SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: a meta-analysis of the EMPEROR-Reduced and DAPA-HF trials

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Summary

Background Both DAPA-HF (assessing dapagliflozin) and EMPEROR-Reduced (assessing empagliflozin) trials showed that sodium-glucose co-transporter-2 (SGLT2) inhibition reduced the combined risk of cardiovascular death or hospitalisation for heart failure in patients with heart failure with reduced ejection fraction (HFrEF) with or without diabetes. However, neither trial was powered to assess effects on cardiovascular death or all-cause death or to characterise effects in clinically important subgroups. Using study-level published data from DAPA-HF and patient-level data from EMPEROR-Reduced, we aimed to estimate the effect of SGLT2 inhibition on fatal and non-fatal heart failure events and renal outcomes in all randomly assigned patients with HFrEF and in relevant subgroups from DAPA-HF and EMPEROR-Reduced trials.

Methods We did a prespecified meta-analysis of the two single large-scale trials assessing the effects of SGLT2 inhibitors on cardiovascular outcomes in patients with HFrEF with or without diabetes: DAPA-HF (assessing dapagliflozin) and EMPEROR-Reduced (assessing empagliflozin). The primary endpoint was time to all-cause death. Additionally, we assessed the effects of treatment in prespecified subgroups on the combined risk of cardiovascular death or hospitalisation for heart failure. These subgroups were based on type 2 diabetes status, age, sex, angiotensin receptor neprilysin inhibitor (ARNI) treatment, New York Heart Association (NYHA) functional class, race, history of hospitalisation for heart failure, estimated glomerular filtration rate (eGFR), body-mass index, and region (post-hoc). We used hazard ratios (HRs) derived from Cox proportional hazard models for time-to-first event endpoints and Cochran's Q test for treatment interactions; the analysis of recurrent events was based on rate ratios derived from the Lin-Wei-Yang-Ying model.

Findings Among 8474 patients combined from both trials, the estimated treatment effect was a 13% reduction in all-cause death (pooled HR 0·87, 95% CI 0·77–0·98; p=0·018) and 14% reduction in cardiovascular death (0·86, 0·76–0·98; p=0·027). SGLT2 inhibition was accompanied by a 26% relative reduction in the combined risk of cardiovascular death or first hospitalisation for heart failure (0·74, 0·68–0·82; p<0·0001), and by a 25% decrease in the composite of recurrent hospitalisations for heart failure or cardiovascular death (0·75, 0·68–0·84; p<0·0001). The risk of the composite renal endpoint was also reduced (0·62, 0·43–0·90; p=0·013). All tests for heterogeneity of effect size between trials were not significant. The pooled treatment effects showed consistent benefits for subgroups based on age, sex, diabetes, treatment with an ARNI and baseline eGFR, but suggested treatment-by-subgroup interactions for subgroups based on NYHA functional class and race.

Interpretation The effects of empagliflozin and dapagliflozin on hospitalisations for heart failure were consistent in the two independent trials and suggest that these agents also improve renal outcomes and reduce all-cause and cardiovascular death in patients with HFrEF.

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Introduction

Large cardiovascular outcome trials in patients with type 2 diabetes have shown that sodium-glucose co-transporter-2 (SGLT2) inhibitors improve cardiovascular and renal outcomes and, in particular, they reduce the risk of hospitalisation for heart failure.[1–4] This reduction was observed in patients with and without a previous history of heart failure.[5–7] However, patients with known heart failure comprised only small proportions of the study populations, typically without systematic documentation of left ventricular ejection fraction (LVEF) or natriuretic peptides. Meta-analyses of these cardiovascular outcome trials in patients with type 2 diabetes showed that these agents reduced the risk of hospitalisation for heart failure and slowed the progression of renal disease.[8,9] These effects on cardiovascular and renal outcomes might not be directly related to glycaemic control, suggesting that the benefits could also extend to patients without diabetes.[10]

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Research in context

Evidence before this study

We studied the only two available trials testing sodium-glucose co-transporter-2 (SGLT2) inhibitors in patients with heart failure with reduced ejection fraction (HFrEF). The Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients With Chronic Heart Failure (DAPA-HF) was the first outcome trial that was specifically designed to assess the effect of SGLT2 inhibitors in patients with HFrEF, with or without diabetes. The Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction (EMPEROR-Reduced) trial also studied the same target population, but was enriched for patients with markedly reduced ejection fraction and elevated natriuretic peptide concentrations. Taken together, the trials enrolled patients with a broader spectrum of severity of heart failure than that of either trial alone. In each trial, the SGLT2 inhibitors reduced the risk of the primary composite endpoint of cardiovascular death or hospitalisation for heart failure. Neither trial was adequately powered to assess treatment effects on secondary outcomes such as all-cause death, cardiovascular death, and serious adverse renal events or to characterise effects in clinically important subgroups.

Added value of this study

Using study-level published data from DAPA-HF and patient-level data from EMPEROR-Reduced, we did a meta-analysis to estimate the effect of SGLT2 inhibition with dapagliflozin and empagliflozin on fatal events, hospitalisation for heart failure, and renal outcomes and in relevant clinical subgroups in a broad spectrum of patients with HFrEF. Our meta-analysis established a solid evidence base supporting an important role of empagliflozin and dapagliflozin primarily to reduce hospitalisations for heart failure and, secondarily, to improve renal outcomes and decrease all-cause and cardiovascular death. These benefits were seen regardless of age and sex and irrespective of the presence or absence of diabetes or treatment with a neprilysin inhibitor.

Implications of all the available evidence

The evidence supports the use of the SGLT2 inhibitors empagliflozin or dapagliflozin as an integral part of a comprehensive therapy that improves the event-free survival of patients with HFrEF.

The Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients With Chronic Heart Failure (DAPA-HF) was the first published outcome trial specifically designed to assess the effect of SGLT2 inhibitors in patients with heart failure and a reduced ejection fraction (HFrEF) with or without diabetes.[11] The Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction (EMPEROR-Reduced) trial was simultaneously designed to study the same target population but was enriched for patients with markedly reduced ejection fraction and elevated natriuretic peptide concentrations.[11,12] Taken together, the trials enrolled a broader spectrum of severity of HFrEF than that of either trial alone. In each trial, SGLT2 inhibitors reduced the risk of the composite endpoint of cardiovascular death or hospitalisation for heart failure. Neither trial was adequately powered to assess treatment effects on secondary outcomes such as all-cause death, cardiovascular death, and serious adverse renal events or to characterise effects in clinically important subgroups.

