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RESEARCH ARTICLE

Cardiac and kidney benefits of empagliflozin in heart failure across the spectrum of kidney function: insights from the EMPEROR-Preserved trial

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Aim

In the EMPEROR-Preserved trial, empagliflozin improved clinical outcomes of patients with heart failure (HF) with preserved ejection fraction. In this pre-specified analysis, we aim to study the effect of empagliflozin on cardiovascular and kidney outcomes across the spectrum of kidney function.

Methods and results

Patients were categorized by the presence or absence of chronic kidney disease (CKD) at baseline (CKD defined by an estimated glomerular filtration rate [eGFR] <60 ml/min/1.73 m^2 or urine albumin to creatinine ratio >300 mg/g). The primary and key secondary outcomes were (i) a composite of cardiovascular death or first HF hospitalization (primary outcome); (ii) total number of HF hospitalization, (iii) eGFR slope; and a pre-specified exploratory composite kidney outcome including a sustained ≥40% decline in eGFR, chronic dialysis or renal transplant. The median follow-up was 26.2 months. A total of 5988 patients were randomized to empagliflozin or placebo, of whom 3198 (53.5%) had CKD. Irrespective of CKD status, empagliflozin reduced the primary outcome (with CKD: hazard ratio [HR] 0.80, 95% confidence interval [CI] 0.69–0.94; without CKD: HR 0.75, 95% CI 0.60–0.95; interaction $p = 0.67$) and total (first and recurrent) hospitalizations for HF (with CKD: HR 0.68, 95% CI 0.54–0.86; without CKD: HR 0.89, 95% CI 0.66–1.21; interaction $p = 0.17$). Empagliflozin slowed the slope of eGFR decline by 1.43 (1.01–1.85) ml/min/1.73 m^2/year in patients with CKD and 1.31 (0.88–1.74) ml/min/1.73 m^2/year in patients without CKD (interaction $p = 0.70$). Empagliflozin did not reduce the pre-specified kidney outcome in patients with or without CKD (with CKD: HR 0.97, 95% CI 0.71–1.34; without CKD: HR 0.92, 95% CI 0.58–1.48; interaction $p = 0.86$) but slowed progression to macroalbuminuria and reduced the risk of acute kidney injury. The effect of empagliflozin on the primary composite outcome and the key secondary outcomes was consistent across five baseline eGFR categories (all interaction $p > 0.05$). Empagliflozin was well tolerated independent of CKD status.

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Conclusions In EMPEROR-Preserved, empagliflozin had a beneficial effect on the key efficacy outcomes in patients with and without CKD. Overall, the benefit and safety of empagliflozin was consistent across a wide range of kidney function spectrum, down to a baseline eGFR of 20 ml/min/1.73 m^2.

Keywords Empagliflozin • Glomerular filtration rate • Heart failure • Renal insufficiency • Chronic

Introduction

Randomized trials have shown that sodium–glucose cotransporter 2 inhibitors (SGLT2i) prevent hospitalizations for heart failure (HF) and slow the decline of renal function in patients with type 2 diabetes (T2D),[1–8] chronic kidney disease (CKD),[9,10] and HF with reduced ejection fraction.[11,12]

While pharmacologic therapies to improve cardiovascular outcomes have been demonstrated across multiple therapeutic classes in patients with HF and reduced ejection fraction, there has been few therapeutic options for those with a preserved ejection fraction.[13] Recently, in the EMPEROR-Preserved (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction) trial, empagliflozin versus placebo reduced the composite of cardiovascular death or HF hospitalization and total (first and recurrent) hospitalizations for HF, and slowed the progressive decline in kidney function.[14] For the first time, a therapeutic option is now available for patients with HF and preserved ejection fraction.

Among those with HF and preserved ejection fraction, CKD is one of the most common comorbidities being present in up to 50% of patients.[15–17] Reduced renal function, as measured by estimated glomerular filtration rate (eGFR), portends worse prognosis in patients with HF and preserved ejection fraction.[16,17] Furthermore, the high prevalence of CKD potentially limits the therapeutic options for patients with HF and preserved ejection fraction.[18,19] Within EMPEROR-Reduced (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Reduced Ejection Fraction), empagliflozin reduced the risk of the primary outcome of time to cardiovascular death or first hospitalization for HF and the decline in eGFR slope in patients with and without CKD.[20]

Within EMPEROR-Preserved, patients with an eGFR as low as 20 ml/min/1.73 m^2 were eligible for enrolment; as more than half of the patients had prevalent CKD at baseline, a robust assessment could be conducted regarding the efficacy and safety of empagliflozin on cardiac and kidney outcomes according to the presence of CKD and across a wide range of baseline kidney function. The present analysis reports the pre-specified analysis of EMPEROR-Preserved on cardiovascular and kidney outcomes among patients with and without CKD.

Methods

The design and rationale of the EMPEROR-Preserved trial have been previously published.[14,21] To summarize, EMPEROR-Preserved was a double-blind, placebo-controlled trial that randomized 5988 patients with symptomatic HF (New York Heart Association [NYHA] class ≥II) and a left ventricular ejection fraction (LVEF) of >40% to receive empagliflozin (10 mg orally once daily) or matching placebo.

Randomization was performed with a permuted block design and was stratified by geographic region, diabetes status, eGFR <60 or ≥60 ml/min/1.73 m^2, and a LVEF <50% or ≥50% (all measured at screening). The primary outcome and the first two secondary outcomes were included in a hierarchical testing procedure. The primary outcome was analysed as the time to the first event of the composite of adjudicated cardiovascular death or hospitalization for HF. The first secondary outcome was the occurrence of all adjudicated hospitalizations for HF, including first and recurrent events. The second secondary outcome was the rate of decline in the eGFR during double-blind treatment. In the main trial, empagliflozin, versus placebo, reduced the risk of the primary composite outcome (13.8% in the empagliflozin group vs. 17.1% in the placebo group; hazard ratio [HR] 0.79; 95% confidence interval [CI] 0.69–0.90). Ethics approval was obtained at each study site, and all patients provided informed consent to participate in the study; the registration identifier at ClinicalTrials.gov is NCT03057951.

Baseline categorization of kidney impairment

For the pre-specified subgroup analyses, patients were categorized by the presence or absence of CKD at baseline. Prevalent CKD at baseline was defined by the presence of an eGFR <60 ml/min/1.73 m^2 (as measured by the CKD Epidemiology Collaboration equation) or urine albumin-to-creatine ratio (UACR) >300 mg/g. Conversely, no CKD was defined by an eGFR ≥60 ml/min/1.73 m^2 and UACR ≤300 mg/g. We evaluated the treatment effect on all three of the hierarchically-ranked outcomes and on several cardio-kidney outcomes within the following patients: (i) presence or absence of baseline CKD; and (ii) five baseline eGFR categories (<30, 30–<45, 45–<60, 60–<90, and ≥90 ml/min/1.73 m^2).

