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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Research in context:

Evidence before this study: Large cardiovascular outcome trials in patients with type 2 diabetes (T2D) have demonstrated that sodium-glucose cotransporter 2 inhibitors (SGLT2i) improve cardiovascular and renal outcomes, and reduce the risk of heart failure (HF) hospitalisation in patients with and without prior history of HF. These effects on cardiovascular and renal outcomes may not be directly related to glycaemic control, suggesting that the benefits could also extend to patients without diabetes. 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 evaluate the effect of SGLT2i in patients with heart failure and a reduced ejection fraction (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 levels. Taken together, the trials enrolled a broader spectrum of severity of HF than either trial alone. In each trial, the SGLT2i reduced the risk of the primary composite endpoint of cardiovascular death or HF hospitalisation.

Added value of this study: Neither trial was adequately powered to evaluate treatment effects on secondary outcomes such as all-cause mortality, cardiovascular death, serious adverse renal events, or to characterize effects in clinically important subgroups. Using study-level published data from DAPA-HF and patient-level data from EMPEROR-Reduced, we performed a meta-analysis to estimate the effect of SGLT2 inhibition with dapagliflozin and empagliflozin on fatal events, hospitalisation

for HF and renal outcomes and in relevant clinical subgroups in a broad spectrum of patients with HFrEF.

Implications of all the available evidence: Our meta-analysis establishes a solid evidence base confirming an important role of empagliflozin and dapagliflozin primarily to reduce hospitalizations for heart failure, and secondarily, to improve renal outcomes and decrease all-cause and cardiovascular mortality. These benefits are seen regardless of age and sex and irrespective of the presence or absence of diabetes or treatment with a neprilysin inhibitor.

Abstract:

Background: Both the DAPA-HF (dapagliflozin) and EMPEROR-Reduced (empagliflozin) trials showed that sodium-glucose cotransporter 2 inhibition reduced the combined risk of cardiovascular death and hospitalisation for heart failure in patients with heart failure and a reduced ejection fraction (HFrEF), with or without diabetes. However, neither trial was powered to evaluate effects on cardiovascular death or all-cause mortality or to characterize effects in clinically important subgroups.

Aims: Using study-level published data from DAPA-HF and patient-level data from EMPEROR-Reduced, we prospectively estimated the effect of SGLT2 inhibition in patients with HFrEF on fatal and non-fatal heart failure events and renal outcomes in all randomized patients and in relevant subgroups.

Methods: The primary outcome was all-cause mortality. The effects of treatment in subgroups focused on the combined risk of cardiovascular death or hospitalisation for heart failure.

Findings: Among 8474 patients combined, the estimated treatment effect gave a 13% reduction in all-cause mortality (pooled HR 0.87, 95%CI 0.77-0.98, P =0.018) and 14% reduction in cardiovascular death (pooled HR 0.86, 95%CI 0.76-0.98, P=0.02). SGLT2 inhibition was accompanied by a 26% relative reduction in the combined risk of cardiovascular death or first HF hospitalisation (pooled HR 0.74, 95%CI 0.68-0.82, P<0.001), and by a 25% decrease in the composite of recurrent hospitalizations for HF or cardiovascular death (pooled HR 0.75, 95%CI 0.68-0.84, P<0.001). The risk of the composite renal endpoint was also reduced (pooled HR 0.62, 95%CI 0.43-0.90, P=0.013). All tests for heterogeneity of effect size between trials were non-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 NYHA functional class and race.

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

Key-words: dapagliflozin; empagliflozin; heart failure; mortality; renal outcomes.

Introduction:

Large cardiovascular outcome trials in patients with type 2 diabetes (T2D) have demonstrated that sodium-glucose cotransporter 2 inhibitors (SGLT2i) improve cardiovascular and renal outcomes, and in particular, they reduce the risk of heart failure (HF) hospitalisation[1-4]. The latter was observed in patients with and without prior history of HF[5-7]. However, patients with known HF comprised only small proportion of the study populations, typically without systematic documentation of left ventricular ejection fraction (LVEF) or natriuretic peptides. Meta-analysis of these cardiovascular outcome trials in patients with T2D showed that these agents reduced the risk of HF hospitalisation and slowed the progression of renal disease[8, 9]. These effects on cardiovascular and renal outcomes may not be directly related to glycaemic control, suggesting that the benefits could also extend to patients without diabetes[10].

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 evaluate the effect of SGLT2i 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 levels[11,12]. Taken together, the trials enrolled a broader spectrum of severity of HFrEF than either trial alone. In each trial, the SGLT2i reduced the risk of the composite endpoint of cardiovascular death or HF hospitalisation. Neither trial was adequately powered to evaluate treatment effects on secondary outcomes such as all-cause

mortality, cardiovascular death, and serious adverse renal events, or to characterize effects in clinically important subgroups.

Because DAPA-HF and EMPEROR-Reduced are the only trials, to date, that included patients with symptomatic HFrEF, elevated natriuretic peptides, with and without type 2 diabetes, we aim to assess the effect 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 HF. However, no investigations such as natriuretic peptide measurements or echocardiography were performed to verify or further characterize the HF diagnoses. Using study-level published data from DAPA-HF and patient-level data from EMPEROR-Reduced, we performed a meta-analysis to estimate the effect of SGLT2 inhibition with dapagliflozin and empagliflozin on fatal events, hospitalisation for HF and renal outcomes and in relevant clinical subgroups in a broad spectrum of patients with HFrEF.

Methods

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

We undertook a pre-specified meta-analysis of the two single large-scale cardiovascular outcomes trials published so far that evaluated SGLT2i in patients with HFrEF, with or without diabetes: DAPA-HF (dapagliflozin) and EMPEROR-Reduced (empagliflozin). The patient characteristics and treatment effects overall and in subgroups in individual trials have been previously published[11, 12]. In brief, both trials

included patients with symptomatic heart failure with reduced ejection fraction and elevated natriuretic peptide levels. EMPEROR-Reduced tested empagliflozin 10 mg/day p.o. vs. placebo and DAPA-HF tested dapagliflozin 10 mg/day p.o. vs. placebo. The median follow-up time was 16 months in EMPEROR-Reduced and 18 months in DAPA-HF. We did not include small trials (<300 patients) of short duration (12 weeks or less), because these provided no meaningful information on major outcomes.

EMPEROR-Reduced ClinicalTrials.gov Identifier NCT03057977. DAPA-HF ClinicalTrials.gov Identifier NCT03036124.

Outcomes and subgroups

Time to all-cause mortality was the pre-defined primary endpoint in this meta-analysis. Secondary endpoints assessed were time to cardiovascular death, first hospitalisation for HF or cardiovascular death, first hospitalisation for HF, recurrent hospitalisations for HF or cardiovascular death, and a renal composite defined as ≥50% sustained decline in eGFR, end stage renal disease (ESRD) or renal death. Effects in subgroups on the combined risk of cardiovascular death and hospitalisation for heart failure were also evaluated in pre-defined 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 HF, including urgent visits with intravenous therapy for HF. Since very few patients experienced only an urgent HF visit 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% sustained decline in eGFR, ESRD or renal death, where ESRD was defined as either sustained eGFR <15 ml/min/1.73m^2, chronic dialysis or a renal transplant.

