for inclusion (appendix p 4). Data from the DELIVER trial, which were unpublished at the time of the analysis, were included with the involvement of the trial's steering committee. Data were extracted using standardised forms for outcomes of interest by two authors (MV and KFD) and any discrepancies were resolved by consensus. If outcomes published in other trials were not publicly available from the DELIVER and DAPA-HF trials, then we did individual participant-data level analyses to derive treatment effect estimates for these outcomes. Data from key secondary papers were used from the EMPEROR program to support data harmonisation.[10–16]

See Online for appendix

Outcomes and subgroups

The primary endpoint of the meta-analysis was a composite of time to cardiovascular death or first hospitalisation for heart failure. Secondary endpoints examined included cardiovascular death, first hospitalisation for heart failure, cardiovascular death or any worsening heart failure event (hospitalisation for heart failure or urgent heart failure visit requiring intravenous heart failure therapies), and death from any cause. Outcomes were adjudicated by masked clinical endpoints committees, except for urgent heart failure visits, which were not adjudicated in EMPEROR-Preserved and SOLOIST-WHF, which relied on investigator-reports for all events. Treatment effects on health status and quality of life were assessed using the Kansas City Cardiomyopathy Questionnaire (KCCQ, scores ranging from 0 to 100, with higher scores reflecting better health status and fewer symptoms and physical limitations) analysed at baseline and 8 months after randomisation.

The effect of SGLT2 inhibitors on the primary endpoint was examined across 14 subgroups of interest: left ventricular ejection fraction (LVEF), history of diabetes, age, sex, race, geographical region, KCCQ total symptom

score, body-mass index, estimated glomerular filtration rate (eGFR), history of atrial fibrillation or flutter, New York Heart Association (NYHA) functional class, hospitalisation for heart failure within 12 months, N-terminal prohormone of B-type natriuretic peptide (NT-proBNP) concentration, baseline use of mineralocorticoid receptor antagonists (MRAs), and baseline use of angiotensin receptor neprilysin inhibitors (ARNIs). The outcome of cardiovascular death or first hospitalisation for heart failure was not available in the SOLOIST-WHF trial for subgroups.

Select adverse events (amputations, diabetic ketoacidosis, hypoglycaemia, and renal events) were collated from DELIVER and EMPEROR-Preserved, but not directly compared or meta-analysed given differential data capture and exact definitions for these safety events (appendix p 2).

Statistical analysis

All effect sizes were extracted as point estimates with 95% CIs. For the time-to-first event endpoints, the meta-analysis included data from Cox proportional hazards models reported as hazard ratios (HRs) and 95% CIs. For health status and quality of life, we did responder analyses to identify participants with clinically meaningful improvement (≥5 point increase) or deterioration (≥5 point decrease) in each of the KCCQ scores from baseline to 8 months, analysed by logistic regression. For efficacy endpoints, participants included in the intention-to-treat datasets were considered and analyses included all randomised participants. We did a fixed-effects meta-analysis with inverse-variance weighting for each outcome and for individual subgroups to generate pooled estimates for the effect of SGLT2 inhibitors compared with placebo. Between-trial heterogeneity of treatment effect was examined using Cochran's Q test. We tested treatment-by-subgroup heterogeneity of effect using Cochran's Q test. We calculated the number needed to treat (NNT) using the method of Altman and Anderson.[17] We calculated a weighted mean of the median follow-up times for NNT reporting. We considered p values below 0·05 to be statistically significant

The protocol for the meta-analysis of the DELIVER and EMPEROR-preserved trials was prespecified in the DELIVER academic statistical analysis plan and preregistered with PROSPERO (CRD42022327527) before unmasking of the DELIVER trial results. The addition of the three other trials was done *post* hoc. All trials were assessed as high quality with a low risk of bias across the five trials (appendix p 3). All participants provided written consent and the study protocols were approved by the institutional review boards at all participating sites.

	DAPA-HF (n=4744)	DELIVER (n=6263)	EMPEROR-Reduced (n=3730)	EMPEROR-Preserved (n=5988)	SOLOIST-WHF (n=1222)
Investigational drug	Dapagliflozin	Dapagliflozin	Empagliflozin	Empagliflozin	Sotagliflozin
Enrollment period	2017–18	2018–21	2017–19	2017–20	2018–20
Sites	410 sites in 20 countries	350 sites in 20 countries	520 sites in 20 countries	622 sites in 23 countries	306 sites in 32 countries
Key inclusion criteria	LVEF ≤40%; elevated NT-proBNP; NYHA functional class II–IV	LVEF >40% and evidence of structural heart disease; elevated NT-proBNP; NYHA functional class II–IV; ambulatory or hospitalised patients	LVEF ≤40%; elevated NT-proBNP; NYHA functional class II–IV	LVEF >40%; evidence of structural heart disease or history of heart failure hospitalisation within 12 months; elevated NT-proBNP; NYHA functional class II–IV	Type 2 diabetes; admitted to the hospital, or urgent heart failure visit for worsening heart failure; previous treatment with loop diuretic for >30 days; previous diagnosis of heart failure (>3 months); elevated BNP or NT-proBNP; randomised when haemodynamically stable, before hospital discharge or within 3 days of discharge
Key exclusion criteria	eGFR <30mL/min/1·73m^2; SBP <95 mm Hg	eGFR <25 mL/min/1·73 m^2; SBP <95 mm Hg	eGFR <20 mL/min/1·73 m^2; SBP <100 mm Hg	eGFR <20 mL/min/1·73 m^2; SBP <100 mm Hg	eGFR <30 mL/min/1·73 m^2
Median follow-up time	18·2 months	28·1 months	16 months	26·2 months	9·0 months
Primary outcome	Time to first cardiovascular death or heart failure hospitalisation or urgent visit	Time to first cardiovascular death or heart failure hospitalisation or urgent visit	Time to first cardiovascular death or heart failure hospitalisation	Time to first cardiovascular death or heart failure hospitalisation	Total number of cardiovascular death and heart failure hospitalisations and urgent visits
Placebo-group event rates					
Heart failure hospitalisation	9·8/100 person-years	6·5/100 person-years	15·5/100 person-years	8·7/100 person-years	..
Cardiovascular death	7·9/100 person-years	3·8/100 person-years	8·1/100 person-years	3·8/100 person-years	12·5/100 person-years
All-cause death	9·5/100 person-years	7·6/100 person-years	10·7/100 person-years	6·7/100 person-years	16·3/100 person-years