Kidney endpoint definition

The pre-specified composite kidney outcome was defined as time to first occurrence of chronic dialysis, kidney transplant, sustained reduction of ≥40% eGFR or sustained eGFR <15 ml/min/1.73 m^2 if baseline eGFR was >30 ml/min/1.73 m^2 or <10 ml/min/1.73 m^2 for patients with baseline eGFR <30 ml/min/1.73 m^2.

Further, to better align with definitions used in other trials, we explored alternative definitions. These include (i) sustained reduction of ≥40% eGFR, end-stage kidney disease (ESKD) or renal death, (ii) sustained reduction of ≥50% eGFR or ESKD, (iii) sustained reduction of ≥50% eGFR, ESKD or renal death, (iv) sustained reduction of 57% eGFR or ESKD, and (v) sustained reduction of 57% eGFR, ESKD or renal death. A blinded independent external Clinical Event Committee (CEC) adjudicated all fatal events. Non-cardiovascular deaths were categorized into several categories (i.e. infections, malignancies,

other non-cardiovascular causes, trauma, gastrointestinal, pulmonary, neurological, haemorrhage, non-cardiovascular procedure or surgery, hepatobiliary causes, suicide, pancreatic causes). The category 'renal cause' was used for 'renal death'.

Statistical analyses

Patient characteristics and adverse events were analysed descriptively. Time-to-first event analyses were performed with a Cox proportional-hazards model, adjusted for age, sex, region, diabetes status, and ejection fraction at baseline. These analyses were performed according to the intention-to-treat principle for all randomized patients, and included data up to the end of the planned treatment period. Total (first and recurrent) hospitalizations for HF were evaluated accordingly with a joint frailty model that accounted for cardiovascular death, adjusted for the same covariates as the Cox model. As pre-specified, the slope of eGFR decline was analysed based on on-treatment data (baseline and other off-treatment data were not included in the model) by a random coefficient model allowing for random intercept and random slope per patient. Continuous endpoints were analysed in a mixed model with repeated measures (MMRM). An ANCOVA analysis was used to compare eGFR change from baseline to follow-up (planned 30 days after treatment discontinuation) between the two treatment groups.

The slope model, the MMRM, and the ANCOVA model included baseline eGFR and the covariates of the Cox model. To assess the consistency of effects across CKD subgroups, subgroup-by-treatment interaction terms were added to the models. Adverse event analyses were based on patients with events occurring during the on-treatment period (including 7 days after last drug consumption by the patient). SAS® version 9.4 (SAS Institute Inc., Cary, NC, USA) was used for all analyses.

Results

Patient characteristics

Among the 5976 patients in the trial, who could be classified according to CKD categories (99.8% of the trial population), 3198 (53.5%) had prevalent CKD at baseline (*Table 1*). Compared with patients without CKD, those with CKD were older (74.2 vs. 69.2 years), had a longer duration of HF (mean time since diagnosis: 4.6 vs. 4.1 years), were more likely to have a hospitalization for HF in the past 12 months (24.9 vs. 20.5%), and were more likely to have diabetes (52.3 vs. 45.3%). Furthermore, compared to those without CKD, those with CKD were less likely to be treated with an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker (76.9 vs. 80.5%). Compared to those without CKD, as expected and reflective of the subgroup definition for prevalent CKD, baseline eGFR was lower for patients with CKD (mean: 46.3 vs. 77.1 ml/min/1.73 m^2), and UACR was higher (median: 32 vs. 15 mg/g). The baseline characteristics in the placebo and empagliflozin groups were well balanced in patients with and without CKD as described in online supplementary *Table S1*. The patient characteristics across the five eGFR categories are presented in online supplementary *Table S2*.

Table 1 Baseline characteristics of the patients by chronic kidney disease status at baseline

	No CKD ($n = 2778$)	CKD ($n = 3198$)	*p*-value
Age, years	69.2 ± 9.6	74.2 ± 8.7	<0.0001
Female sex	1119 (40.3)	1555 (48.6)	<0.0001
Race			0.0150
White	2053 (73.9)	2478 (77.5)	
Black	128 (4.6)	129 (4.0)	
Asian	418 (15.0)	406 (12.7)	
Other	177 (6.4)	185 (5.8)	
Missing	2 (0.1)	0	
Region			<0.0001
North America	271 (9.8)	446 (13.9)	
Latin America	747 (26.9)	768 (24.0)	
Europe	1237 (44.5)	1443 (45.1)	
Asia	344 (12.4)	342 (10.7)	
Other	179 (6.4)	199 (6.2)	
Time since diagnosis of heart failure, years	4.1 ± 5.0	4.6 ± 5.2	0.0001
NYHA functional class			<0.0001
II	2378 (85.6)	2497 (78.1)	
III	394 (14.2)	685 (21.4)	
IV	4 (0.1)	14 (0.4)	
BMI, kg/m^2	29.55 ± 5.94	30.08 ± 5.80	0.0004
Heart rate, bpm	70.4 ± 11.6	70.4 ± 12.1	0.9387
Systolic blood pressure, mmHg	131.5 ± 15.1	132.1 ± 16.1	0.1503
Diastolic blood pressure, mmHg	76.6 ± 10.2	75.0 ± 10.8	<0.0001
LVEF, %	53.7 ± 8.7	54.9 ± 8.8	<0.0001
NT-proBNP, pg/ml	1085 ± 1213	1789 ± 2379	<0.0001
Principal cause of heart failure			
Ischaemic	1005 (36.2)	1106 (34.6)	0.1952
Medical history			
HHF in last 12 months	570 (20.5)	796 (24.9)	0.0003
Atrial fibrillation/flutter[a]	1312 (47.2)	1818 (56.8)	<0.0001
Hypertension	2454 (88.3)	2960 (92.6)	<0.0001
Diabetes	1259 (45.3)	1671 (52.3)	<0.0001
eGFR (CKD-EPI), ml/min/1.73 m^2	77.1 ± 12.0	46.3 ± 12.9	<0.0001
eGFR (CKD-EPI) <60 ml/min/1.73 m^2	NA	2988 (93.4)	NA
UACR, mg/g, median (IQR)	15 (6–38)	32 (9–168)	<0.0001
UACR, >300 mg/g	NA	629 (19.7)	NA
Device therapy			
Implantable cardioverter-defibrillator[b]	95 (3.4)	126 (3.9)	0.2878
Heart failure medication			
ACE inhibitor	1212 (43.6)	1192 (37.3)	<0.0001
ARB[c]	1030 (37.1)	1282 (40.1)	0.0172
ARNI	65 (2.3)	68 (2.1)	0.5768
Diuretics[d]	2085 (75.1)	2714 (84.9)	<0.0001
MRA	1018 (36.6)	1223 (38.2)	0.2032
Beta-blocker	2409 (86.7)	2748 (85.9)	0.3768
Cardiac glycosides	285 (10.3)	270 (8.4)	0.0158
Nitrates	282 (10.2)	464 (14.5)	<0.0001
Ivabradine	45 (1.6)	26 (0.8)	0.0041
Hydralazine	25 (0.9)	131 (4.1)	<0.0001
Other medication			
Lipid-lowering drugs	1929 (69.4)	2305 (72.1)	0.0252
Anti-thrombotic drugs	2375 (85.5)	2853 (89.2)	<0.0001