The pre-defined study subgroups were type 2 diabetes (yes/no), sex, ARNI treatment (yes/no), NYHA class II or III/IV, race (White, Black, Asian), region (North America, Latin America, Europe and Asia), age below or above 65 years (and additionally, <55, 55-64, 65-74, and ≥75 years), history of HF hospitalisation (yes/no), eGFR below or above 60 ml/min/1.73m^2, and body mass index (BMI) below or above 30 Kg/m^2. The region subgroup was added post-hoc in order to clarify whether the treatment effects would reflect the results observed on race.

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

Statistical analysis

We used the point estimates and 95% confidence intervals as reported for the individual trials for the meta-analysis, based on an intention-to-treat analysis of all randomized patients. For the time-to-first event endpoints, the meta-analysis is based on hazard ratios derived from Cox proportional hazard models, and the analysis of recurrent events is based on rate ratios derived from the Lin-Wei-Yang-Ying model[14]. A fixed effect model with inverse variance weights was used 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 based on the overlap of the confidence intervals and was formally assessed based on the p-value derived from Cochran's Q test. The latter was used to test for treatment-by-subgroup interactions[15].

Role of the funder

Representatives (Martina Brueckmann, Anne Pernille Ofstad, Egon Pfarr, Waheed Jamal) of Boehringer Ingelheim were involved in the design and conduct of the meta-analysis, interpretation of the data, and the preparation, review, and approval of the manuscript. Egon Pfarr and Faiez Zannad had access to all the data. The decision to submit the manuscript for publication was taken by the academic leadership of the steering committee.

Results

DAPA-HF and EMPEROR-Reduced comparison

The characteristics of the DAPA-HF and EMPEROR-Reduced trial populations are depicted in *Table 1*, and the major inclusion and exclusion criteria in the *Supplemental Table 1*. Both studies included patients with HFrEF (LVEF≤40%) with and without diabetes. As compared with DAPA-HF, the patients enrolled in the EMPEROR-Reduced trial had a lower ejection fraction (27% vs. 31%), and higher levels of NT-pro BNP and lower eGFR, and were more likely to have been treated with a neprilysin inhibitor at baseline (20% vs. 11%).

Pooled effects on survival and cardiovascular events

Among 8474 patients in the two trials, the treatment effect for mortality was a 13% reduction in all-cause mortality (pooled HR 0.87, 95%CI 0.77-0.98, P =0.018) and 14%

reduction in cardiovascular death (pooled HR 0.86, 95%CI 0.76-0.98, P=0.027), Figure 1. SGLT2 inhibition was accompanied by a 26% reduction in the combined risk of cardiovascular death or first HF hospitalisation (pooled HR 0.74, 95%CI 0.68-0.82, P<0.001), by a 25% decrease in the composite of recurrent hospitalisations for HF or cardiovascular death (pooled RR 0.75, 95%CI 0.68-0.84, P<0.001), and by a 31% reduction in the risk of first hospitalisation for HF (pooled HR 0.69, 95%CI 0.62-0.78, P<0.001). There was no statistical evidence for heterogeneity of the treatment effect for any of these endpoints. *Figure 1*.

Pooled effects on renal outcomes

The risk of experiencing the composite renal endpoint (i.e., chronic dialysis or renal transplant or a ≥50% sustained reduction of eGFR) was reduced by SGLT2 inhibition (pooled HR 0.62, 95%CI 0.43-0.90, P=0.013). The changes in eGFR over time were similar in both trials; the treatment-related difference in eGFR slopes was 2.1 (1.5-2.7) ml/min/1.73 m^2 between empagliflozin and placebo in EMPEROR-Reduced and 1.8 ml/min/1.73 m^2 between dapagliflozin and placebo in DAPA-HF, both P<0.001. *Figure 1*.

Pooled effects in subgroups

The pooled treatment effects for the respective primary endpoint in each trial (time to first HF hospitalisation or cardiovascular death) are shown in *Figure 2* for subgroups according to diabetes, age, sex, treatment with an ARNI, history of HF hospitalisation, eGFR, and BMI. For each of these subgroups, there was no evidence for a treatment-by-subgroup interaction. Nominally significant treatment-by-subgroup interactions were observed for NYHA functional class, race and region, Figure 2. The pooled HR of 0.67 (95%CI 0.59-0.76) in class II patients differed from the pooled HR of 0.87 (95%CI 0.75-1.01) in patients in NYHA class III/IV, interaction P=0.009. The pooled

HR of 0.83 (95%CI 0.74-0.93) in white patients differed from the pooled HR of 0.53 (95%CI 0.37-0.76) in Black patients and the pooled HR of 0.61 (95% CI: 0.49-0.75) in Asian patients, interaction P=0.006. Finally, the pooled HR of 0.88 (95%CI 0.76-0.92) in Europe differed from the pooled HR ratios seen in North America (0.71, 95%CI 0.55-0.92), in Latin America (0.70, 95%CI 0.57-0.84) and in Asia (0.61, 95%CI 0.49-0.76), interaction P=0.037. Despite these observed difference between subgroups, none of the analyses indicates heterogeneity between dapagliflozin and empagliflozin within a subgroup category. *Figure 2*.

Safety

Although absolute numbers of adverse events cannot be validly compared between the two trials due to different AE definitions and observation periods, the safety profile of both SGLT2i indicated no excess in adverse events of interest versus the respective placebo arms. Specifically, the incidence of severe hypoglycemic 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 arms and respective placebo groups in each trial. There were no cases of ketoacidosis in EMPEROR, and 3(0.1%) patients experienced a diabetic ketoacidosis in DAPA-HF. *Table 2*.

Discussion

The present report is the first meta-analysis of the two major outcome trials assessing the effect of SGLT2i in HFrEF with or without diabetes. In 8474 patients with a broad spectrum of severity of HFrEF, SGLT2 inhibition with empagliflozin and dapagliflozin — when added to all appropriate treatments for heart failure — reduced all-cause and cardiovascular mortality, hospitalisations for heart failure, and serious adverse renal

279 outcomes, without heterogeneity between the two trials. No excess in serious adverse
280 effect was seen in either study. Furthermore, no important imbalances for adverse
281 events of interest were raised in either the DAPA-HF or EMPEROR-Reduced trials,
282 and the SGLT2 inhibitors were well-tolerated in both studies.