(Table 1 continues on next page)

	DAPA-HF (n=4744)	DELIVER (n=6263)	EMPEROR-Reduced (n=3730)	EMPEROR-Preserved (n=5988)	SOLOIST-WHF (n=1222)
(Continued from previous page)					
Baseline characteristics					
Mean age, years	66·3 (10·9)	71·7 (9·6)	66·5 (11·2)	71·9 (9·6)	70 (64–76)*
Sex					
Women	1109 (23·4%)	2747 (43·9%)	893 (23·9%)	2676 (44·7%)	412 (33·7%)
Men	3635 (76·6%)	3516 (56·1%)	2837 (76·1%)	3312 (55·3%)	810 (66·3%)
NYHA functional class					
II	3203 (67·5)	4713 (75·3)	2800 (75·1)	4883 (81·5%)	..
III–IV	1541 (32·5)	1549 (24·7)	930 (24·9)	1101 (18·4)	..
Mean LVEF, %	31·1% (6·8)	54·2% (8·8)	27·2% (6·1)	54·3% (8·8)	35% (28–45)*
Median NT-proBNP, pg/mL	1437 (857–2650)	1011 (623–1751)	1910 (1115–3480)	974 (499–1731)	1800 (843–3582)
Mean eGFR, mL/min/1·73 m²	65·8 (19·4)	61·0 (19·1)	62·2 (21·5)	60·6 (19·9)	49·7 (40·5–64·6)*
Diabetes	2139 (45·1%)	2806 (44·8%)	1856 (49·8%)	2938 (49·1%)	1222 (100%)
History of heart failure hospitalisation	2251 (47·4%)	2539 (40·5%)	1151 (30·9%)†	1369 (22·9%)†	1222 (100%)
Heart failure medical therapy					
ACE inhibitor	2661 (56·1%)	2295 (36·6%)	1703 (45·7%)	4832 (80·7%)‡	495 (40·5%)
ARB	1307 (27·6%)	2272 (36·3%)	908 (24·3%)	4832 (80·7%)‡	515 (42·1%)
ARNI	508 (10·7%)	301 (4·8%)	727 (19·5%)	134 (2·2%)	205 (16·8%)
MRA	3370 (71·0%)	2667 (42·6%)	2661 (71·3%)	2244 (37·5%)	788 (64·5%)
β blocker	4558 (96·1%)	5177 (82·7%)	3533 (94·7%)	5167 (86·3%)	1125 (92·1%)
Device therapy					
CRT-P or CRT-D	354 (7·5%)	100 (1·6%)	442 (11·8%)	..	..
ICD or CRT-D	1242 (26·2%)	168 (2·7%)	1171 (31·4%)	..	..

Data are n (%), unless otherwise indicated. If pooled data of both treatment groups for each trial were not available, then the data for the placebo group are displayed. ACE=angiotensin converting enzyme. ARB=angiotensin receptor blocker. ARNI=angiotensin receptor neprilysin inhibitor. CRT-D=cardiac resynchronization therapy-defibrillator. CRT-P=cardiac resynchronisation therapy-pacemaker. eGFR=estimated glomerular filtration rate. ICD=implantable cardioverter defibrillator. MRA=mineralocorticoid receptor antagonist. NT-proBNP=N-terminal prohormone of B-type natriuretic peptide. NYHA=New York Heart Association. *Median (IQR). †Heart failure hospitalisation within the preceding 12 months. ‡Number of patients taking a renin-angiotensin system inhibitor alone or in combination with a neprilysin inhibitor.

Table 1: **Characteristics of included trials and randomly assigned patients**

Meta-analysis calculations were done using STATA (version 16.1).

Role of the funding source

There was no funding source for this study.

Results

Overall, 21 947 participants were included across five trials. Median follow-up time ranged from 9 months in SOLOIST-WHF to 2·3 years in DELIVER (table 1). Except for SOLOIST-WHF, which randomly assigned patients shortly after an episode of worsening heart failure, and DELIVER, in which a small proportion of patients (10%) were randomly assigned during or shortly after hospitalisation for heart failure, most patients included in this meta-analysis had chronic ambulatory heart failure. All trials required evidence of increased concentrations of natriuretic peptides, although the minimum threshold for eligibility differed between trials, ranging from 300 pg/mL in patients in sinus rhythm in DELIVER and EMPEROR-Preserved to 5000 pg/mL for patients in atrial fibrillation or flutter and an LVEF of 36–40% in EMPEROR-Reduced. Minimum eGFR for inclusion ranged from at least 20 mL/min/1·73 m² in the EMPEROR trials to at least 30 mL/min/1·73m² in DAPA-HF and SOLOIST-WHF. All trials were placebo-controlled and examined oral doses of the investigational therapy (dapagliflozin 10 mg once daily in DELIVER and DAPA-HF; empagliflozin 10 mg once daily in the EMPEROR trials; and sotagliflozin 200 mg once daily [with dose titration to 400 mg once daily depending on side-effects] in SOLOIST-WHF).

The rates of incident hospitalisation for heart failure, cardiovascular death, and all-cause mortality were higher in trials enrolling outpatients with heart failure with reduced ejection fraction than in those enrolling patients with heart failure with mildly reduced or preserved ejection fraction, and the highest event rates were reported in the SOLOIST-WHF trial, reflecting that patients were randomly assigned following an episode of worsening heart failure (table 1).

Patients in trials of heart failure with reduced ejection fraction were younger and more frequently men compared

with those enrolled in trials of heart failure with mildly reduced or preserved ejection fraction (table 1). Most patients in each trial were in NYHA functional class II. Baseline median NT-proBNP across the trials ranged from 974 pg/mL in EMPEROR-Preserved to 1910 pg/mL in EMPEROR-Reduced (table 1). Median eGFR was lowest in SOLOIST-WHF (50 mL/min/1·73m²). We found differences in background medical treatment according to ejection fraction, with greater use of ARNI and an MRA in patients with reduced ejection fraction (table 1).