Data are mean ± SD or *n* (%) for randomized patients, unless otherwise stated.
ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; BMI, body mass index; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration equation; eGFR, estimated glomerular filtration rate; HHF, hospitalization for heart failure; IQR, interquartile range; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NA, not available; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; UACR, urine albumin-to-creatinine ratio.
[a]Atrial fibrillation/flutter reported in any electrocardiogram before treatment intake or history of atrial fibrillation/flutter reported as medical history.
[b]Implantable cardioverter defibrillator with or without cardiac resynchronization therapy.
[c]Excluding valsartan when taken with sacubitril.
[d]Diuretics other than MRAs.

Table 2 Event rates by chronic kidney disease status at baseline

	Empagliflozin				Placebo			
	CKD ($n = 1615$)		No CKD ($n = 1378$)		CKD ($n = 1583$)		No CKD ($n = 1400$)	
	n (%)	Rate per 100 patient-years	*n* (%)	Rate per 100 patient-years	*n* (%)	Rate per 100 patient-years	*n* (%)	Rate per 100 patient-years
Adjudicated HHF or CV death	292 (18.1)	9.24	123 (8.9)	4.27	344 (21.7)	11.52	165 (11.8)	5.71
First HHF	189 (11.7)	5.98	70 (5.1)	2.43	254 (16.0)	8.51	97 (6.9)	3.36
CV death	151 (9.3)	4.46	68 (4.9)	2.26	152 (9.6)	4.54	91 (6.5)	3.0
First and recurrent HHF	284	–	123	–	395	–	144	–
All-cause hospitalization	795 (49.2)	33.45	474 (34.4)	20.15	807 (51.0)	35.70	528 (37.7)	22.74
All-cause mortality	281 (17.4)	8.30	140 (10.2)	4.66	273 (17.2)	8.15	153 (10.9)	5.04
Composite kidney endpoint[a]	75 (4.6)	2.82	33 (2.4)	1.37	74 (4.7)	2.87	37 (2.6)	1.52

Data for randomized patients.
CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration equation; CV, cardiovascular; eGFR, estimated glomerular filtration rate (ml/min/1.73 m^2 by CKD-EPI); HHF, hospitalization for heart failure.
[a]Composite exploratory endpoint included chronic dialysis or renal transplant or sustained reduction of ≥40% in eGFR or sustained eGFR <15 ml/min/1.73 m^2 (for patients with baseline eGFR ≥30) or sustained eGFR <10 (for patients with baseline eGFR <30).

Primary and key secondary endpoints

Compared to patients without CKD, those with CKD had a higher rate of the primary composite outcome, first and recurrent hospitalizations for HF, composite kidney outcome, all-cause hospitalizations, cardiovascular and all-cause death (*Table 2*).

Compared to placebo, empagliflozin reduced the primary outcome of time-to-first cardiovascular death or hospitalization for HF irrespective of CKD status (*Figure 1* and online supplementary *Figure S1*): HR 0.80 (95% CI 0.69–0.94) in patients with CKD and HR 0.75 (95% CI 0.60–0.95) in patients without CKD (interaction $p = 0.67$). Empagliflozin reduced the key secondary endpoint of total (first and recurrent) HF hospitalizations irrespective of CKD status: HR 0.68 (95% CI 0.54–0.86) in patients with CKD and HR 0.89 (95% CI 0.66–1.21) in patients without CKD (interaction $p = 0.17$) (*Figure 1*). Empagliflozin reduced the absolute difference in the slope of decline in eGFR irrespective of CKD: 1.43 (95% CI 1.01–1.85) ml/min/1.73 m^2/year in patients with CKD and 1.31 (95% CI 0.88–1.74) ml/min/1.73 m^2/year in patients without CKD; (interaction $p = 0.70$) (*Table 3*). Results were consistent across eGFR and UACR categories (*Table 3*). The change of eGFR over time for patients with and without CKD is shown in *Figure 2*. An early eGFR decrease ('dip') was only observed in the empagliflozin-treated arms. Following this 'dip', stabilization of the eGFR trajectories was observed in the empagliflozin-treated groups; in patients with CKD, eGFR was similar after week 76 in empagliflozin versus placebo; in patients without CKD, the placebo arm had a greater decline in eGFR until the end of the study (*Figure 2*).

In a subset of 3170 patients (1573 with CKD and 1597 without CKD) that had CKD categorization and measurements of eGFR at baseline and 30 days after discontinuation of treatment, empagliflozin reduced the decline in eGFR from baseline to 30 days after drug discontinuation by 2.4 (95% CI 1.3–3.5) ml/min/1.73 m^2 in patients with CKD and by 2.4 (95% CI 1.2–3.5) ml/min/1.73 m^2 in patients without CKD (interaction $p = 0.97$) (*Table 4*).

Event rates by eGFR categories across outcomes are presented in *Figure 3*. The effect of empagliflozin on the primary composite outcome and the key secondary outcomes across the five eGFR categories, is shown in *Figure 3*. Overall, baseline kidney function did not influence the impact of empagliflozin on the primary endpoint, total hospitalizations for HF, or other outcomes (all trend *p*-values >0.05; *Figure 3*).

Additional kidney outcomes

The pre-specified composite kidney outcome (of a greater than 40% sustained decline in eGFR, chronic dialysis or kidney transplant or sustained eGFR <15 ml/min/1.73 m^2 [for patients with baseline eGFR ≥30] or sustained eGFR <10 [for patients with baseline eGFR <30]) was not reduced in patients with and without CKD: HR 0.97 (95% CI 0.71–1.34) in patients with CKD and HR 0.92 (95% CI 0.58–1.48) in patients without CKD (interaction $p = 0.86$) (*Figure 4*). The results were consistent across eGFR categories (*Figure 5*) and across alternative definitions of kidney outcomes (online supplementary *Figure S2*).