283 Prior to this meta-analysis, it was known that treatment of patients with type 2
284 diabetes with SGLT2i had major impact to reduce the risk of HF hospitalisations
285 (relative reduction of at least 30%) and to slow the progression of renal disease
286 (relative reduction of at least 40%)[8]. The benefits on HF hospitalisations and on the
287 progression of renal disease were of similar magnitude regardless of the presence of
288 established cardiovascular disease or a history of HF[8, 9]. The DAPA-HF and
289 EMPEROR-Reduced trials expanded these findings to patients with established
290 HFrEF populations with and without diabetes who were receiving appropriate
291 background treatments for heart failure[11, 12]. The two trials enrolled overlapping and
292 complementary patient populations, which spanned the broad spectrum of patients
293 with HFrEF seen in clinical practice. This meta-analysis highlights the striking
294 consistency of the findings of cardiovascular and renal benefits with empagliflozin and
295 dapagliflozin in patients with HFrEF across the two trials.

296 The benefit of empagliflozin and dapagliflozin on the primary endpoint of both
297 trials — the combined risk of cardiovascular death and hospitalisation for heart failure
298 — is primarily driven by a ~30% relative reduction in the risk of hospitalisation for heart
299 failure. A benefit on heart failure hospitalisations was observed whether the analysis
300 is confined to first events or to all (first and recurrent) events. When compared with
301 the effect on heart failure hospitalisations, the effect of these drugs on cardiovascular
302 mortality is more modest (a 14% relative reduction) but is statistically significant. The
303 modest size of the cardiovascular mortality benefit may explain why it is observed

304 inconsistently in individual trials. Specifically, the relative reduction in cardiovascular
305 death was 18% (HR 0.82, 95%CI 0.69 to 0.98) in DAPA-HF (with dapagliflozin) and
306 8% (HR 0.92, 95%CI 0.75 to 1.12) in EMPEROR-Reduced (with empagliflozin). In
307 contrast, in trials of patients with type 2 diabetes (with or without heart failure), the
308 reduction in cardiovascular death was 2% (HR 0.98, 95%CI 0.82 to 1.17) in
309 DECLARE-TIMI58 (with dapagliflozin) and 38% (HR 0.62, 95%CI 0.49 to 0.77) in
310 EMPA-REG OUTCOME (with empagliflozin)[1, 3]. The pattern of inconsistent findings
311 in individual trials and in different disease states may be explicable by the modest,
312 although statistically significant, reduction in cardiovascular death observed in our
313 meta-analysis. In contrast, the 38% reduction in the risk of the renal composite
314 endpoint was clinically important.

315 The effect on the combined risk of cardiovascular death or hospitalisation for
316 heart failure was consistent across most subgroups, including those based on age and
317 sex, regardless of the presence or absence of diabetes, and impaired renal function.
318 Of note, the consistent effect of dapagliflozin and empagliflozin in patients with an
319 estimated glomerular filtration rate of less than 60 ml/min/1.73m^2 provides evidence of
320 an important reduction of cardiovascular death or hospitalisation for heart failure in this
321 high-risk subgroup. However, nominally significant treatment-by-subgroup interactions
322 were observed for NYHA functional class, race, and geographical region, raising the
323 possibility of an attenuated, although still meaningful, effect in patients with class III/IV
324 symptoms, in white patients and in patients enrolled in Europe.

325 The exact mechanisms by which SGLT2i exerted their benefits in these
326 populations are not completely established, but they may not be directly related to
327 glucose control and appear to be due to direct cardioprotective and nephroprotective

effects, which may be related to actions on sodium balance, energy homeostasis, and to their actions to mitigate cellular stress[10, 16, 17].

Limitations

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. No correction for multiplicity of subgroup testing was performed, 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.

Conclusion

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

Authors` contribution

The statistical analysis was performed by Egon Pfarr who is an employee of Boehringer Ingelheim and a named author of this manuscript, working closely with

Stuart Pocock, who is not an employee of the sponsor and is also a named author. Faiez Zannad and João Pedro Ferreira, who are 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.

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Declaration of interest

FZ reports personal fees from Boehringer Ingelheim during the conduct of the study; personal fees from Janssen, Novartis, Boston Scientific, Amgen, CVRx, other from cardiorenal, personal fees from AstraZeneca, Vifor Fresenius, Cardior, Cereno pharmacuetical , Applied Therapeutics , Merck, other from CVCT , personal fees from BAYER and Cellprothera, outside the submitted work; JPF reports consulting fees from Boehringer Ingelheim during the conduct of the study; SP reports personal fees from Boehringer Ingelheim during the conduct of the study; SDA reports grants from Vifor Int, personal fees from Vifor Int, Bayer, Boehringer Ingelheim, Novartis, Servier, Impulse Dynamics, Cardiac Dimensions, Thermo Fisher Scientific, grants and personal fees from Abbott Vascular, outside the submitted work; JB reports consultancy fees from Boehringer Ingelheim during the conduct of the study;

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Data sharing statement

The study protocol and statistical analysis plan are available upon request to the corresponding author. Stuart Pocock at the London School of Hygiene served as external statistician and approved all the data.

Figure legends

Figure 1: Meta-analysis of EMPEROR-Reduced and DAPA-HF: Overall treatment effects on, a) all-cause mortality, b) cardiovascular death, c) first hospitalization for heart failure or CV death d) first hospitalization for heart failure, e) first kidney composite*, and f) all (first and recurrent) hospitalization for HF or cardiovascular death

* Defined as time to first occurrence of any of the components of ≥50% sustained decline in eGFR, ESRD or renal death. ERSD was defined as either sustained eGFR <15 ml/min/1.73m2, chronic dialysis treatment or receiving a renal transplant. For patients with eGFR<30 ml/min/1.73 m2 in EMPEROR (these were excluded from DAPA-HF), ESRD was defined as sustained eGFR <10 ml/min/1.73m2, chronic dialysis treatment or receiving a renal transplant.

Figure 2: Pooled treatment effects of empagliflozin and dapagliflozin on the composite of first hospitalisation for heart failure or CV death in relevant subgroups: a) by diabetes status, b) by sex, c) by use of ARNI, d) by age* (≤65 and >65 years), and e) (<55, 55 to 64, 65 to 74, and ≥75 years), f) by history of a hospitalisation for heart failure**, g) by eGFR, h) by NYHA functional class, i) by race, j) by region, and k) by BMI.