DAPA-HF and EMPEROR-Reduced are the only trials to date that included patients with symptomatic HFrEF, elevated natriuretic peptides, and with and without type 2 diabetes, assessing the effect of SGLT2 inhibitors on morbidity and mortality in such patients. Therefore, we aimed to assess the effects of SGLT2 inhibition in this specific population. Other cardiovascular outcome trials using SGLT2 inhibitors included patients with type 2 diabetes, among whom a small proportion had investigator-reported heart failure. However, no investigations such as natriuretic peptide measurements or echocardiography were done to verify or further characterise the heart failure diagnoses. Using data from DAPA-HF and EMPEROR-Reduced, we did a meta-analysis to estimate the effects of SGLT2 inhibition with dapagliflozin and empagliflozin on fatal events, hospitalisation for heart failure, and renal outcomes and in relevant clinical subgroups in a broad spectrum of patients with HFrEF.

Methods

Overview

We undertook a prespecified meta-analysis of the two single large-scale cardiovascular outcomes trials published to date that assessed SGLT2 inhibitors in patients with HFrEF with or without diabetes: DAPA-HF (assessing dapagliflozin) and EMPEROR-Reduced (assessing empagliflozin). The patient characteristics and treatment effects overall and in subgroups in each individual trial have been previously published.[11,12] Briefly, both trials included patients with symptomatic HFrEF and elevated natriuretic peptide concentrations. EMPEROR-Reduced tested empagliflozin 10 mg per day orally versus placebo, and DAPA-HF tested dapagliflozin 10 mg per day orally versus placebo. The median follow-up time was 16 months in EMPEROR-Reduced and 18 months in DAPA-HF. We used study-level published data from DAPA-HF and patient-level data from EMPEROR-Reduced. This meta-analysis was prespecified to include the only two available

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outcome trials assessing the efficacy and safety of SGLT2 inhibitors in patients with HFrEF. Therefore, no formal literature search was undertaken. We did not include small trials (<300 patients) of short duration (12 weeks or fewer), because these provided no meaningful information on major outcomes. Data extraction was done by EP, APO, and Eva Kleine (statistician at Boehringer Ingelheim).

For this meta-analysis, we used the methods proposed in the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement.[13] The methods and outcome measures were prespecified before unmasking of the data from EMPEROR-Reduced.[11]

Outcomes and subgroups

Time to all-cause death was the predefined primary endpoint in this meta-analysis. Secondary endpoints assessed were time to cardiovascular death, first hospitalisation for heart failure or cardiovascular death, first hospitalisation for heart failure, recurrent hospitalisations for heart failure or cardiovascular death, and a renal composite defined as 50% or higher sustained decline in estimated glomerular filtration rate (eGFR), end-stage renal disease (ESRD), or renal death. Effects in subgroups on the combined risk of cardiovascular death or hospitalisation for heart failure were also assessed in predefined subgroups, relying on published data from DAPA-HF.

Because the definition of some endpoints differed slightly between the two trials, we used patient-level data from the EMPEROR-Reduced trial to replicate the DAPA-HF definitions for selected endpoints. The primary endpoint was slightly different between the two trials. In DAPA-HF, the primary endpoint was a composite of cardiovascular death or hospitalisation for heart failure, including urgent visits with intravenous therapy for heart failure. Because very few patients had only an urgent visit for heart failure and the treatment effects on the primary endpoint were nearly identical when such visits were included or excluded, we assumed that the subgroup effects on the DAPA-HF primary endpoint represented the treatment effects on the EMPEROR-Reduced primary endpoint, which did not include urgent-care visits.

Because the definition of the composite renal endpoints assessed in DAPA-HF and EMPEROR-Reduced also differed slightly, we used the definition of the DAPA-HF trial that included a 50% or higher sustained decline in eGFR; end-stage renal disease, defined as either sustained eGFR lower than 15 mL/min per 1·73 m², chronic dialysis, or a renal transplantation; or renal death.

The predefined study subgroups were type 2 diabetes (yes or no), sex, angiotensin receptor neprilysin inhibitor (ARNI) treatment (yes or no), New York Heart Association (NYHA) class II or III–IV, race (White, Black, or Asian), region (North America, Latin America, Europe, or Asia), age younger or older than 65 years (and additionally <55, 55–64, 65–74, and ≥75 years), history of hospitalisation for heart failure (yes or no), eGFR lower or higher than 60 mL/min per 1·73m², and body-mass index (BMI) lower or higher than 30 kg/m². The region subgroup was added post-hoc to clarify whether the treatment effects would reflect the results observed on race.

Because the definitions of adverse events varied between the two trials, we provide only descriptive data about selected safety endpoints of interest (eg, for volume depletion, hypoglycaemia, non-traumatic lower limb amputations, fractures, and ketoacidosis).

Statistical analysis

We used the point estimates and 95% CI as reported for the individual trials for the meta-analysis, on the basis of an intention-to-treat analysis of all randomly assigned patients. For the time-to-first event endpoints, the meta-analysis is based on hazard ratios (HRs) derived from Cox proportional hazard models, and the analysis of

	EMPEROR-Reduced		DAPA-HF	
	Empagliflozin	Placebo	Dapagliflozin	Placebo
Number of participants	1863	1867	2373	2371
Age, years	67·2 (10·8)	66·5 (11·2)	66·2 (11·0)	66·5 (10·8)
Sex				
Men	1426 (76·5%)	1411 (75·6%)	1809 (76·2%)	1826 (77·0%)
Women	437 (23·5%)	456 (24·4%)	564 (23·8%)	545 (23·0%)
NYHA functional classification				
II	1399 (75·1%)	1401 (75·0%)	1606 (67·7%)	1597 (67·4%)
III	455 (24·4%)	455 (24·4%)	747 (31·5%)	751 (31·7%)
IV	9 (0·5%)	11 (0·6%)	20 (0·8%)	23 (1·0%)
Mean LVEF, %	27·7 (6·0)	27·2 (6·1)	31·2 (6·7)	30·9 (6·9)
NT-pro BNP, pg/mL	1887 (1077–3429)	1926 (1153–3525)	1428 (857–2655)	1446 (857–2641)
Medical history				
Hospitalisation for heart failure*	577 (31·0%)	574 (30·7%)	1124 (47·4%)	1127 (47·5%)
Diabetes†	927 (49·8%)	929 (49·8%)	1075 (45·3%)	1064 (44·9%)
eGFR, mL/min per 1·73 m²‡	61·8 (21·7)	62·2 (21·5)	66·0 (19·6)	65·5 (19·3)
Heart failure medications				
ACE inhibitor	867 (46·5%)	836 (44·8%)	1332 (56·1%)	1329 (56·1%)
ARB	451 (24·2%)	457 (24·5%)	675 (28·4%)	632 (26·7%)
Mineralocorticoid receptor antagonist	1306 (70·1%)	1355 (72·6%)	1696 (71·5%)	1674 (70·6%)
ARNI	340 (18·3%)	387 (20·7%)	250 (10·5%)	258 (10·9%)
Device therapy				
ICD or CRT-D	578 (31·0%)	593 (31·8%)	622 (26·2%)	620 (26·1%)
CRT-D or CRT-P	220 (11·8%)	222 (11·9%)	190 (8·0%)	164 (6·9%)