Among 12 251 participants from DELIVER and EMPEROR-Preserved, SGLT2 inhibitors reduced composite cardiovascular death or first hospitalisation for heart failure (HR 0·80 [95% CI 0·73–0·87]), without evidence of heterogeneity by trial (figure 1). The results were consistent across both components of the composite endpoint, including cardiovascular death (0·88 [0·77–1·00]) and first hospitalisation for heart failure (0·74 [0·67–0·83]) and similar if worsening heart failure events (including both hospitalisations and urgent visits for heart failure), instead of hospitalisations alone, were included in the composite outcome (0·80 [0·73–0·87]; appendix p 5). For the cardiovascular death endpoint, we found consistent meta-analysis results if unknown or undetermined deaths were instead classified as cardiovascular deaths in both trials (0·90 [0·80–1·01]). We found no significant effect on all-cause death (0·97 [0·88–1·06]). Treatment effects for the composite endpoint of cardiovascular death or first hospitalisation for heart failure were consistent across all subgroups of interest (appendix p 6).

Although the incidence of adverse events could not be directly compared across trials because of differences in event ascertainment and reporting, any serious adverse event occurred numerically less frequently in the SGLT2 inhibitor groups compared with in the placebo groups in both trials (table 2). Rates of select adverse events were infrequent and well-balanced between groups in both trials (table 2).

In incorporating data from all five outcomes trials of SGLT2 inhibitors, the pooled estimates of the treatment effect of SGLT2 inhibitors compared with that of placebo on the outcomes of interest are shown in figure 1. Overall, treatment with an SGLT2 inhibitor reduced the risk of cardiovascular death or hospitalisation for heart failure (HR 0·77 [95% CI 0·72–0·82), with an NNT of 25 (20–31) over a weighted mean of 23 months' follow-up (figure 1). The risk of a first hospitalisation for heart failure was reduced in patients randomly assigned to an SGLT2

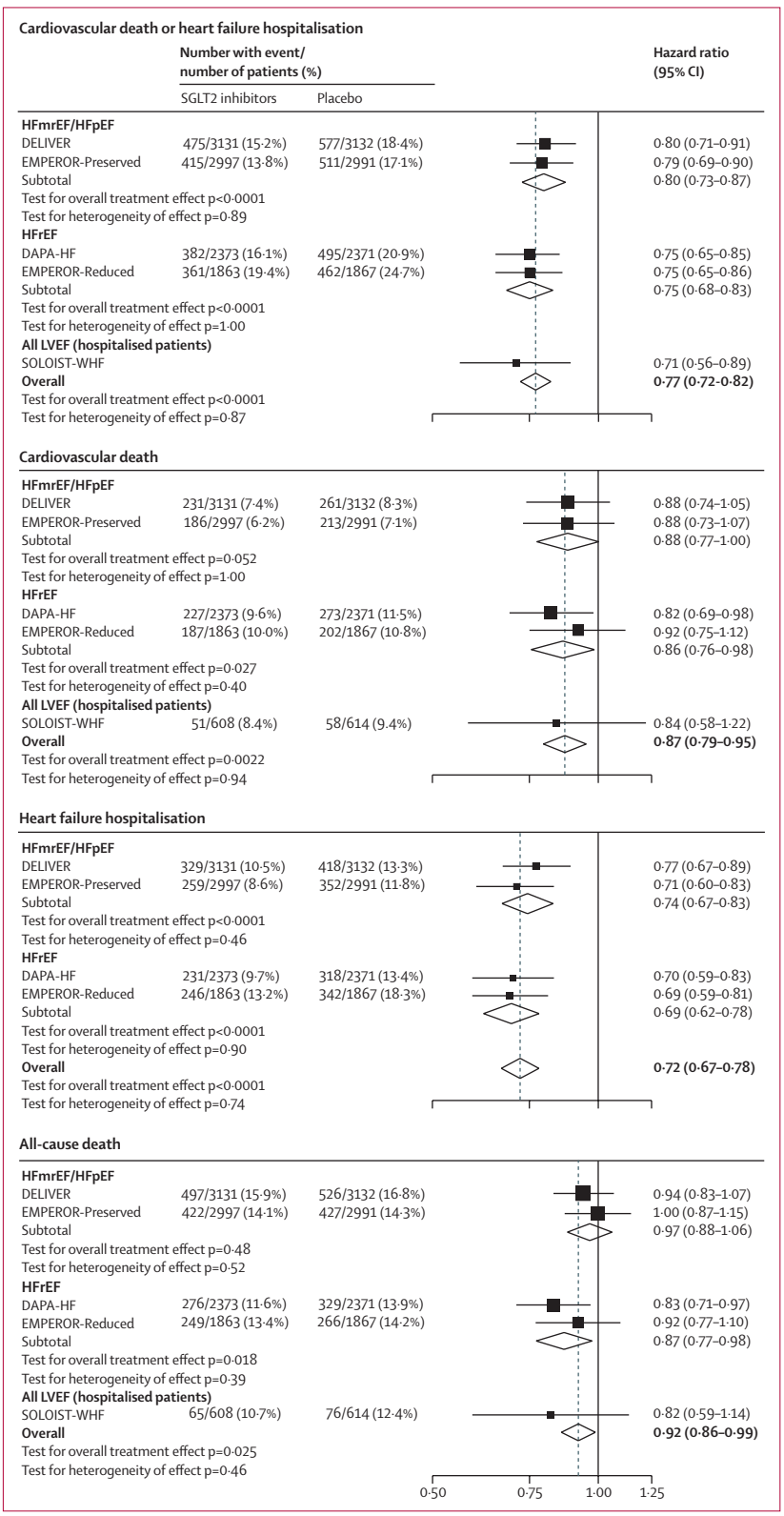


Figure 1: **Pooled treatment effect estimates of SGLT2 inhibitors compared with placebo on cardiovascular outcomes in patients with heart failure**
To harmonise with the DELIVER definition, the endpoint of cardiovascular death alone in EMPEROR-Preserved excludes unknown or undetermined deaths. HFmrEF=heart failure with mildly reduced ejection fraction. HFpEF=heart failure with preserved ejection fraction. HFrEF=heart failure with reduced ejection fraction. LVEF=left ventricular ejection fraction.