* For EMPEROR-Reduced, the age subgroups were <65 and ≥65 years, and <50, 50 to 64, 65 to 74, and ≥74 years

** In EMPEROR-Reduced: a history of a hospitalization for heart failure the last 12 months

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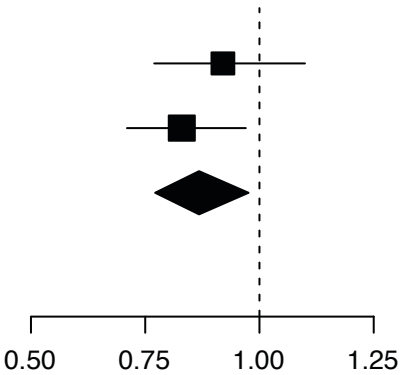
Figure 1

a) All-cause mortality

	SGLT2i	Placebo	HR (95% CI)
	no. with event/no. of patients (%)		
EMPEROR–Reduced	249/1863 (13.4)	266/1867 (14.2)	0.92 (0.77, 1.10)
DAPA–HF	276/2373 (11.6)	329/2371 (13.9)	0.83 (0.71, 0.97)
Total			0.87 (0.77, 0.98)

Test for overall treatment effect, p=0.018

Test for heterogeneity of effect, p=0.39

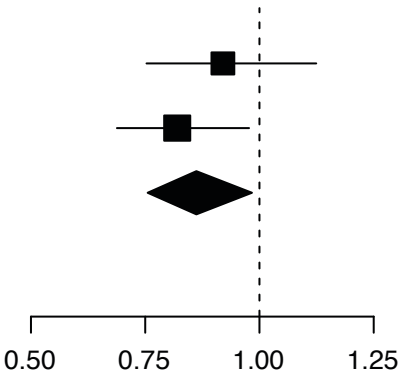


b) Cardiovascular death

	SGLT2i	Placebo	HR (95% CI)
	no. with event/no. of patients (%)		
EMPEROR–Reduced	187/1863 (10.0)	202/1867 (10.8)	0.92 (0.75, 1.12)
DAPA–HF	227/2373 (9.6)	273/2371 (11.5)	0.82 (0.69, 0.98)
Total			0.86 (0.76, 0.98)

Test for overall treatment effect, p=0.027

Test for heterogeneity of effect, p=0.40

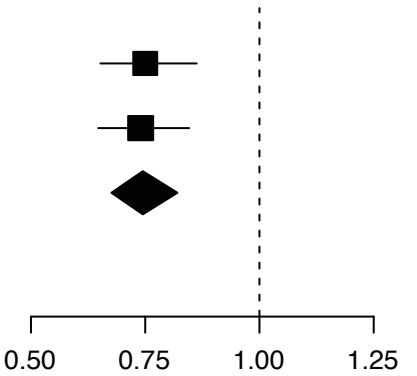


c) First hospitalisation for heart failure or cardiovascular death

	SGLT2i	Placebo	HR (95% CI)
	no. with event/no. of patients (%)		
EMPEROR–Reduced	361/1863 (19.4)	462/1867 (24.7)	0.75 (0.65, 0.86)
DAPA–HF	386/2373 (16.3)	502/2371 (21.2)	0.74 (0.65, 0.85)
Total			0.74 (0.68, 0.82)

Test for overall treatment effect, p<0.0001

Test for heterogeneity of effect, p=0.89

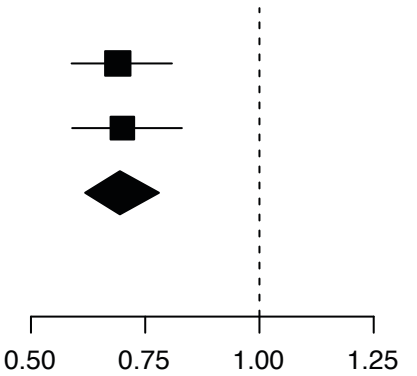


d) First hospitalisation for heart failure

	SGLT2i	Placebo	HR (95% CI)
	no. with event/no. of patients (%)		
EMPEROR–Reduced	246/1863 (13.2)	342/1867 (18.3)	0.69 (0.59, 0.81)
DAPA–HF	231/2373 (9.7)	318/2371 (13.4)	0.70 (0.59, 0.83)
Total			0.69 (0.62, 0.78)

Test for overall treatment effect, p<0.0001

Test for heterogeneity of effect, p=0.90

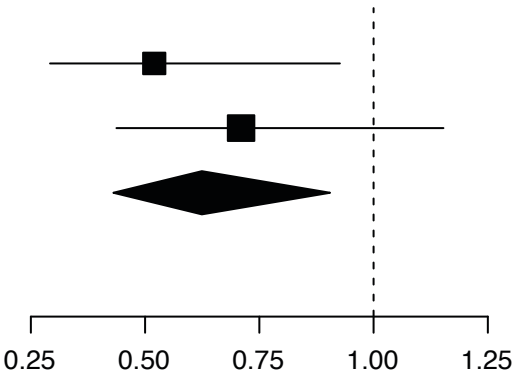


e) First kidney composite*

	SGLT2i	Placebo	HR (95% CI)
	no. with event/no. of patients (%)		
EMPEROR–Reduced	18/1863 (1.0)	33/1867 (1.8)	0.52 (0.29, 0.92)
DAPA–HF	28/2373 (1.2)	39/2371 (1.6)	0.71 (0.44, 1.16)
Total			0.62 (0.43, 0.90)

Test for overall treatment effect, p=0.0128

Test for heterogeneity of effect, p=0.42



f) All (first and recurrent) hospitalisation for heart failure or cardiovascular death

	SGLT2i	Placebo	RR (95% CI)
	no. of events/no. of patients (% rate)		
EMPEROR–Reduced	575/1863 (30.9)	753/1867 (40.3)	0.76 (0.65, 0.89)
DAPA–HF	567/2373 (23.9)	742/2371 (31.3)	0.75 (0.65, 0.88)
Total			0.75 (0.68, 0.84)

Test for overall treatment effect, p<0.0001

Test for heterogeneity of effect, p=0.91

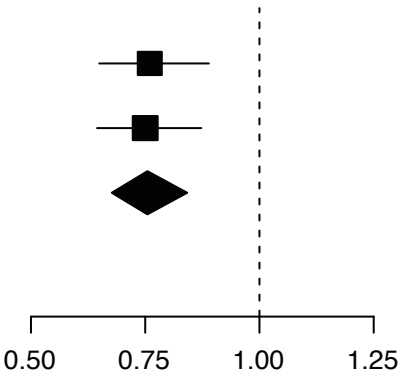
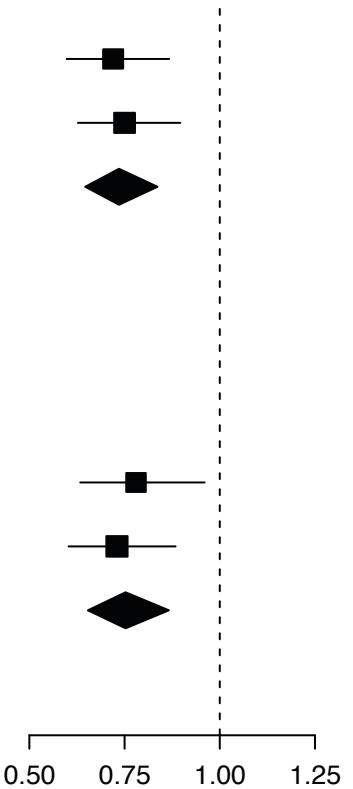