Data are n (%), mean (SD), or median (IQR). ACE=angiotensin converting enzyme. ARB=angiotensin receptor blocker. ARNI=angiotensin receptor neprilysin inhibitor. CRT-D=cardiac resynchronisation therapy defibrillator. CRT-P=cardiac resynchronisation therapy pacemaker. eGFR=estimated glomerular filtration rate. ICD=implantable cardiac defibrillator. LVEF=left ventricular ejection fraction. NT-pro BNP=N-terminal pro B-type natriuretic peptide. NYHA=New York Heart Association. *For EMPEROR-Reduced: preceding 12 months. †Determined by a combination of medical history and pre-treatment glycated haemoglobin. ‡Chronic Kidney Disease Epidemiology Collaboration formula.

Table 1: **Overview of main characteristics of the two trial populations at baseline**

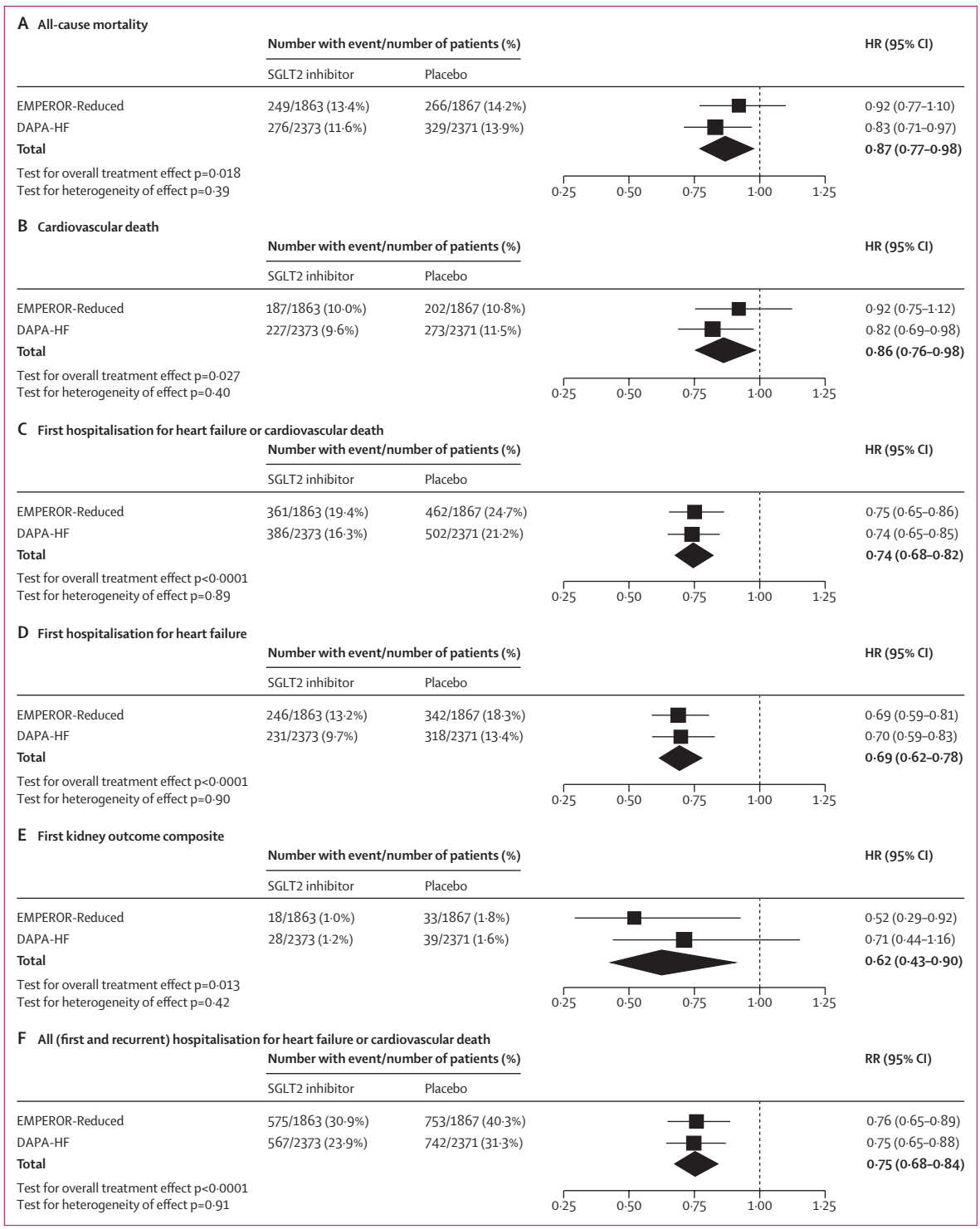
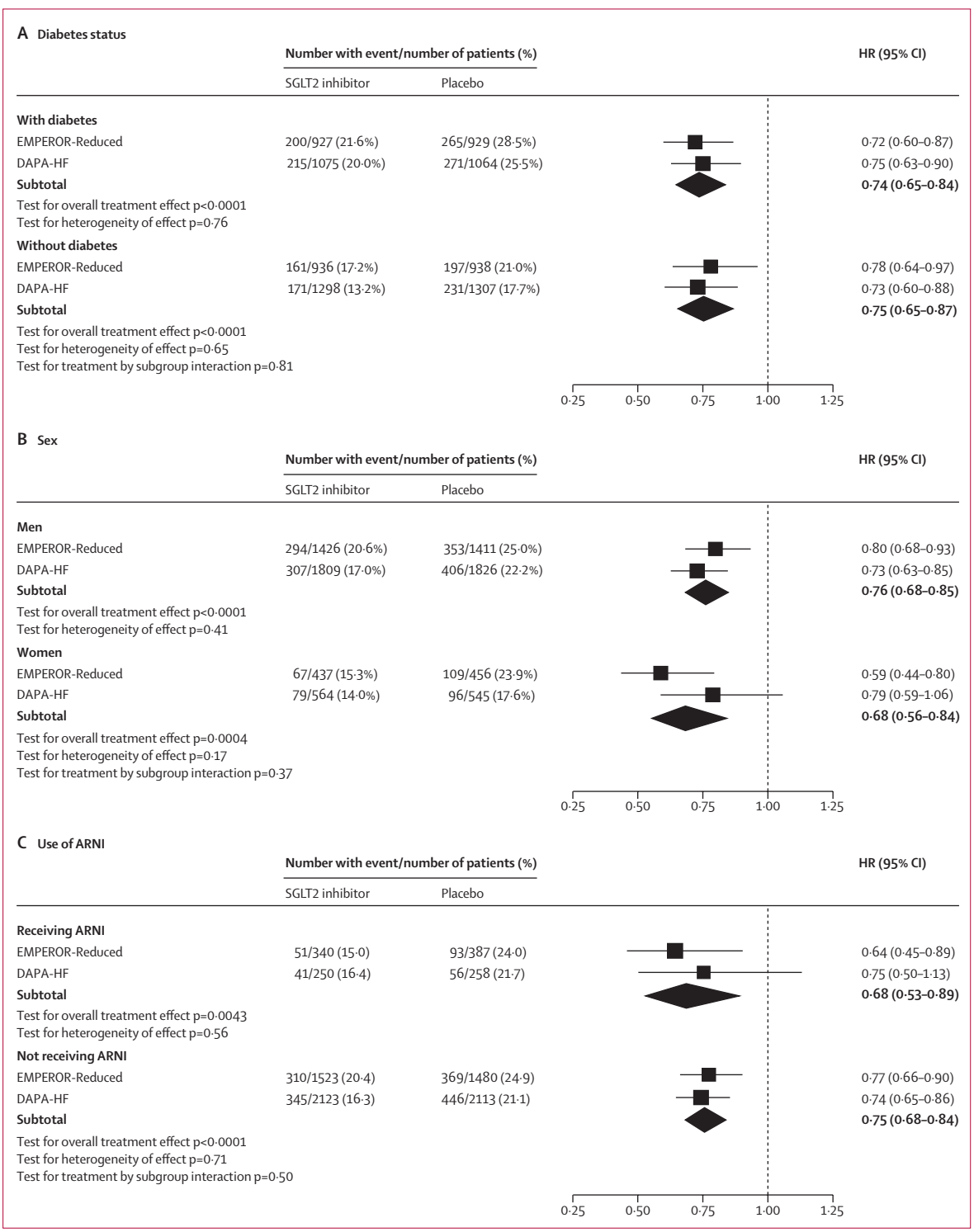