Investigator-reported acute kidney injury was less frequent in the empagliflozin group (HR 0.73, 95% CI 0.56–0.95; $p = 0.0193$), both in patients with CKD and without CKD: HR 0.76 (95% CI 0.56–1.02) with CKD and HR 0.66 (95% CI 0.38–1.15) without CKD (interaction $p = 0.67$). Furthermore, empagliflozin reduced progression to macroalbuminuria (HR 0.82, 95% CI 0.68–0.98], $p = 0.0264$) in patients who at baseline were normo/microalbuminuric: HR 0.80 (95% CI 0.63–1.01) with CKD and HR 0.84 (95% CI 0.64–1.10) without CKD (interaction $p = 0.77$) (*Figure 4* and online supplementary *Figure S3*).

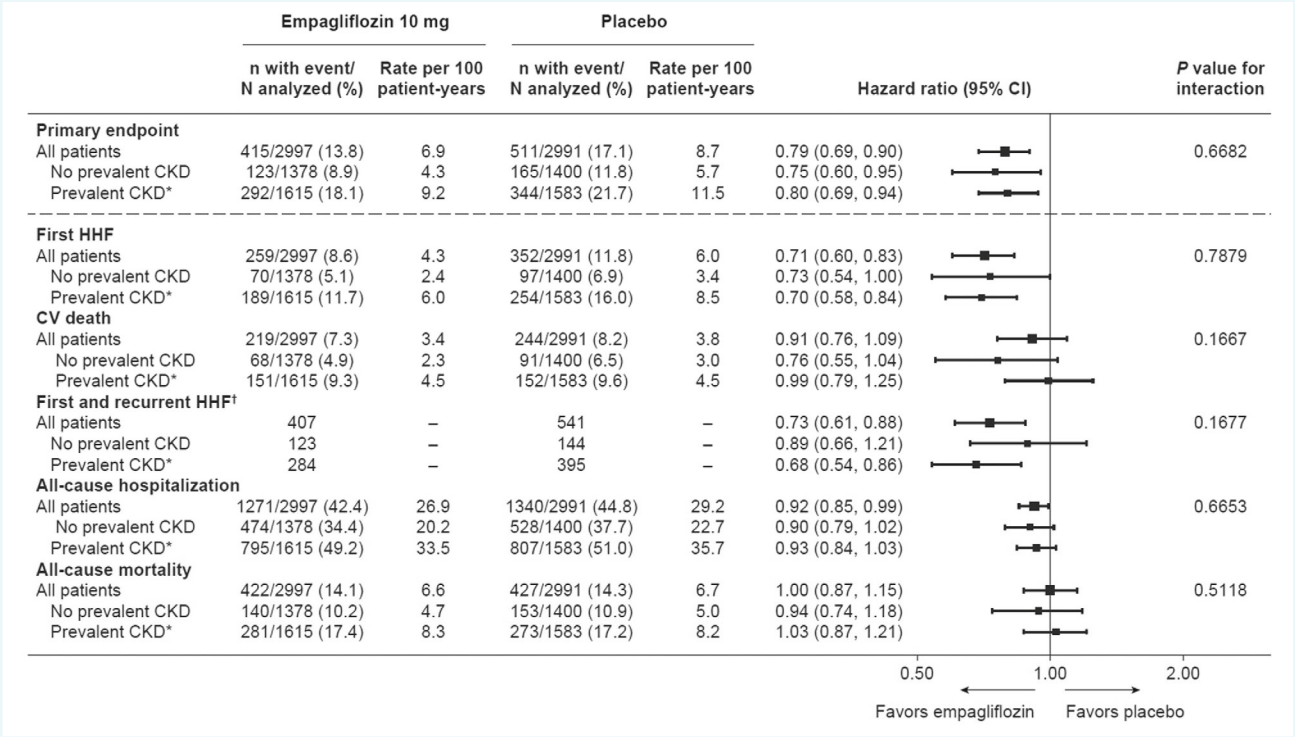

Figure 1 Primary and key secondary outcomes by chronic kidney disease (CKD) status at baseline. Data for randomized patients; hazard ratio and 95% confidence interval (CI) from Cox proportional-hazards model unless otherwise noted. CV, cardiovascular; HHF, hospitalization for heart failure. *Prevalent CKD defined as estimated glomerular filtration rate (CKD Epidemiology Collaboration equation) <60 ml/min/1.73 m^2 or urine albumin-to-creatinine ratio >300 mg/g. †Evaluated using a joint frailty model together with CV death.

Table 3 Estimated glomerular filtration rate slope analyses by chronic kidney disease status at baseline

Slope of change in eGFR, ml/min/1.73 m^2 per year[a]	Empagliflozin (mean ± SE)	Placebo (mean ± SE)	Absolute difference (95% CI)	*p*-value	*p*-value for interaction/ trend*
All patients ($n = 5836$)[a]	−1.25 ± 0.11	−2.62 ± 0.11	1.36 (1.06–1.66)	<0.001	
By prevalent CKD status[b]					
No prevalent CKD ($n = 2707$)	−1.87 ± 0.16	−3.19 ± 0.15	1.31 (0.88–1.74)	<0.0001	0.7045
Prevalent CKD ($n = 3120$)	−0.70 ± 0.15	−2.13 ± 0.15	1.43 (1.01–1.85)	<0.0001	
By eGFR (CKD-EPI) category, ml/min/1.73 m^2					
≥90 ($n = 457$)	−2.84 ± 0.38	−3.98 ± 0.38	1.14 (0.09–2.19)	0.0327	0.4892
60 to <90 ($n = 2465$)	−1.82 ± 0.16	−3.25 ± 0.16	1.44 (0.98–1.89)	<0.0001	
45 to <60 ($n = 1529$)	−0.94 ± 0.21	−2.50 ± 0.21	1.56 (0.98–2.14)	<0.0001	
30 to <45 ($n = 1090$)	−0.00 ± 0.26	−1.26 ± 0.26	1.26 (0.54–1.97)	0.0006	
<30 ($n = 295$)	−0.46 ± 0.55	−0.68 ± 0.55	0.22 (−1.30 to 1.75)	0.7733	
By UACR category, mg/g					
<30 (normoalbuminuria) ($n = 3393$)	−0.97 ± 0.14	−2.40 ± 0.14	1.43 (1.05–1.81)	<0.0001	0.9711
30–300 (microalbuminuria) ($n = 1810$)	−1.45 ± 0.20	−2.58 ± 0.19	1.13 (0.59–1.67)	<0.0001	
>300 (macroalbuminuria ($n = 610$)	−2.44 ± 0.34	−4.28 ± 0.36	1.84 (0.86–2.81)	0.0002	

CI, confidence interval; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration equation; eGFR, estimated glomerular filtration rate; UACR, urine albumin-to-creatinine ratio; SE, standard error.
[a]Data for the treated set of patients from random coefficient model; intercept and slope allowed to vary randomly between patients.
[b]Prevalent CKD defined as eGFR (CKD-EPI) <60 ml/min/1.73 m^2 or UACR >300 mg/g.
*Interaction test for prevalent CKD, trend test for eGFR and UACR subgroups.