Figure 2

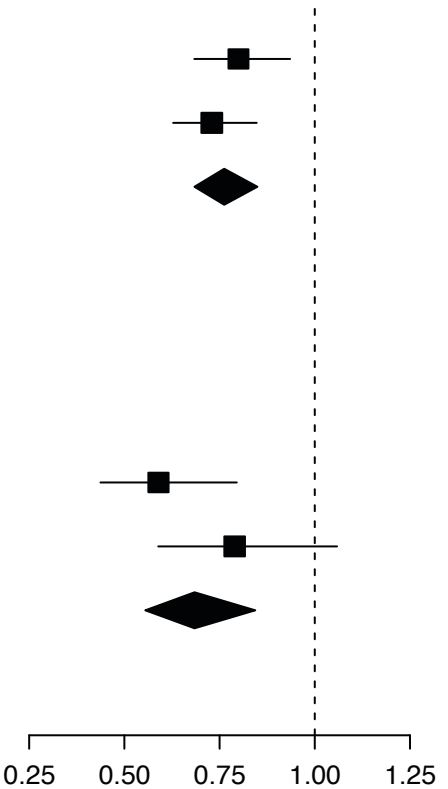
a) Diabetes status

	SGLT2i	Placebo	HR (95% CI)
	no. with event/no. of patients (%)		
With diabetes			
EMPEROR–Reduced	200/927 (21.6)	265/929 (28.5)	0.72 (0.60, 0.87)
DAPA–HF	215/1075 (20.0)	271/1064 (25.5)	0.75 (0.63, 0.90)
Subtotal			0.74 (0.65, 0.84)
Test for overall treatment effect, p<0.0001			
Test for heterogeneity of effect, p=0.76			
Without diabetes			
EMPEROR–Reduced	161/936 (17.2)	197/938 (21.0)	0.78 (0.64, 0.97)
DAPA–HF	171/1298 (13.2)	231/1307 (17.7)	0.73 (0.60, 0.88)
Subtotal			0.75 (0.65, 0.87)
Test for overall treatment effect, p<0.0001			
Test for heterogeneity of effect, p=0.65			
Test for treatment by subgroup interaction, p=0.81			



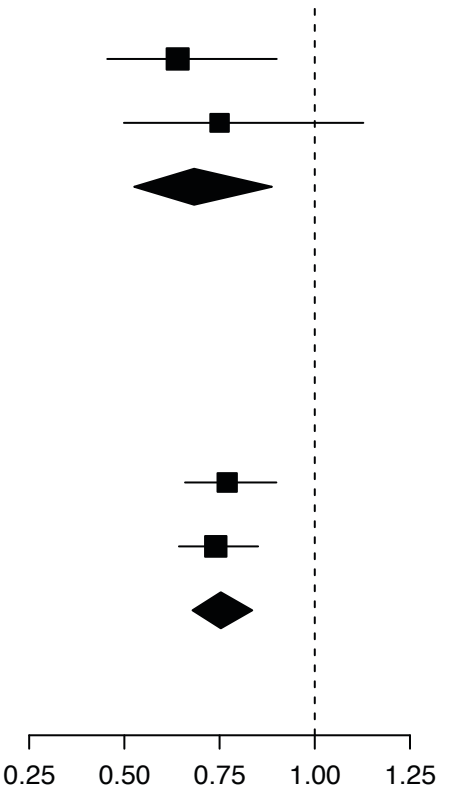
b) Sex

	SGLT2i	Placebo	HR (95% CI)
	no. with event/no. of patients (%)		
Men			
EMPEROR–Reduced	294/1426 (20.6)	353/1411 (25.0)	0.80 (0.68, 0.93)
DAPA–HF	307/1809 (17.0)	406/1826 (22.2)	0.73 (0.63, 0.85)
Subtotal			0.76 (0.68, 0.85)
Test for overall treatment effect, p<0.0001			
Test for heterogeneity of effect, p=0.41			
Women			
EMPEROR–Reduced	67/437 (15.3)	109/456 (23.9)	0.59 (0.44, 0.80)
DAPA–HF	79/564 (14.0)	96/545 (17.6)	0.79 (0.59, 1.06)
Subtotal			0.68 (0.56, 0.84)
Test for overall treatment effect, p=0.0004			
Test for heterogeneity of effect, p=0.17			
Test for treatment by subgroup interaction, p=0.37			



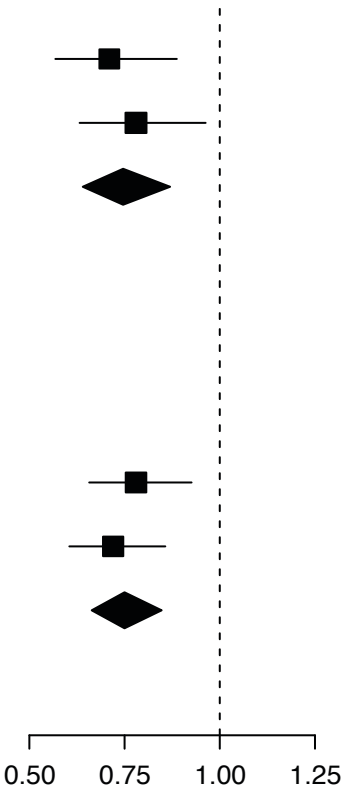
c) Use of ARNi

	SGLT2i	Placebo	HR (95% CI)
	no. with event/no. of patients (%)		
Receiving ARNi			
EMPEROR–Reduced	51/340 (15.0)	93/387 (24.0)	0.64 (0.45, 0.89)
DAPA–HF	41/250 (16.4)	56/258 (21.7)	0.75 (0.50, 1.13)
Subtotal			0.68 (0.53, 0.89)
Test for overall treatment effect, p=0.0043			
Test for heterogeneity of effect, p=0.56			
Not receiving ARNi			
EMPEROR–Reduced	310/1523 (20.4)	369/1480 (24.9)	0.77 (0.66, 0.90)
DAPA–HF	345/2123 (16.3)	446/2113 (21.1)	0.74 (0.65, 0.86)
Subtotal			0.75 (0.68, 0.84)
Test for overall treatment effect, p<0.0001			
Test for heterogeneity of effect, p=0.71			
Test for treatment by subgroup interaction, p=0.50			