	DELIVER		EMPEROR-Preserved	
	Dapagliflozin (n=3126)	Placebo (n=3127)	Empagliflozin (n=2996)	Placebo (n=2989)
Any serious adverse event	1361 (43·5%)	1423 (45·5%)	1436 (47·9%)	1543 (51·6%)
Amputation	19 (0·6%)	25 (0·8 %)	16 (0·5%)	23 (0·8%)
Diabetic ketoacidosis	2 (0·1%)	0 (0·0 %)	4 (0·1%)	5 (0·2%)
Hypoglycaemia	6 (0·2 %)	7 (0·2 %)	73 (2·4%)	78 (2·6%)
Renal	73 (2·3 %)	79 (2·5 %)	363 (12·1%)	384 (12·8%)

Adverse events were not directly compared or meta-analysed because of differential data capture and exact definitions for these safety events in both trials. In both trials, the safety analyses were done in treated patients who received at least a single dose of the study medication. In EMPEROR-Preserved, although limb amputations were reported through the end of the trial, other adverse events were only reported up to 7 days after discontinuation of study medication. Similarly, in DELIVER, all reported adverse events were on-treatment or within 30 days of discontinuation of study medication. In DELIVER, diabetes ketoacidosis includes events that were adjudicated as definite or probable cases, and hypoglycaemic events represent major hypoglycaemia. DELIVER collected adverse event data from serious adverse events, adverse events leading to drug discontinuation or interruption, and selected adverse events, except in select countries that required reporting of all adverse events. The appendix (p 2) juxtaposes the relevant definitions for these adverse events in both trials.

Table 2: **Adverse events in DELIVER and EMPEROR-Preserved**

inhibitor (0·72 [0·67–0·78]), with an NNT of 28 (24–35; figure 1). SGLT2 inhibitors also reduced cardiovascular death (0·87 [0·79–0·95]; NNT 88 [54–229]) and death from any cause (0·92 [0·86–0·99]; NNT 92 [52–733]; figure 1). We found no evidence of between-trial heterogeneity of treatment effect for any of these outcomes (figure 1). More participants in the SGLT2 inhibitor groups than in placebo groups had clinically meaningful improvements and fewer participants had clinically meaningful deterioration in each of the three KCCQ summary scores by 8 months, without evidence of heterogeneity by trial (appendix p 7).

The effect of SGLT2 inhibitors on the composite of cardiovascular death or first hospitalisation for heart failure was consistent across 14 clinically relevant subgroups (figure 2), except for NYHA functional classification, in which we found an attenuation of effect in patients with NYHA functional classification III or IV (HR 0·86 [95% CI 0·77–0·95]) compared with those with NYHA functional classification II (0·72 [0·67–0·79]; p value for heterogeneity 0·015; figure 2). However, the effect of SGLT2 inhibitor treatment was similar across tertiles of baseline KCCQ-total symptom score (p value for heterogeneity 0·98; figure 2). We found consistent benefits across ejection fraction groups: 40% or less (0·75 [0·68–0·83]), 41–49% (0·78 [0·67–0·90]), 50–59% (0·79 [0·68–0·93]), and at least 60% (0·81 [0·69–0·96]; p value for heterogeneity 0·83).

Discussion

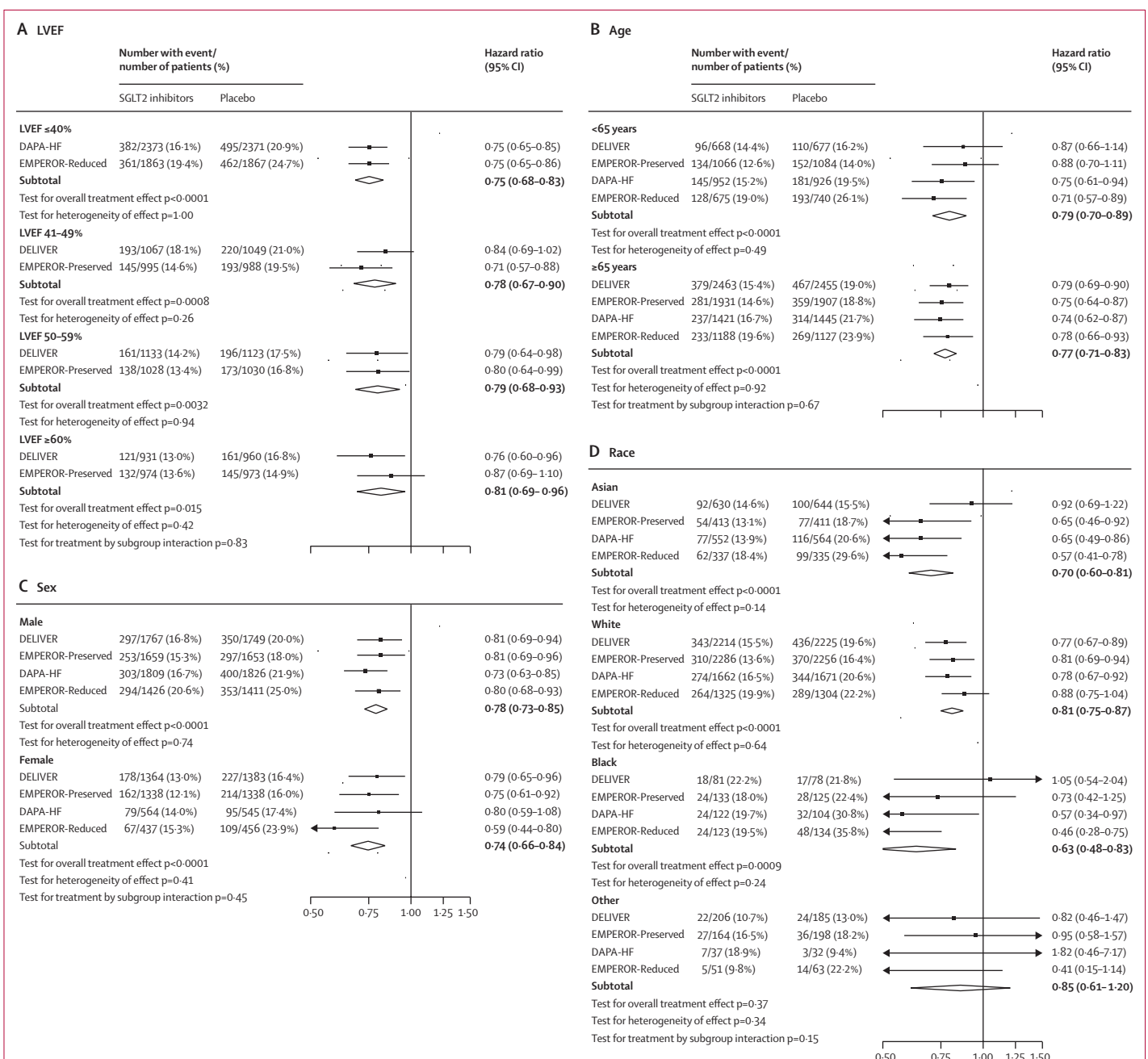
This meta-analysis of two large, dedicated outcomes trials of SGLT2 inhibitors in heart failure with mildly reduced or preserved ejection fraction showed that the SGLT2 inhibitors dapagliflozin and empagliflozin similarly and robustly reduced cardiovascular death or hospitalisation for heart failure, without evidence of heterogeneity between trials. In the more comprehensive examination of evidence from five trials enrolling over 20 000 participants, SGLT2 inhibitors reduced the risk of mortality and worsening heart failure across a broad range of patients with heart failure, irrespective of LVEF or care setting. SGLT2 inhibitors were shown to ameliorate symptoms and confer clinically meaningful improvements in health-related quality of life, with benefits seen rapidly within months of treatment initiation. The clinical benefit of SGLT2 inhibitors appeared consistent across a broad range of patients, and extended to patients with LVEF of at least 60% as well as those already treated with an MRA or ARNI. SGLT2 inhibitors were safe and well-tolerated, without excess in serious adverse events or key adverse events of interest.