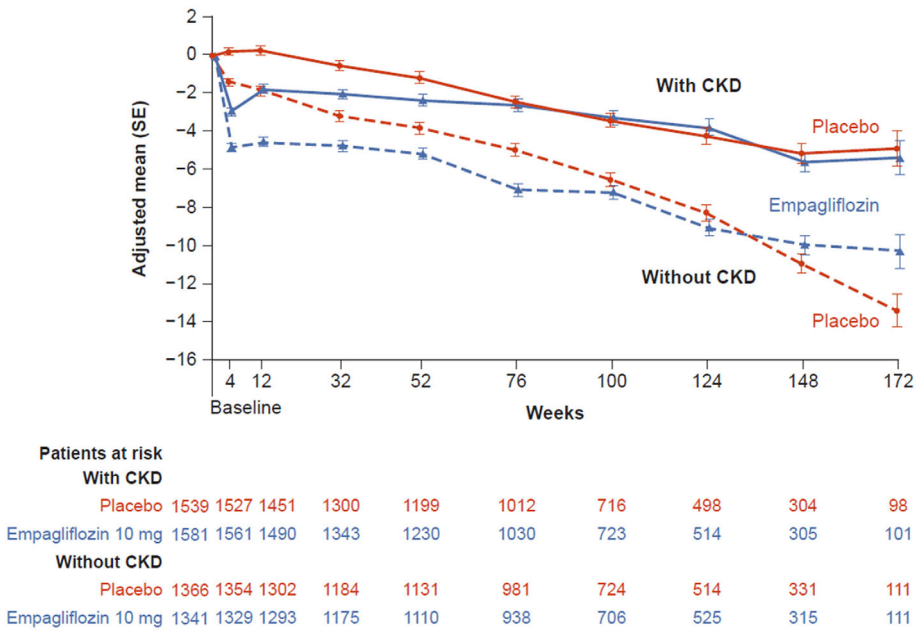

Figure 2 Estimated glomerular filtration rate change from baseline over time by chronic kidney disease (CKD) status at baseline. Data for treated patients from a mixed model for repeated measures based on on-treatment data. CKD defined as estimated glomerular filtration rate (CKD Epidemiology Collaboration equation) <60 ml/min/1.73 m^2 or urine albumin-to-creatinine ratio >300 mg/g.

Table 4 Change in estimated glomerular filtration rate (eGFR) from baseline to follow-up (30 days after treatment discontinuation) by chronic kidney disease status and eGFR and urine albumin-to-creatinine ratio categories at baseline

Total change in eGFR from baseline to follow-up (30 days after treatment discontinuation)[a], ml/min/1.73 m^2	Empagliflozin (mean ± SE)	Placebo (mean ± SE)	Absolute difference (95% CI)	*p*-value	*p*-value for interaction/ trend*
All patients (*n* = 3176)	−3.3 ± 0.3	−5.7 ± 0.3	2.4 (1.6–3.2)	<0.0001	
By prevalent CKD status[b]					
No prevalent CKD (*n* = 1597)	−5.7 ± 0.4	−8.0 ± 0.4	2.4 (1.2–3.5)	<0.0001	0.9748
Prevalent CKD (*n* = 1573)	−0.9 ± 0.4	−3.3 ± 0.4	2.4 (1.3–3.5)	<0.0001	
By eGFR (CKD-EPI) category, ml/min/1.73 m^2					
≥90 (*n* = 274)	−7.8 ± 1.0	−10.8 ± 1.0	3.0 (0.3–5.7)	0.0282	0.3295
60 to <90 (*n* = 1432)	−5.4 ± 0.4	−7.9 ± 0.4	2.5 (1.3–3.6)	<0.0001	
45 to <60 (*n* = 828)	−1.0 ± 0.6	−4.1 ± 0.6	3.1 (1.6–4.7)	<0.0001	
30 to <45 (*n* = 535)	0.2 ± 0.7	−0.9 ± 0.7	1.1 (−0.8 to 3.0)	0.2583	
<30 (*n* = 107)	2.8 ± 1.5	0.9 ± 1.6	1.9 (−2.4 to 6.2)	0.3856	
By UACR category, mg/g					
<30 (normoalbuminuria) (*n* = 1987)	−2.7 ± 0.4	−5.5 ± 0.4	2.7 (1.8–3.7)	<0.0001	0.7385
30–300 (microalbuminuria) (*n* = 913)	−3.7 ± 0.5	−5.3 ± 0.5	1.6 (0.1–3.0)	0.0317	
>300 (macroalbuminuria) (*n* = 263)	−5.6 ± 1.0	−9.3 ± 1.0	3.8 (1.1–6.5)	0.0065	

CI, confidence interval; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration equation; SE, standard error; UACR, urine albumin-to-creatinine ratio.

[a]Data for patients with baseline data, on-treatment and data of approximately 30 days after treatment discontinuation, without open label sodium–glucose cotransporter inhibitor use between treatment discontinuation and follow-up measurement.

[b]Prevalent CKD defined as eGFR (CKD-EPI) <60 ml/min/1.73 m^2 or UACR >300 mg/g.

*Interaction test for prevalent CKD, trend test for eGFR and UACR subgroups.