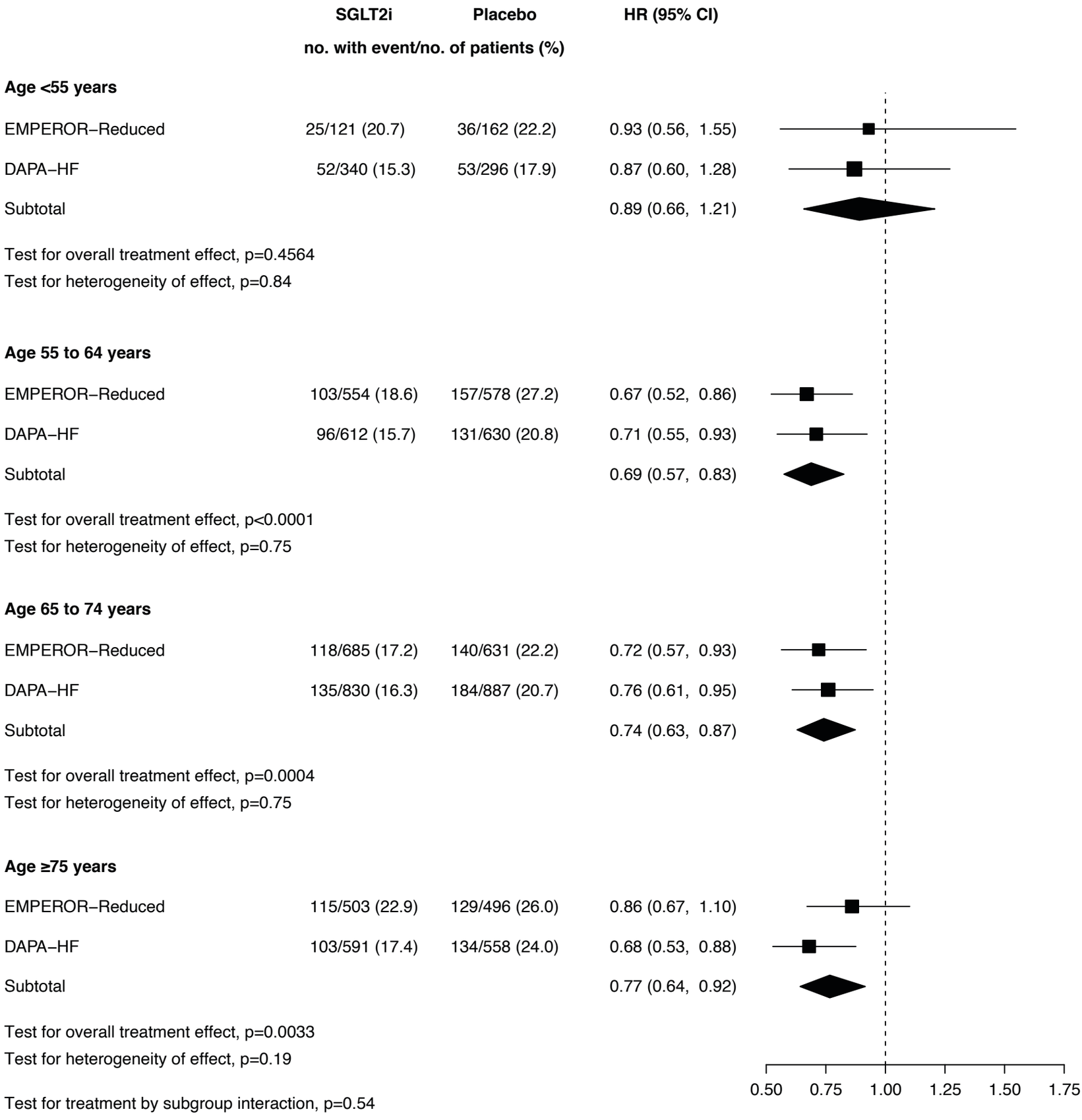


d) Age (≤65 and >65 years)

	SGLT2i	Placebo	HR (95% CI)
	no. with event/no. of patients (%)		
Age ≤65 years			
EMPEROR–Reduced	128/675 (19.0)	193/740 (26.1)	0.71 (0.57, 0.89)
DAPA–HF	162/1032 (15.7)	196/998 (19.6)	0.78 (0.63, 0.96)
Subtotal			0.75 (0.64, 0.87)
Test for overall treatment effect, p=0.0002			
Test for heterogeneity of effect, p=0.55			
Age >65 years			
EMPEROR–Reduced	233/1188 (19.6)	269/1127 (23.9)	0.78 (0.66, 0.93)
DAPA–HF	224/1341 (16.7)	306/1373 (22.3)	0.72 (0.60, 0.85)
Subtotal			0.75 (0.66, 0.85)
Test for overall treatment effect, p<0.0001			
Test for heterogeneity of effect, p=0.52			
Test for treatment by subgroup interaction, p=0.96			

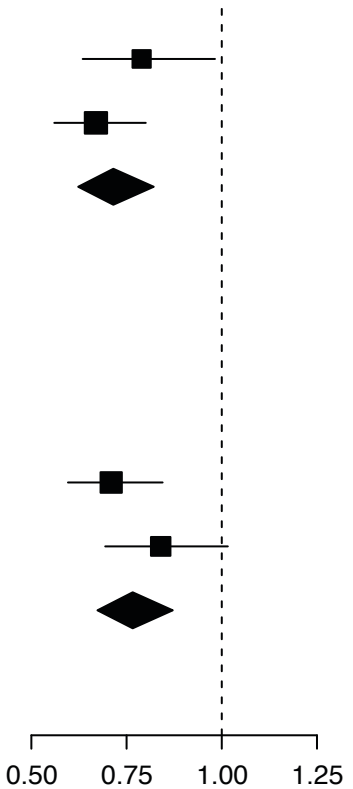


e) Age (<55, 55 to 64, 65 to 74, and ≥75 years)



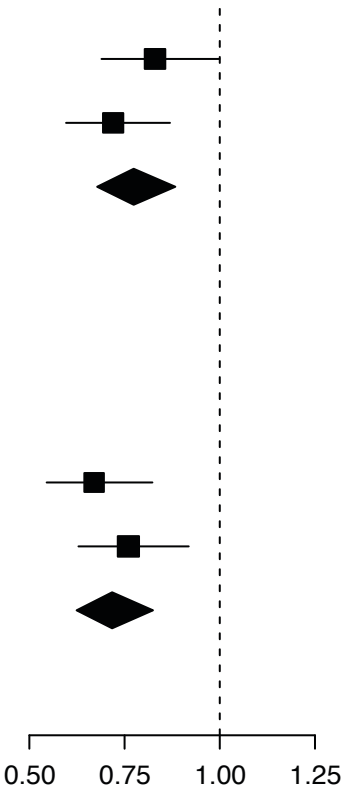
f) History of hospitalisation for heart failure

	SGLT2i	Placebo	HR (95% CI)
	no. with event/no. of patients (%)		
History of HHF			
EMPEROR–Reduced	153/577 (26.5)	177/574 (30.8)	0.79 (0.64, 0.99)
DAPA–HF	195/1124 (17.3)	279/1127 (24.8)	0.67 (0.56, 0.80)
Subtotal			0.72 (0.62, 0.82)
Test for overall treatment effect, p<0.0001			
Test for heterogeneity of effect, p=0.25			
No history of HHF			
EMPEROR–Reduced	208/1286 (16.2)	285/1293 (22.0)	0.71 (0.60, 0.85)
DAPA–HF	191/1249 (15.3)	223/1244 (17.9)	0.84 (0.69, 1.01)
Subtotal			0.77 (0.67, 0.87)
Test for overall treatment effect, p<0.0001			
Test for heterogeneity of effect, p=0.20			
Test for treatment by subgroup interaction, p=0.48			