Figure 1: **Meta-analysis of EMPEROR-Reduced and DAPA-HF trials**
Figure shows overall treatment effects on all-cause death (A), cardiovascular death (B), first hospitalisation for heart failure or cardiovascular death (C), first hospitalisation for heart failure (D), first kidney composite outcome (E), and all (first and recurrent) hospitalisations for heart failure or cardiovascular death (F). Kidney composite was defined as time to first occurrence of any of the components of 50% or higher sustained decline in eGFR, end-stage renal disease, or renal death. End-stage renal disease was defined as either sustained eGFR lower than 15 mL/min per 1·73 m², chronic dialysis treatment, or receiving a renal transplant. For patients with eGFR lower than 30 mL/min per 1·73 m² in EMPEROR-Reduced (these were excluded from DAPA-HF), end-stage renal disease was defined as sustained eGFR lower than 10 mL/min per 1·73 m², chronic dialysis treatment, or receiving a renal transplant. eGFR=estimated glomerular filtration rate. HR=hazard ratio. RR=rate ratio. SGLT2=sodium-glucose co-transporter-2.

recurrent events is based on rate ratios (RRs) derived from the Lin-Wei-Yang-Ying model.[14] We used a fixed-effect model with inverse variance weights to combine the relative effect measures from both studies on a logarithmic scale. Statistical heterogeneity of the treatment effect from individual studies was descriptively assessed on the basis of the overlap of the CIs and was formally assessed on the basis of the p value derived



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from Cochran's Q test. This test was used to test for treatment-by-subgroup interactions.[15] The statistical analyses were done with use of the meta package, version 4.9-6, in R statistical software.