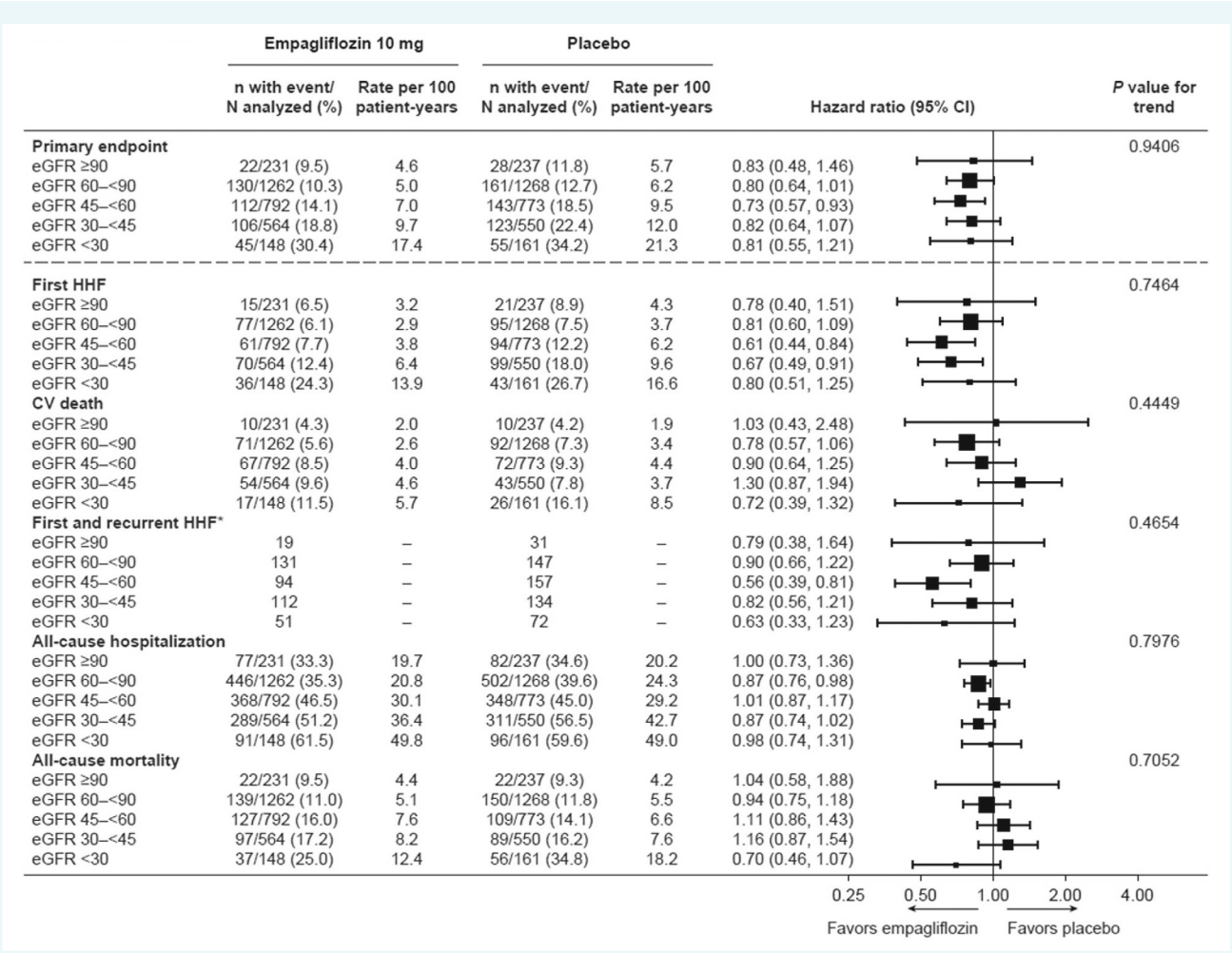

Figure 3 Primary and key secondary outcomes by estimated glomerular filtration rate (eGFR) categories. Data for randomized patients; hazard ratio and 95% confidence interval (CI) from Cox proportional-hazards model unless otherwise noted. CV, cardiovascular; HHF, hospitalization for heart failure. *Evaluated using a joint frailty model together with CV death.

Adverse events by chronic kidney disease status at baseline

Compared to those without CKD, patients with CKD were more likely to have adverse events including symptomatic hypotension (8.1% vs. 4.8%), hyperkalaemia (9.1% vs. 4.1%), volume depletion (14.4% vs. 9.0%), and urinary tract infection (11.0% vs. 8.6%) (% with event in CKD vs. without CKD within empagliflozin group; *Table 5*). However, empagliflozin appeared to be well-tolerated and frequencies of adverse events were similar between those randomized to empagliflozin versus placebo regardless of CKD status (*Table 5*).

Discussion

This pre-specified study of the EMPEROR-Preserved trial evaluated the effect of empagliflozin versus placebo in HF patients with prevalent CKD at baseline on the primary outcome, key secondary outcomes, and kidney outcomes. Our study has the following key findings: (i) empagliflozin reduced the risk of the primary composite outcome of cardiovascular death or hospitalization for HF, the key secondary outcome of total hospitalizations for HF, and of eGFR slope, in patients with and without CKD; (ii) the benefit across the primary and key secondary outcomes was consistent across the spectrum of eGFR; (iii) empagliflozin reduced the reporting of acute kidney injury and slowed progression to macroalbuminuria overall and across CKD and eGFR categories; and (iv) empagliflozin was well-tolerated in patients with and without CKD.

Overall, among patients with T2D, HF across the range of ejection fraction, CKD, and acute HF, SGLT2i have demonstrated broad clinical benefit.[1,14,22–25] These findings also extended to subgroups of those with CKD among patients with T2D[26] or in HF with reduced ejection fraction.[20,27] A pooled meta-analysis of the DAPA-HF (Dapagliflozin and Adverse Events in Chronic Heart Failure and a Reduced Ejection Fraction) and EMPEROR-Reduced trial have demonstrated efficacy of the empagliflozin dapagliflozin and empagliflozin to reduce the risk of the composite of cardiovascular death or first hospitalization for HF in patients with eGFR