We first examined the pooled treatment effects of SGLT2 inhibitor in the two dedicated trials of heart failure with mildly reduced or preserved ejection fraction, a population in which the identification of effective therapeutics has historically been challenging. Trials have only identified modest clinical benefits with previously examined therapies, and no trial to date has definitively shown a reduction in risk of all-cause or cause-specific mortality. These findings might partly be due to greater phenotypic heterogeneity and lower risks of death from cardiovascular causes in this population compared with patients with heart failure with reduced ejection fraction. Clinical practice guidelines similarly convey this uncertainty, with no class I recommendations offered for heart failure with mildly reduced or preserved ejection fraction for any individual therapy (aside from diuretics).[1,2] This large-scale meta-analysis of DELIVER and EMPEROR-Preserved with harmonised data capture of patient profiles and endpoint definitions increased power to assess various clinical endpoints, including cardiovascular death. Risk reductions in the primary composite endpoint were driven by substantial and statistically robust treatment effects on hospitalisations for heart failure, with more modest and statistically borderline effects on cardiovascular death. Point estimates for both components were highly concordant between the two trials and were similar across variant endpoint definitions. These data complement the clinically important health status benefits seen with SGLT2 inhibitors in this population in previous dedicated trials.[19,20] Taken together, these data should inform clinical decision making and guidelines.

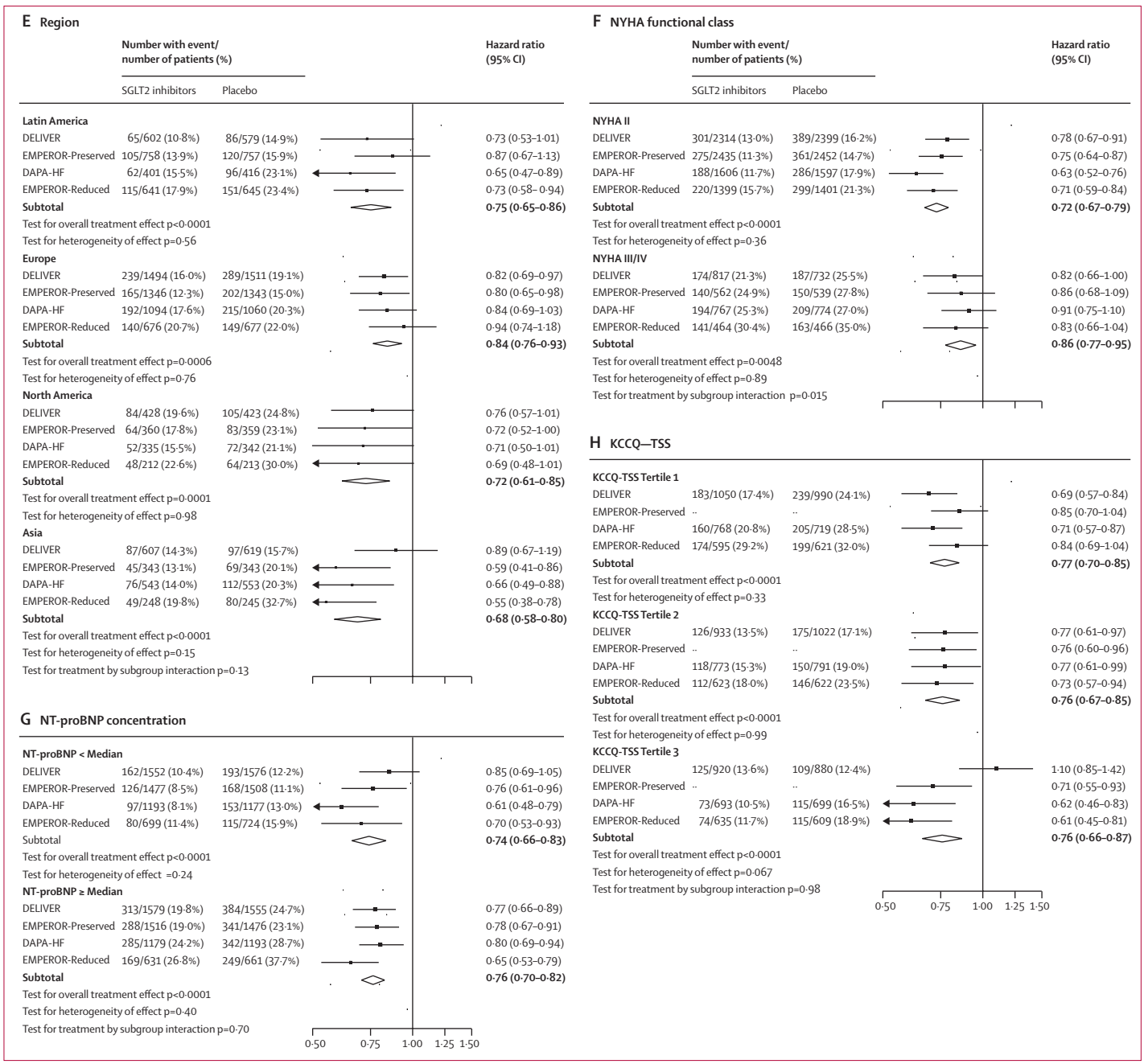
The five trials of SGLT2 inhibitors in heart failure enrolled complementary populations and provided broader context to examine therapeutic effects across the spectrum of disease severity and patient profiles. The greatest benefit of the addition of an SGLT2 inhibitor to standard therapy in patients with heart failure was a 28% relative reduction in the risk of hospitalisation for heart failure, with an NNT of 28 to prevent one event over a follow-up of 23 months. Although smaller, the effect on mortality was significant. These effects should be interpreted in the context of very high background rates of use of guideline-recommended therapy for heart failure in all trials included in the meta-analysis. These estimates for reductions in cardiovascular death are also highly