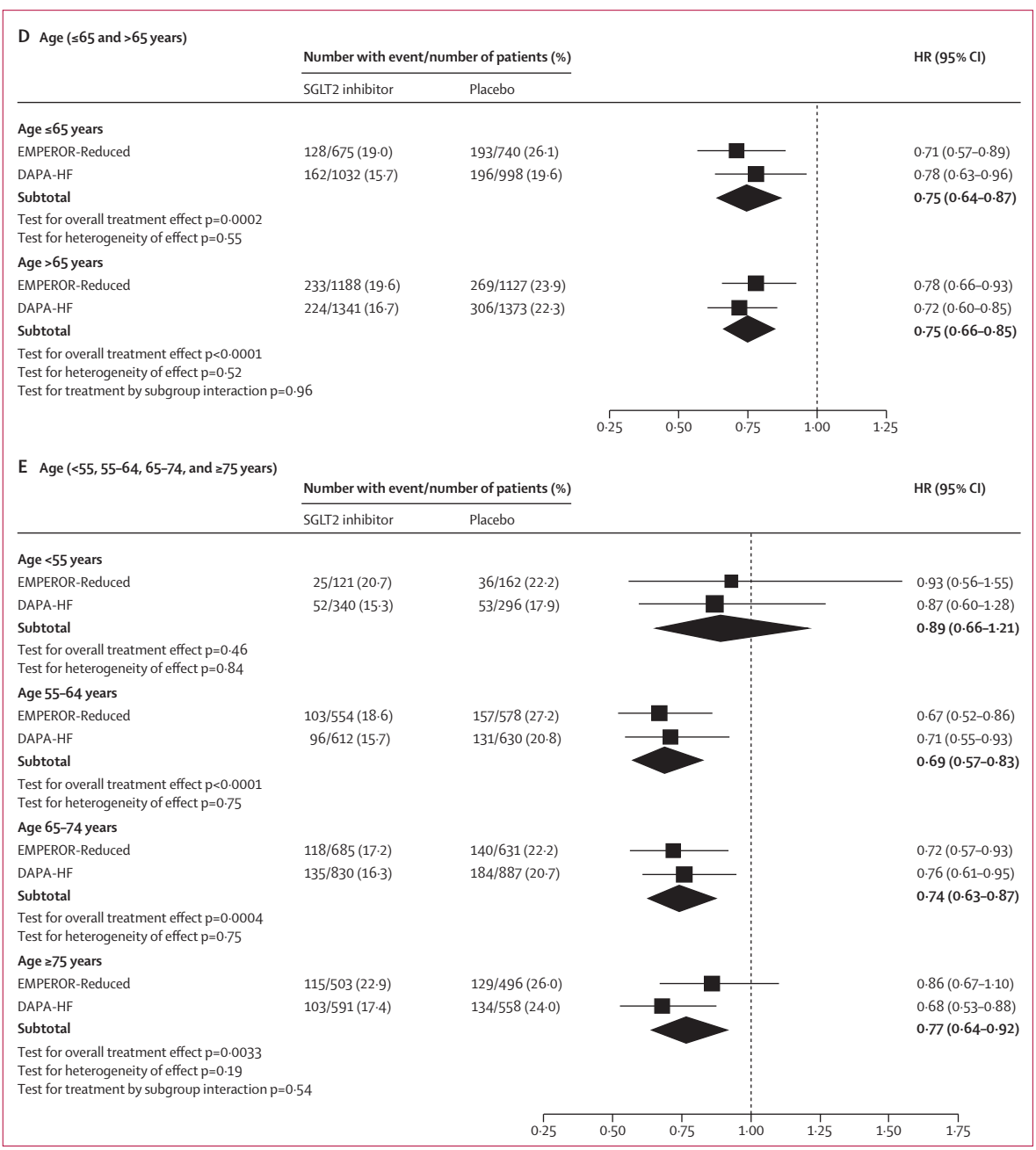
Role of the funding source

Representatives of Boehringer Ingelheim (MB, APO, EP, and WJ) were involved in the study design, data collection, data analysis, data interpretation, and the preparation, review, and approval of the manuscript. EP and FZ had access to all the data. The decision to submit the manuscript for publication was taken by the academic leadership of the steering committee.

See Online for appendix

Results

The characteristics of the DAPA-HF and EMPEROR-Reduced trial populations are depicted in table 1, and the major inclusion and exclusion criteria are presented in the appendix (p 2). Both studies included patients with HFrEF (LVEF ≤40%) with and without diabetes.



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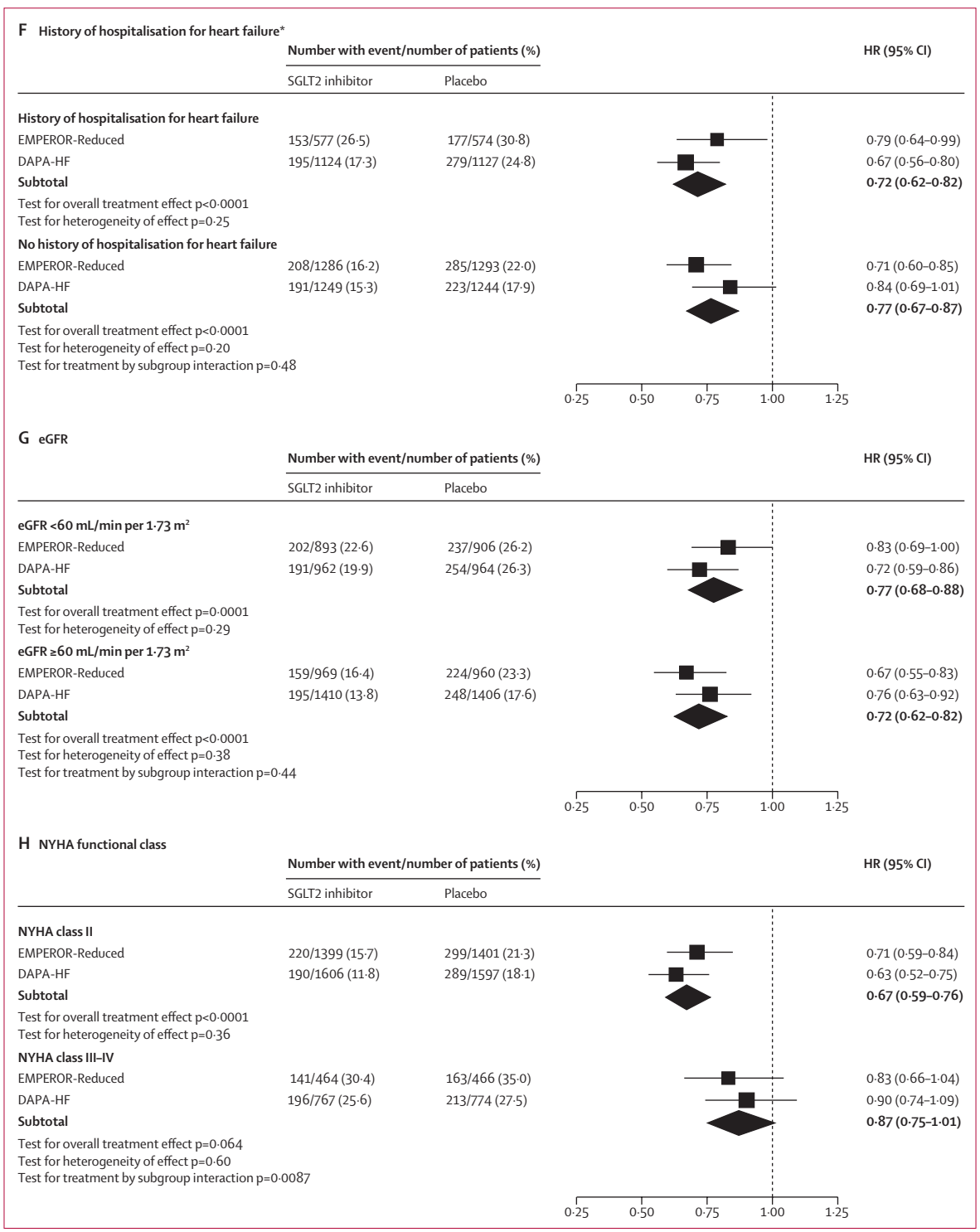
Compared with those in DAPA-HF, patients enrolled in the EMPEROR-Reduced trial had lower ejection fraction (27% *vs* 31%), higher concentrations of N-terminal pro B-type natriuretic peptide, and lower eGFR and were more likely to have been treated with a neprilysin inhibitor at baseline (20% *vs* 11%).