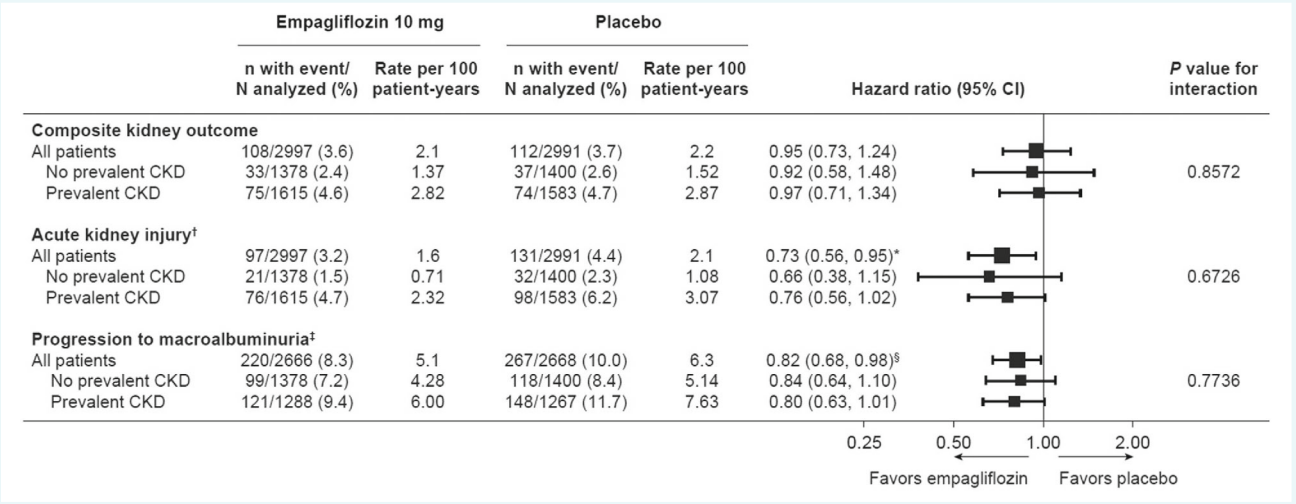

Figure 4 Kidney outcomes by chronic kidney disease (CKD) status at baseline. Data for randomized patients; hazard ratio and 95% confidence interval (CI) from Cox proportional-hazards model. Prevalent CKD defined as estimated glomerular filtration rate (eGFR) (CKD Epidemiology Collaboration equation) <60 ml/min/1.73 m^2 or urine albumin-to-creatinine ratio >300 mg/g. The composite kidney outcome was an exploratory endpoint that included chronic dialysis or kidney transplant or sustained reduction of ≥40% in eGFR or sustained eGFR <15 ml/min/1.73 m^2 (for patients with baseline eGFR ≥30) or sustained eGFR <10 (for patients with baseline eGFR <30). *$p = 0.0193$. †Acute kidney injury based on Medical Dictionary for Regulatory Activities (MedDRA) preferred term based on investigator-reported adverse events. ‡Urine albumin-to-creatinine ratio (UACR) >300 mg/g in patients with baseline UACR ≤300 mg/g. §$p = 0.0264$.

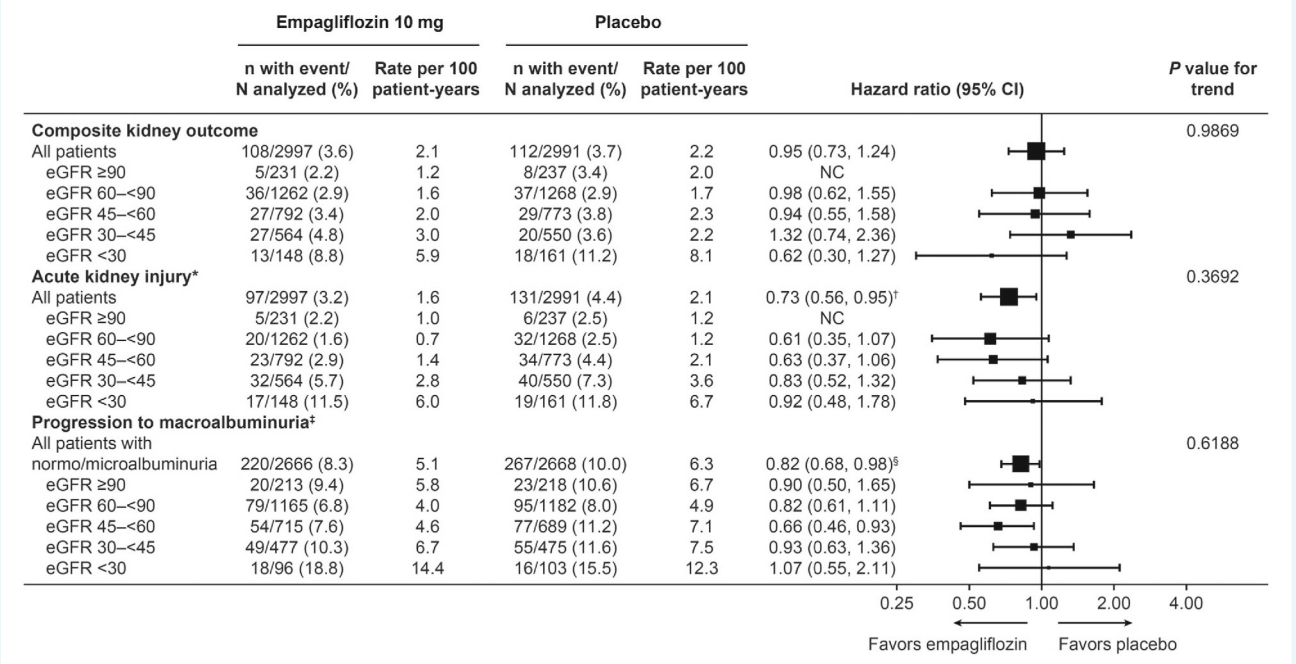

Figure 5 Kidney outcomes by estimated glomerular filtration rate (eGFR) categories. Data for randomized patients; hazard ratio and 95% confidence interval (CI) from Cox proportional-hazards model. The composite kidney outcome was an exploratory endpoint that included chronic dialysis or kidney transplant or sustained reduction of ≥40% in eGFR or sustained eGFR (Chronic Kidney Disease Epidemiology Collaboration equation) <15 ml/min/1.73 m^2 (for patients with baseline eGFR ≥30) or sustained eGFR <10 (for patients with baseline eGFR <30). NC: not calculated due to <14 patients with event in a subgroup category. *Acute kidney injury based on Medical Dictionary for Regulatory Activities (MedDRA) preferred term based on investigator-reported adverse events. †$p = 0.0193$. ‡Urine albumin-to-creatinine ratio (UACR) >300 mg/g in patients with baseline UACR ≤300 mg/g. §$p = 0.0264$.

Table 5 Adverse events by chronic kidney disease status at baseline

	Empagliflozin		Placebo	
	n/*N* (%)	Rate per 100 patient-years	*n*/*N* (%)	Rate per 100 patient-years
Any AE				
No prevalent CKD	1135/1378 (82.4)	113.17	1167/1400 (83.4)	125.03
Prevalent CKD	1436/1614 (89.0)	160.47	1411/1581 (89.2)	175.78
Serious AE				
No prevalent CKD	555/1378 (40.3)	26.54	612/1400 (43.7)	29.87
Prevalent CKD	879/1614 (54.5)	42.09	928/1581 (58.7)	49.52
AE leading to discontinuation of trial drug				
No prevalent CKD	210/1378 (15.2)	7.86	196/1400 (14.0)	7.24
Prevalent CKD	359/1614 (22.2)	12.24	353/1581 (22.3)	12.32
Symptomatic hypotension				
No prevalent CKD	66/1378 (4.8)	2.54	66/1400 (4.7)	2.50
Prevalent CKD	131/1614 (8.1)	4.64	90/1581 (5.7)	3.21
Hyperkalaemia				
No prevalent CKD	56/1378 (4.1)	2.14	56/1400 (4.0)	2.11
Prevalent CKD	130/1614 (8.1)	4.61	164/1581 (10.4)	6.08
Volume depletion				
No prevalent CKD	124/1378 (9.0)	4.92	113/1400 (8.1)	4.36
Prevalent CKD	232/1614 (14.4)	8.52	172/1581 (10.9)	6.35
Urinary tract infection				
No prevalent CKD	118/1378 (8.6)	4.62	87/1400 (6.2)	3.31
Prevalent CKD	178/1614 (11.0)	6.40	154/1581 (9.7)	5.64
Confirmed hypoglycaemia[a]				
No prevalent CKD	16/1378 (1.2)	0.60	26/1400 (1.9)	0.97
Prevalent CKD	57/1614 (3.5)	1.97	52/1581 (3.3)	1.84
Genital infection				
No prevalent CKD	34/1378 (2.5)	1.28	11/1400 (0.8)	0.41
Prevalent CKD	33/1614 (2.0)	1.13	11/1581 (0.7)	0.38
Bone fracture				
No prevalent CKD	56/1378 (4.1)	2.13	46/1400 (3.3)	1.72
Prevalent CKD	78/1614 (4.8)	2.71	79/1581 (5.0)	2.82