concordant with those observed in other patient populations extensively studied with SGLT2 inhibitors, such as those with type 2 diabetes.[21] Furthermore, patients treated with SGLT2 inhibitors were 10–20% more likely to have improvements in health status and, conversely, were 10–20% less likely to face important deterioration in health status compared with patients in control groups. This composite evidence underscores the benefits of SGLT2 inhibitors on meaningful clinical events, symptom burden, and overall health status in patients with heart failure. We found no statistical heterogeneity across the five trials for any endpoint and thus the clinical benefits of the three tested therapies are assumed to be similar. However, because these were not head-to-head comparisons, we cannot exclude the possibility that select differences in clinical efficacy and safety might still exist.

This meta-analysis also clarifies previous uncertainties in the efficacy of SGLT2 inhibitors in specific patient groups. A previous meta-analysis of DAPA-HF and EMPEROR-Reduced reported potential heterogeneity in



(Figure 2 continues on next page)



(Figure 2 continues on next page)

treatment effects by both race and region;[22] in the present meta-analysis with over twice the number of patients, no evidence of heterogeneity was seen. We found a nominally significant interaction for the treatment effect according to NYHA functional class, with an attenuated effect in patients in NYHA class III or IV compared with NYHA class II. However, subgroup analysis of patient-reported symptom burden, assessed using the KCCQ total symptom score, did not show any evidence of heterogeneity in treatment effects and other measures of severity of heart failure, including natriuretic peptides, recency of hospitalisation, and LVEF, did not show any evidence of heterogeneity. Data from this meta-analysis support the safety and benefits of commencing SGLT2 inhibitor, irrespective of care setting, although an ongoing trial is investigating a strategy of in-hospital initiation of an SGLT2 inhibitor (NCT04363697).

Previous trials of renin-angiotensin system inhibitors, MRAs, and ARNIs have identified attenuation of benefits