Among 8474 patients in the two trials, the treatment effect for death was a 13% reduction in all-cause death



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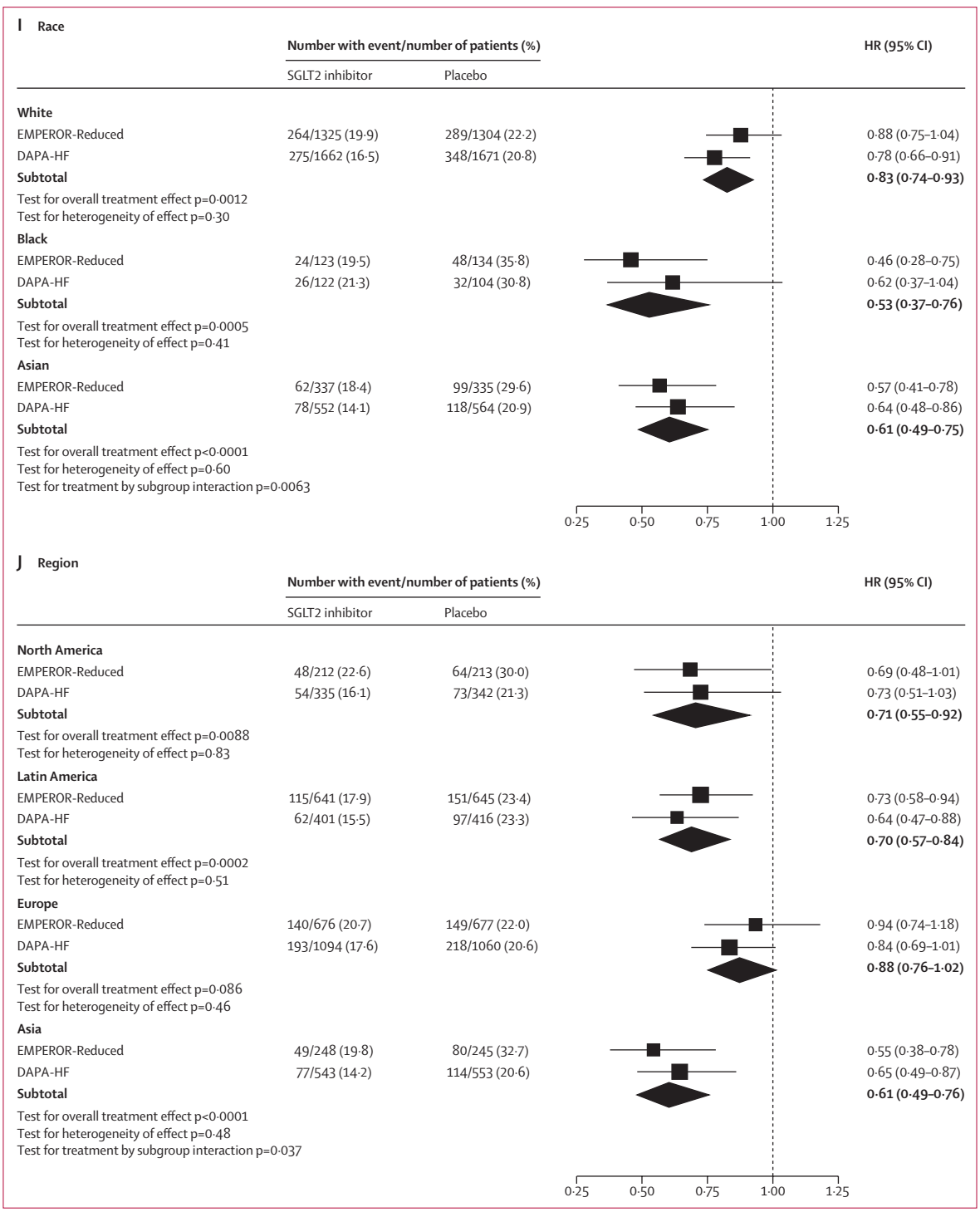
(pooled HR 0·87, 95%CI 0·77–0·98; p=0·018) and 14% reduction in cardiovascular death (0·86, 0·76–0·98; p=0·027; figure 1A, B). SGLT2 inhibition was accompanied by a significant 26% reduction in the combined risk of cardiovascular death or first hospitalisation for heart failure, a significant 25% decrease in the composite of recurrent hospitalisations for heart failure or cardiovascular death, and a significant 31% reduction in the risk of first hospitalisation for heart failure. We found no statistical evidence for heterogeneity



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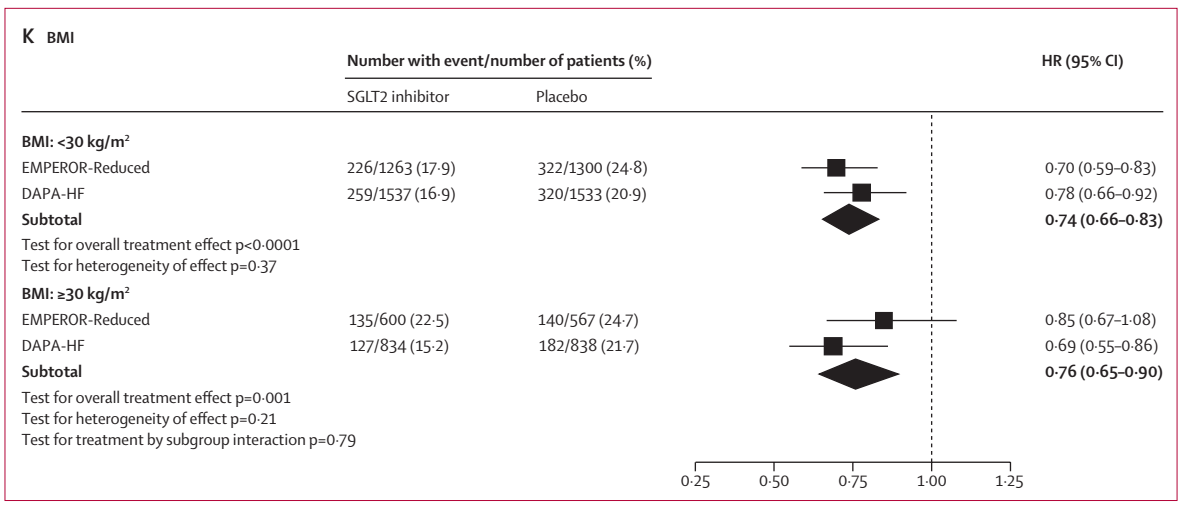