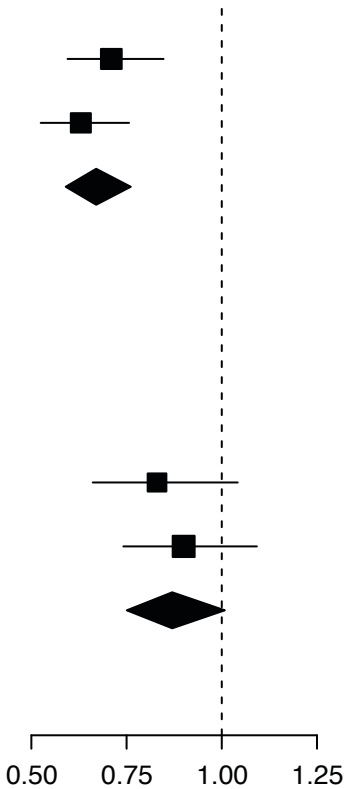
g) eGFR

	SGLT2i	Placebo	HR (95% CI)
	no. with event/no. of patients (%)		
eGFR: <60ml			
EMPEROR–Reduced	202/893 (22.6)	237/906 (26.2)	0.83 (0.69, 1.00)
DAPA–HF	191/962 (19.9)	254/964 (26.3)	0.72 (0.59, 0.86)
Subtotal			0.77 (0.68, 0.88)
Test for overall treatment effect, p=0.0001			
Test for heterogeneity of effect, p=0.29			
eGFR: ≥60ml			
EMPEROR–Reduced	159/969 (16.4)	224/960 (23.3)	0.67 (0.55, 0.83)
DAPA–HF	195/1410 (13.8)	248/1406 (17.6)	0.76 (0.63, 0.92)
Subtotal			0.72 (0.62, 0.82)
Test for overall treatment effect, p<0.0001			
Test for heterogeneity of effect, p=0.38			
Test for treatment by subgroup interaction, p=0.44			



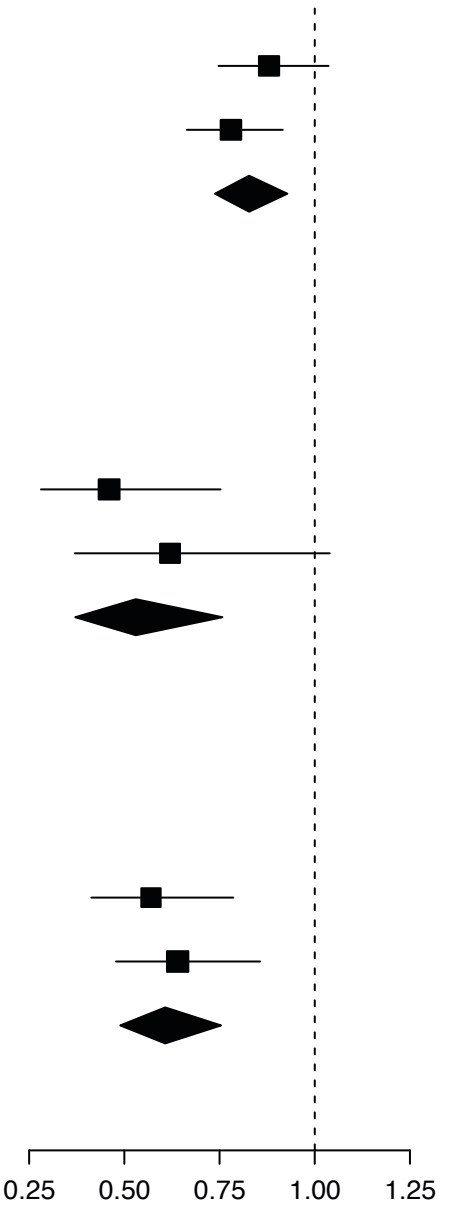
h) NYHA functional class

	SGLT2i	Placebo	HR (95% CI)
	no. with event/no. of patients (%)		
NYHA class: II			
EMPEROR–Reduced	220/1399 (15.7)	299/1401 (21.3)	0.71 (0.59, 0.84)
DAPA–HF	190/1606 (11.8)	289/1597 (18.1)	0.63 (0.52, 0.75)
Subtotal			0.67 (0.59, 0.76)
Test for overall treatment effect, p<0.0001			
Test for heterogeneity of effect, p=0.36			
NYHA class: III–IV			
EMPEROR–Reduced	141/464 (30.4)	163/466 (35.0)	0.83 (0.66, 1.04)
DAPA–HF	196/767 (25.6)	213/774 (27.5)	0.90 (0.74, 1.09)
Subtotal			0.87 (0.75, 1.01)
Test for overall treatment effect, p=0.0638			
Test for heterogeneity of effect, p=0.60			
Test for treatment by subgroup interaction, p=0.0087			



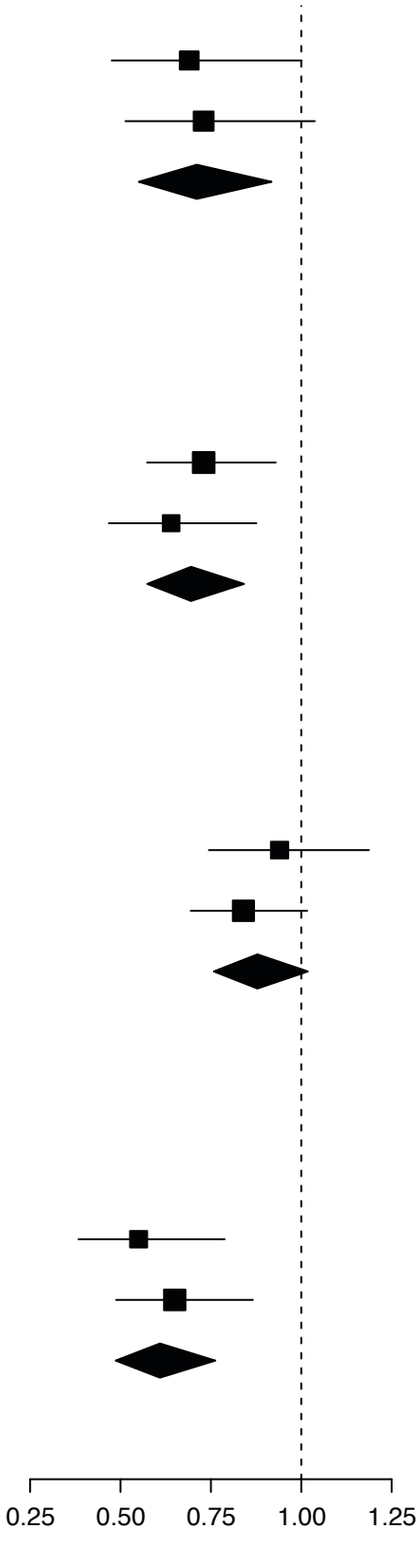
i) Race

	SGLT2i	Placebo	HR (95% CI)
	no. with event/no. of patients (%)		
White			
EMPEROR–Reduced	264/1325 (19.9)	289/1304 (22.2)	0.88 (0.75, 1.04)
DAPA–HF	275/1662 (16.5)	348/1671 (20.8)	0.78 (0.66, 0.91)
Subtotal			0.83 (0.74, 0.93)
Test for overall treatment effect, p=0.0012			
Test for heterogeneity of effect, p=0.30			
Black			
EMPEROR–Reduced	24/123 (19.5)	48/134 (35.8)	0.46 (0.28, 0.75)
DAPA–HF	26/122 (21.3)	32/104 (30.8)	0.62 (0.37, 1.04)
Subtotal			0.53 (0.37, 0.76)
Test for overall treatment effect, p=0.0005			
Test for heterogeneity of effect, p=0.41			
Asian			
EMPEROR–Reduced	62/337 (18.4)	99/335 (29.6)	0.57 (0.41, 0.78)
DAPA–HF	78/552 (14.1)	118/564 (20.9)	0.64 (0.48, 0.86)
Subtotal			0.61 (0.49, 0.75)
Test for overall treatment effect, p<0.0001			
Test for heterogeneity of effect, p=0.60			
Test for treatment by subgroup interaction, p=0.0063			