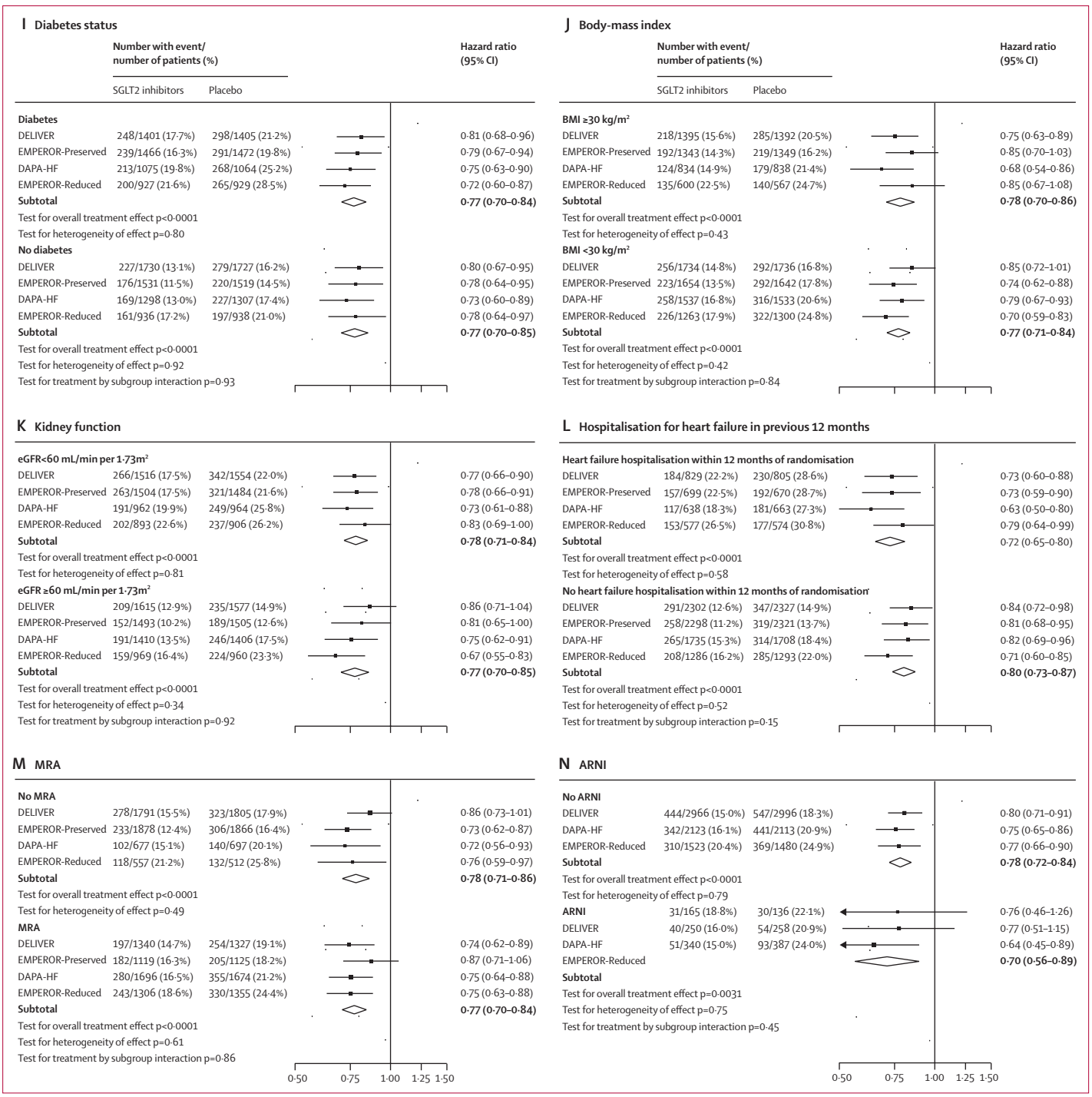


Figure 2: **Treatment effects of SGLT2 inhibitors on the composite of cardiovascular death or first hospitalisation for heart failure across 14 clinically relevant subgroups**
The age-based subgroup for EMPEROR-Preserved was dichotomised at 70 years. In the DELIVER trial, Saudi Arabia was included in the Europe region. The NT-proBNP-based median concentration was calculated on the basis of atrial fibrillation or flutter status in EMPEROR-Preserved. eGFR=estimated glomerular filtration rate. NT-proBNP=N-terminal prohormone of B-type natriuretic peptide. NYHA=New York Heart Association. ARNI=angiotensin receptor neprilysin inhibitor. KCCQ-TSS=Kansas City Cardiomyopathy Questionnaire—Total Symptom Score. MRA=mineralocorticoid receptor antagonists. NY-proBNP=N-terminal prohormone B-type natriuretic peptide.

of these therapies among patients with truly normal LVEF.[23–25] A similar pattern of attenuation at higher LVEF was suggested for select endpoints in the EMPEROR-Preserved trial, although the interaction test for the primary endpoint across LVEF subgroups was not significant.[5] However, when pooling data from subgroups

in both DELIVER and EMPEROR-Preserved, the clinical benefits of SGLT2 inhibitors clearly extend to patients with heart failure and LVEF of at least 60%, with an approximate 20% risk reduction in the primary composite endpoint. As such, SGLT2 inhibitors should not be withheld from patients with heart failure who would otherwise be appropriate candidates for the therapy and yet have an ejection fraction of at least 60%. Indeed, the benefits of SGLT2 inhibitor were seen to be complementary and additive to those of an ARNI and MRA across the range of ejection fraction. In addition to their established role as treatments for heart failure with reduced ejection fraction, both of these medications might be considered at higher ejection fractions in the guidelines based on the post hoc analyses indicating benefit in patients with an LVEF of less than normal (approximately 55–60%). A nominally significant interaction was found in EMPEROR-Preserved for baseline MRA use for the endpoint of first and recurrent hospitalisations for heart failure, with the suggestion of less benefit among those treated with an MRA compared with those who were not.[6] This meta-analysis, however, showed consistency of benefits irrespective of background use of ARNI or MRA. Therefore, these data support the use of SGLT2 inhibitors across the spectrum of ejection fraction, regardless of background therapies.[26] The superior strength of evidence for SGLT2 inhibitors, compared with an MRA and ARNI in heart failure with mildly reduced or preserved ejection fraction, along with their favourable safety profile, the minimal requirement for monitoring, rapid onset of benefit, and beneficial effects on kidney function, supports prioritising initiation of SGLT2 inhibitor use in all patients with heart failure.

Although the meta-analysis of DELIVER and EMPEROR-Preserved was prespecified and preregistered, the supportive five-trial meta-analysis was done post hoc. Furthermore, no alpha was ascribed to this meta-analysis and as such, these results cannot be considered hypothesis testing. We did not have access to individual participant-level data from the EMPEROR trials or SOLOIST-WHF and thus relied on published data available in the public domain; certain subgroup variables might be better modelled as continuous measures rather than at the reported cut-points. Although the meta-analysis improved precision around pooled treatment estimates in subpopulations of interest, interaction testing might still be underpowered. Subgroup data for the outcome of interest were not available for the SOLOIST-WHF trial. The findings from the meta-analysis are most generalisable to patients seen in clinical practice settings similar to those of enrolled trial participants. All trials enrolled fewer than 5–10% Black patients, partly reflective of the global racial representation of populations served by participating sites around the world. None of the included trials enrolled patients with severe kidney dysfunction (eGFR <20 mL/min/1·73 m²) or on dialysis; therefore, no conclusions regarding the efficacy or safety of SGLT2 inhibitors in these patients can be inferred. Urgent heart failure visits were not centrally adjudicated in the EMPEROR-Preserved trial. Although we were able to align definitions of most other efficacy endpoints, safety event definitions could not be reconciled because of differential timeframes of assessment and data ascertainment. A renal composite endpoint was not a prespecified secondary trial endpoint in DELIVER. Consequently, DELIVER did not systematically collect these data and renal events were only available as serious adverse events or adverse events leading to drug discontinuation. As such, renal endpoints could not be compared across trials and thus were omitted from the meta-analysis. No correction was made for multiplicity of testing for subgroup analyses.

In conclusion, this meta-analysis of 21 947 patients with heart failure across the full spectrum of ejection fraction, including both outpatients and hospitalised patients, showed that SGLT2 inhibitors significantly reduce the risk of mortality and worsening heart failure and improve patient symptoms and overall health status when added to standard therapy for heart failure. SGLT2 inhibitors should be considered foundational therapy in all patients with heart failure, irrespective of LVEF or care setting.

Contributors

MV, BLC, PSJ, JJVM, and SDS conceived of and designed the study. MV, KFD, BLC, PSJ, JJVM, and SDS did the analysis. MV and KFD drafted the manuscript. All authors contributed to data interpretation and writing of the final version of the manuscript, and all authors were responsible for the decision to submit the manuscript. MV, KFD, BLC, and SDS accessed and verified the data and all authors had full access to the study data.