Figure 2: **Pooled treatment effects of empagliflozin and dapagliflozin on the composite of first hospitalisation for heart failure or cardiovascular death in relevant subgroups**

Figure shows pooled treatment effects by diabetes status (A), sex (B), use of ARNI (C), age 65 years or younger or older than 65 years (D), age younger than 55 years, 55–64 years, 65–74 years, or 75 years or older (E), history of hospitalisation for heart failure (F), eGFR (G), NYHA functional class (H), race (I), region (J), and BMI (K). For EMPEROR-Reduced, the age subgroups were younger than 65 years and 65 years or older; and age younger than 50 years, 50–64 years, 65–74 years, or 75 years or older. ARNI=angiontensin receptor neprilysin inhibitor. BMI=body-mass index. eGFR=estimated glomerular filtration rate. HR=hazard ratio. NYHA=New York Heart Association. SGLT2=sodium-glucose co-transporter-2. *In EMPEROR-Reduced, a history of a hospitalisation for heart failure in the preceding 12 months.

of the treatment effect for any of these endpoints (figure 1).

The risk of a patient having a composite renal endpoint (ie, chronic dialysis, renal transplantation, or a ≥50% sustained reduction of eGFR) was significantly reduced by SGLT2 inhibition (figure 1E). The changes in eGFR over time were similar in both trials; the treatment-related difference in eGFR slopes was 1·73 (95% CI 1·10–2·37) mL/min per 1·73 m² between empagliflozin and placebo in EMPEROR-Reduced and 1·8 mL/min per 1·73 m² between dapagliflozin and placebo in DAPA-HF, both p<0·0001.

The pooled treatment effects for the respective primary endpoint in each trial (time to first hospitalisation for heart failure or cardiovascular death) are shown in figure 2 for subgroups according to diabetes, age, sex, ARNI treatment, history of hospitalisation for heart failure, eGFR, and BMI. For each of these subgroups, we found no evidence for a treatment-by-subgroup interaction. Nominally, we observed significant treatment-by-subgroup interactions for NYHA functional class, race, and region (figure 2H–J). The pooled HR for patients in NYHA class II differed from that for patients in class III–IV (interaction p=0·0087; figure 2H). The pooled HR for White patients differed from those for Black patients and Asian patients (interaction p=0·0063; figure 2I). Finally, the pooled HR in Europe differed from those in North America, Latin America, and Asia (interaction p=0·037; figure 2J). Despite these observed difference between subgroups, none of the analyses indicated heterogeneity between dapagliflozin and empagliflozin within a subgroup category.

	EMPEROR-Reduced		DAPA-HF	
	Empagliflozin (n=1863)	Placebo (n=1867)	Dapagliflozin (n=2373)	Placebo (n=2371)
Serious adverse events	772 (41·4%)	896 (48·1%)	846 (35·7%)	951(40·2%)
Any renal adverse event	175 (9·4%)	192 (10·3%)	141 (6·0%)	158 (6·7%)
Volume depletion	197 (10·6%)	184 (9·9%)	170 (7·2%)	153 (6·5%)
Ketoacidosis	0	0	3 (0·1%)	0
Severe hypoglycaemic events	6 (0·3%)	7 (0·4%)	4 (0·2%)	4 (0·2%)
Bone fractures	45 (2·4%)	42 (2·3%)	48 (2·0%)	47 (2·0%)
Lower limb amputation	13 (0·7%)	10 (0·5%)	13 (0·5%)	12 (0·5%)
Fournier's Gangrene	1 (0·1%)	0	0	1 (0·1%)

Data are n(%). Definitions of medical concepts describing adverse events of interest were not exactly similar between the two trials. The absolute numbers of events cannot be compared across the two trials because of different definitions and observation periods. For EMPEROR-Reduced, we show here adverse events up to 7 days after discontinuation of study medication, and for lower limb amputations up to the end of the trial. For DAPA-HF, we show here on-treatment analysis set for all adverse events, except for lower limb amputation shown on and off treatment. See appendix (p 4) for additional details on adverse event definitions.

Table 2: **Relevant adverse events reported in the two trials**

Although absolute numbers of adverse events could not be validly compared between the two trials because of different adverse event definitions and observation periods, the safety profile of both SGLT2 inhibitors indicated no excess in adverse events of interest versus those in the respective placebo groups. Specifically, the incidence of severe hypoglycaemic events was low, with no increase in the active treatment groups in both trials (table 2). The incidence of volume depletion, renal adverse events, bone fractures, and lower limb amputations was also balanced between the active treatment groups and respective placebo groups in each trial. No cases were recorded of ketoacidosis in EMPEROR-Reduced, and

three (0·1%) patients had a diabetic ketoacidosis in DAPA-HF (table 2).

Discussion

Our report is the first meta-analysis of the two major outcome trials assessing the effect of SGLT2 inhibitors in patients with HFrEF with or without diabetes. In patients with a broad spectrum of severity of HFrEF, SGLT2 inhibition with empagliflozin or dapagliflozin—when added to all appropriate treatments for heart failure—reduced all-cause and cardiovascular death, hospitalisations for heart failure, and serious adverse renal outcomes, without heterogeneity between the two trials. No excess in serious adverse effect was seen in either trial. Additionally, no important imbalances for adverse events of interest were raised in either the DAPA-HF or EMPEROR-Reduced trials, and the SGLT2 inhibitors were well tolerated in both studies.