j) Region

	SGLT2i	Placebo	HR (95% CI)
	no. with event/no. of patients (%)		
North America			
EMPEROR–Reduced	48/212 (22.6)	64/213 (30.0)	0.69 (0.48, 1.01)
DAPA–HF	54/335 (16.1)	73/342 (21.3)	0.73 (0.51, 1.03)
Subtotal			0.71 (0.55, 0.92)
Test for overall treatment effect, p=0.0088			
Test for heterogeneity of effect, p=0.83			
Latin America			
EMPEROR–Reduced	115/641 (17.9)	151/645 (23.4)	0.73 (0.58, 0.94)
DAPA–HF	62/401 (15.5)	97/416 (23.3)	0.64 (0.47, 0.88)
Subtotal			0.70 (0.57, 0.84)
Test for overall treatment effect, p=0.0002			
Test for heterogeneity of effect, p=0.51			
Europe			
EMPEROR–Reduced	140/676 (20.7)	149/677 (22.0)	0.94 (0.74, 1.18)
DAPA–HF	193/1094 (17.6)	218/1060 (20.6)	0.84 (0.69, 1.01)
Subtotal			0.88 (0.76, 1.02)
Test for overall treatment effect, p=0.0858			
Test for heterogeneity of effect, p=0.46			
Asia			
EMPEROR–Reduced	49/248 (19.8)	80/245 (32.7)	0.55 (0.38, 0.78)
DAPA–HF	77/543 (14.2)	114/553 (20.6)	0.65 (0.49, 0.87)
Subtotal			0.61 (0.49, 0.76)
Test for overall treatment effect, p<0.0001			
Test for heterogeneity of effect, p=0.48			
Test for treatment by subgroup interaction, p=0.04			



k) BMI

	SGLT2i	Placebo	HR (95% CI)
	no. with event/no. of patients (%)		
BMI: <30kg/m²			
EMPEROR–Reduced	226/1263 (17.9)	322/1300 (24.8)	0.70 (0.59, 0.83)
DAPA–HF	259/1537 (16.9)	320/1533 (20.9)	0.78 (0.66, 0.92)
Subtotal			0.74 (0.66, 0.83)
Test for overall treatment effect, p<0.0001			
Test for heterogeneity of effect, p=0.37			
BMI: ≥30kg/m²			
EMPEROR–Reduced	135/600 (22.5)	140/567 (24.7)	0.85 (0.67, 1.08)
DAPA–HF	127/834 (15.2)	182/838 (21.7)	0.69 (0.55, 0.86)
Subtotal			0.76 (0.65, 0.90)
Test for overall treatment effect, p=0.001			
Test for heterogeneity, p=0.21			
Test for treatment by subgroup interaction, p=0.79			

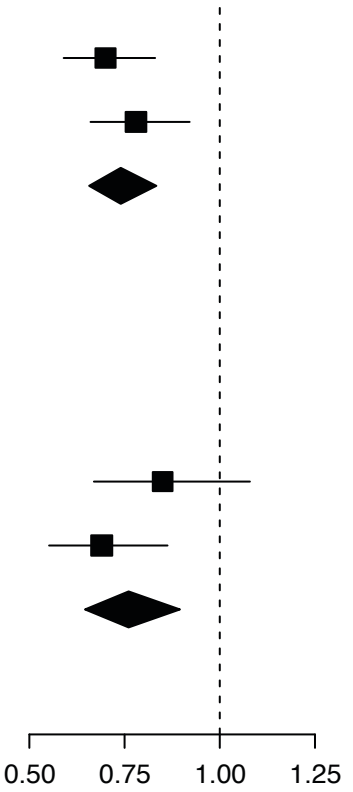


Table 1. Overview of main characteristics of the two trial populations at baseline

	EMPEROR-reduced		**DAPA-HF**	
	Empagliflozin	**Placebo**	**Dapagliflozin**	**Placebo**
Number of participants	1863	1867	2373	2371
Mean±SD age, years	67.2 ± 10.8	66.5 ± 11.2	66.2 ± 11.0	66.5 ± 10.8
Females	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 (%), mean ± SD	27.7 ± 6.0	27.2 ± 6.1	31.2 ± 6.7	30.9 ± 6.9
NT-pro BNP, pg/ml, median (Q1-Q3)	1887 (1077-3429)	1926 (1153-3525)	1428 (857-2655)	1446 (857-2641)
Medical history				
Hospitalisation for HF*	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%)
Mean ± SD eGFR, ml/min/1.73 m^2 * **	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 (%), unless otherwise specified.

* For EMPEROR-Reduced: last 12 months

** determined by a combination of medical history and pre-treatment HbA1c

** *CKD-EPI formula

Legend: LVEF, left ventricular ejection fraction; CV, cardiovascular; HF, heart failure; SD, standard deviation; NYHA, New York Heart Association; eGFR, estimated glomerular filtration rate; ACE, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; ICD, implantable cardiac defibrillator; CRT-D, cardiac resynchronization therapy defibrillator; CRT-P, cardiac resynchronization therapy pacemaker.

Table 2. Relevant adverse events reported in the two trials.

	EMPEROR-Reduced		**DAPA-HF**	
	Empagliflozin (n=1863) N (%)	**Placebo** (n=1863) N (%)	**Dapagliflozin** (n=2373) N (%)	**Placebo** (n=2371) N (%)
Serious AEs*	772 (41.4)	896 (48.1)	846 (35.7)	951(40.2)
Any renal AE	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 (0.0)	0 (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)

* Definitions of medical concepts describing adverse events of interest were not exactly the same across the two trials. The absolute numbers of events cannot be compared across the two trials due to different definitions and observation periods. For EMPEROR-Reduced: Shown are adverse events up to 7 days following discontinuation of study medication, for lower limb amputations up to the end of the trial. For DAPA-HF: On treatment (SAS) analysis set for all AEs, except for lower limb amputation shown on and off treatment.

See supplemental table 3 for further details on adverse event definitions.

Legend: AE, adverse events.