Declaration of interests

MV has received research grant support or served on advisory boards for American Regent, Amgen, AstraZeneca, Bayer, Baxter Healthcare, Boehringer Ingelheim, Cytokinetics, Lexicon Pharmaceuticals, Novartis, Pharmacosmos, Relypsa, Roche Diagnostics, and Sanofi; received speaker fees from AstraZeneca, Novartis, and Roche Diagnostics; and participates on clinical trial committees for studies sponsored by Galmed, Novartis, Bayer, Occlutech, and Impulse Dynamics. KFD's employer has been remunerated by AstraZeneca for clinical trial work. KFD also reports speakers' fees from AstraZeneca and research funding from Boehringer Ingelheim. KFD, PSJ, and JJVM are funded by a British Heart Foundation Centre of Research Excellence Grant. BLC has received consulting fees from Boehringer Ingelheim. PSJ's employer has been remunerated by AstraZeneca, Bayer, and Novo Nordisk for clinical trial work. PSJ also reports consulting and speakers' fees from Novartis, AstraZeneca, and Boehringer Ingelheim; and research funding Boehringer Ingelheim. RadB has received research grant support from AstraZeneca, Abbott, Boehringer Ingelheim, Cardior Pharmaceuticals, Ionis Pharmaceuticals, Novo Nordisk, and Roche; and received speaker fees from Abbott, AstraZeneca, Bayer, Novartis, and Roche. AFH reports research grant support from American Regent, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Merck, Novartis, Somologic, and Verily; and consulting Fees from Amgen, AstraZeneca, Bayer, Biofourmis, Boston Scientific, Cytokinetics, Merck, Novartis and NovoNordisk. SEI has served on clinical trial committees or as a consultant to AstraZeneca, Boehringer Ingelheim, Novo Nordisk, Lexicon, Merck, Pfizer, vTv Therapeutics, Abbott, and Esperion; and has given lectures sponsored by AstraZeneca and Boehringer Ingelheim. MNK reports research grant support from AstraZeneca and Boehringer Ingelheim; and consulting fees from Alnylam, AstraZeneca, Amgen, Bayer, Boehringer Ingelheim, Cytokinetics, Esperion, Eli Lilly, Janssen, Lexicon, Merck (Diabetes and Cardiovascular), Pharmacosmos, Novo Nordisk, Sanofi, and Vifor. CSPL is supported by a Clinician Scientist Award from the National Medical

Research Council of Singapore; has received research support from Bayer and Roche Diagnostics; has served as consultant or on the advisory board, steering committee, or executive committee for Abbott, Actelion, Alleviant Medical, Allysta Pharma, Amgen, AnaCardio, Applied Therapeutics, AstraZeneca, Bayer, Boehringer Ingelheim, Boston Scientific, Cytokinetics, Darma, EchoNous, Impulse Dynamics, Ionis Pharmaceutical, Janssen Research & Development, Medscape/WebMD Global, Merck, Novartis, Novo Nordisk, Prosciento, Radcliffe Group, Roche Diagnostics, Sanofi, Siemens Healthcare Diagnostics, and Us2.ai; and serves as co-founder and non-executive director of Us2.ai. FM has received personal fees from AstraZeneca. SJS reports research grants from the US National Institutes of Health, Actelion, AstraZeneca, Corvia, Novartis, and Pfizer; and consulting fees from Abbott, Actelion, AstraZeneca, Amgen, Aria CV, Axon Therapies, Bayer, Boehringer Ingelheim, Boston Scientific, Bristol Myers Squibb, Cardiora, Coridea, CVRx, Cyclerion, Cytokinetics, Edwards Lifesciences, Eidos, Eisai, Imara, Impulse Dynamics, Intellia, Ionis, Ironwood, Lilly, Merck, MyoKardia, Novartis, Novo Nordisk, Pfizer, Prothena, Regeneron, Rivus, Sanofi, Shifamed, Tenax, Tenaya, and United Therapeutics. ASD reports institutional grant support from Abbott, Alnylam, AstraZeneca, Bayer, Novartis; and consulting fees from Abbott, Alnylam, AstraZeneca, Avidity, Axon Therapeutics, Bayer, Biofourmis, Boston Scientific, Cytokinetics, GlaxoSmithKline, Merck, Novartis, Parel, Regeneron, Roche, and Verily. JJVM has received funding to his institution, Glasgow University, for his work on clinical trials, consulting, and other activities from Alnylam, Amgen, AstraZeneca, Bayer, Bristol Myers Squibb, Cardurion, Cytokinetics, GlaxoSmithKline, Novartis, Pfizer, and Theracos; and has received personal lecture fees from the Corpus, Abbott, Hickma, Sun Pharmaceuticals, and Medsca. SDS has received research grants from Actelion, Alnylam, Amgen, AstraZeneca, Bellerophon, Bayer, Bristol Myers Squibb, Celladon, Cytokinetics, Eidos, Gilead, GlaxoSmithKline, Ionis, Lilly, Mesoblast, MyoKardia, National Institutes of Health/National Heart Lung and Blood Institute, Neurotronik, Novartis, NovoNordisk, Respicardia, Sanofi Pasteur, Theracos, and US2.AI; and has consulted for Abbott, Action, Akros, Alnylam, Amgen, Arena, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Cardior, Cardurion, Corvia, Cytokinetics, Daiichi-Sankyo, GlaxoSmithKline, Lilly, Merck, Myokardia, Novartis, Roche, Theracos, Quantum Genomics, Cardurion, Janssen, Cardiac Dimensions, Tenaya, Sanofi-Pasteur, Dinaqor, Tremeau, CellProThera, Moderna, American Regent, and Sarepta.

Data sharing

The trial sponsor is committed to responsible data sharing principles, including sharing of anonymised individual patient-level data and relevant clinical documents with qualified researchers. The trial data availability is according to the criteria and processes described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure.

Acknowledgments

The DELIVER and DAPA-HF were funded by AstraZeneca, the EMPEROR trials were funded by Boehringer Ingelheim and Eli Lilly, and SOLOIST-WHF was funded by Sanofi and Lexicon Pharmaceuticals.

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