Before this meta-analysis, the treatment of patients with type 2 diabetes with SGLT2 inhibitors was known to have a major effect on reducing the risk of hospitalisations for heart failure (relative reduction of at least 30%) and to slow the progression of renal disease (relative reduction of at least 40%).[8] The benefits on hospitalisations for heart failure and on the progression of renal disease were of similar magnitude regardless of the presence of established cardiovascular disease or history of heart failure.[8,9] The DAPA-HF and EMPEROR-Reduced trials expanded these findings to patients with established HFrEF with and without diabetes who were receiving appropriate background treatments for heart failure.[11,12] The two trials enrolled overlapping and complementary patient populations, which spanned the broad spectrum of patients with HFrEF seen in clinical practice. This meta-analysis highlights the striking consistency of the findings of cardiovascular and renal benefits with empagliflozin and dapagliflozin in patients with HFrEF across the two trials.

The benefit of empagliflozin and dapagliflozin on the primary endpoint of both trials—the combined risk of cardiovascular death or hospitalisation for heart failure—is primarily driven by an approximately 30% relative reduction in the risk of hospitalisation for heart failure. A benefit on hospitalisations for heart failure was observed whether the analysis was confined to first events or to all events (first and recurrent). When compared with the effect on hospitalisations for heart failure, the effect of these drugs on cardiovascular death was more modest (a 14% relative reduction) but significant. The modest size of the cardiovascular death benefit might explain why it is observed inconsistently in individual trials. Specifically, the relative reduction in cardiovascular death was 18% (HR 0·82, 95% CI 0·69–0·98) in DAPA-HF (with dapagliflozin) and 8% (0·92, 0·75–1·12) in EMPEROR-Reduced (with empagliflozin). By contrast, in trials of patients with type 2 diabetes (with or without heart failure), the reduction in cardiovascular death was 2% (0·98, 0·82–1·17) in DECLARE-TIMI 58 (with dapagliflozin) and 38% (0·62, 0·49–0·77) in EMPA-REG OUTCOME (with empagliflozin).[1,3] The pattern of inconsistent findings in individual trials and in different disease states might be explained by the modest, although significant, reduction in cardiovascular death observed in our meta-analysis. The reduction of the renal composite endpoint was of greater magnitude, reaching a 38% relative reduction.

The effect on the combined risk of cardiovascular death or hospitalisation for heart failure was consistent across most subgroups, including those based on age and sex, regardless of the presence or absence of diabetes and impaired renal function. Of note, the consistent effect of dapagliflozin and empagliflozin in patients with an eGFR lower than 60 mL/min per 1·73m² provides evidence of an important reduction of cardiovascular death or hospitalisation for heart failure in this high-risk subgroup. However, nominally significant treatment-by-subgroup interactions were observed for NYHA functional class, race, and geographical region, raising the possibility of an attenuated, although still meaningful, effect in patients with class III–IV symptoms, in White patients, and in patients enrolled in Europe.

The exact mechanisms by which SGLT2 inhibitors exerted their benefits in these populations are not completely established, but they might not be directly related to glucose control and appear to be due to direct cardioprotective and nephroprotective effects, which might be related to actions on sodium balance, energy homoeostasis, and mitigation of cellular stress.[10,16,17]

Several limitations should be highlighted in this meta-analysis. We did not have access to the individual patient data from DAPA-HF. Therefore, we could only evaluate the endpoints and subgroups that were publicly available from DAPA-HF. We did not do a correction for multiplicity of subgroup testing, hence, subgroup findings should be regarded as hypothesis generating. In general, subgroup effects and interaction p values should be interpreted cautiously because they are subject to the play of chance. Additionally, it is understood that statistical heterogeneity cannot be reliably discerned if an analysis is based on only two studies. However, the point estimates for the treatment effect for all endpoints are remarkably consistent.

Our meta-analysis establishes a solid evidence base confirming an important role of empagliflozin or dapagliflozin for reducing hospitalisations for heart failure in patients with HFrEF and suggesting that these agents also reduce all-cause and cardiovascular death and improve renal outcomes. These benefits were seen whether patients had diabetes or not, were women or men, were younger or older, and were receiving neprilysin inhibitors or not. Such a combination of benefits is unique among available drugs for heart failure.

Contributors

EP (an employee of Boehringer Ingelheim) did the statistical analysis, working closely with SJP (not an employee of the sponsor). FZ and JPF

(not employees of the sponsor) drafted the first version of the manuscript and subsequent revisions. All the other authors read and edited the manuscript. All the authors approved the final version and the decision to submit the manuscript.

Declaration of interests

FZ reports personal fees from Boehringer Ingelheim during the conduct of the study; personal fees from Janssen, Novartis, Boston Scientific, Amgen, CVRx, AstraZeneca, Vifor Fresenius, Cardior, Cereno pharmacuetical, Applied Therapeutics, Merck, Bayer, and Cellprothera outside the submitted work; and other support from CVCT and Cardiorenal, outside the submitted work. JPF reports consulting fees from Boehringer Ingelheim during the conduct of the study. SJP reports personal fees from Boehringer Ingelheim during the conduct of the study. SDA reports grants from Vifor; personal fees from Vifor, Bayer, Boehringer Ingelheim, Novartis, Servier, Impulse Dynamics, Cardiac Dimensions, and Thermo Fisher Scientific; and grants and personal fees from Abbott Vascular, outside the submitted work. JB reports consultancy fees from Boehringer Ingelheim during the conduct of the study; and consultancy fees from Abbott, Adrenomed, Amgen, Applied Therapeutics, Array, AstraZeneca, Bayer, BerlinCures, Boehringer Ingelheim, Cardior, CVRx, Foundry, G3 Pharma, Imbria, Impulse Dynamics, Innolife, Janssen, LivaNova, Luitpold, Medtronic, Merck, Novartis, NovoNordisk, Relypsa, Roche, Sanofi, Sequana Medical, V-Wave, and Vifor, outside the submitted work. GF reports receiving payment from Boehringer Ingelheim for being a trial committee member during the conduct of the study and from Medtronic, Vifor, Servier, and Novartis for being a trial committee member outside the submitted work. MB, APO, EP, and WJ are employees of Boehringer Ingelheim. MP reports personal fees from Boehringer Ingelheim, during the conduct of the study; personal fees from AbbVie, Akcea, Amarin, AstraZeneca, Amgen, Boehringer Ingelheim, Cardiorentis, Daiichi Sankyo, Johnson & Johnson, Lilly, Novartis, Pfizer, Relypsa, Sanofi, Synthetic Biologics, Theravance, and NovoNordisk, outside the submitted work.

Data sharing

The study protocol and statistical analysis plan are available upon request to the corresponding author.

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