Data are AEs in the treated set of patients classified using MedDRA version 23.0. Prevalent CKD defined as eGFR (CKD-EPI) <60 ml/min/1.73 m^2 or UACR >300 mg/g.
AE, adverse event; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration equation; eGFR, estimated glomerular filtration rate; MedDRA, Medical Dictionary for Regulatory Activities; UACR, urine albumin-to-creatinine ratio.
[a]Plasma glucose ≤70 mg/dl or requiring assistance.

<60 ml/min/1.73 m^2 (HR 0.77, 95% CI 0.86–0.88) and those with eGFR ≥60 ml/min/1.73 m^2 (HR 0.72, 95% CI 0.62–0.82).[23] However, a detailed analysis of the benefit of empagliflozin across CKD populations in patients with HF and preserved ejection fraction, including evaluation of eGFR slopes, has not been conducted. The present findings further expand on the existing literature by demonstrating that among patients with HF with LVEF >40%, in those with and without CKD, empagliflozin reduces the risk of cardiovascular death or hospitalization for HF and reduces the decline in eGFR slopes.

Real-world registries clearly indicate an increase in the risk of cardiovascular outcomes in patients with HF and preserved ejection fraction associated with worse baseline eGFR.[16,17] Until recently, there were limited therapeutic options for patients with HF and preserved ejection fraction with reduced eGFR. The EMPEROR-Preserved trial recruited patients with eGFR as low as 20 ml/min/1.73 m^2 aligning with the EMPEROR-Reduced trial eGFR exclusion criteria.[11] The DAPA-HF trial excluded patients with eGFR <30 ml/min/1.73 m^2 while the DELIVER trial (Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure) excluded patients with eGFR <25 ml/min/1.73 m^2. The EMPEROR-Preserved trial had a similar proportion of patients with eGFR <60 ml/min/1.73 m^2 (50%) when compared to EMPEROR-Reduced (48%),[20] DAPA-HF (41%),[26] and DELIVER (49.9%).[27] The present results highlight the efficacy of empagliflozin in reducing the risk of the primary and key secondary outcomes across the spectrum of eGFR categories, even in those with baseline eGFR ranging from 20 to 30 ml/min/1.73 m^2. Given the large proportion of patients with reduced eGFR in those with HF and preserved ejection fraction, our results support a treatment strategy with empagliflozin in patients who would have limited therapeutic options.

The kidney-protective effects of SGLT2i have previously been shown in patients with T2D and CKD in the CREDENCE trial[9] and in patients irrespective of diabetic status in the DAPA-CKD[10] and EMPA-KIDNEY[28] trials. The EMPEROR-Preserved trial demonstrated that empagliflozin significantly reduced the rate of decline in eGFR – a pre-specified outcome that was explored within the hierarchical testing model for the trial – and slowed the progression to macroalbuminuria. Such results align with the data from previously published randomized trials of SGLT2i in patients with T2D[2] and HF.[20,26] However, empagliflozin did not reduce the risk of major renal outcomes in those with or without CKD, consistent with the findings from the overall trial. This is in contrast to the effect in EMPEROR-Reduced, whereby empagliflozin reduced the risk of major renal outcomes (which was defined in the same way in EMPEROR-Preserved) in patients with and without CKD (HR 0.53, 95% CI 0.31–0.91 with CKD and HR 0.46, 95% CI 0.22–0.99 without CKD).[20] There was a greater eGFR decline in participants without baseline CKD (*Figure 2*, *Table 3*), a finding noted also within the EMPEROR-Reduced trial. With lower baseline values for eGFR in patients with prevalent CKD, the magnitude of benefit on eGFR slope with empagliflozin was proportionally similar in patients with and without CKD. In EMPEROR-Preserved, there was no significant difference in the effect of empagliflozin versus placebo on the eGFR slope by prevalent baseline CKD. Whilst in both treatment arms, participants with higher baseline eGFR have larger absolute decline, loss in eGFR is likely to be more clinically meaningful in patients with CKD in whom even smaller decline in eGFR indicates more earlier progression towards ESKD. Overall, the incidence of renal events was relatively small and lower in EMPEROR-Preserved than EMPEROR-Reduced in patients with CKD (2.87 vs. 3.77 per 100 patient-years, respectively) and without CKD (1.52 vs. 2.27 per 100 patient-years, respectively). The manuscript evaluating data from EMPROR-Reduced identified a (nominally) significant treatment effect when evaluating baseline eGFR interaction for the effect of empagliflozin on eGFR slope. This was identified whether the analysis categorized patients by CKD or by five eGFR subgroups. However, these analyses are model-dependent and are based on absolute differences. Our analysis did not indicate a significant interaction of the treatment effect with baseline eGFR. The differences between the two trials may have arisen due to differences in trial inclusion criteria, duration of follow-up, comorbidity burden which may influence risk of progression of CKD, or chance (due to multiple hypothesis testing). Longer follow-up may have uncovered whether slowing both, the eGFR decline and progression to macroalbuminuria, would have translated into a difference in renal outcomes over time.

The proposed mechanisms of action of SGLT2i on glomerular function remain unclear. Potentially, the initial drop in eGFR with initiation of SGLT2i is related to the haemodynamic effect of diminishment of proximal nephron sodium reabsorption resulting in a restoration of tubuloglomerular feedback and a decrease in intraglomerular hydrostatic pressures.[29,30] However, animal models evaluating gene knock out of SGLT2 suggests that the haemodynamic effect may not be related to longer term renal protection.[31,32] Emerging evidence suggests that a critical determinant of injury in the diabetic kidney is through oxidative and endoplasmic reticulum stress; such stress impacts glomerular podocytes and renal tubules by dysregulating autophagy processes which increases susceptibility to injury.[33,34] SGLT2i may be able to reduce oxidative stress by inducing a state of nutrient and oxygen deprivation by increasing sirtuin-1 (SIRT1), AMP-activated protein kinase (AMPK), and hypoxia-inducible factors (HIF-1α and HIF-2α) which can exert renoprotective effects through the promotion of autophagic flux in addition to direct effects on sodium transport and inflammasome activation.[34–36] The impact of SGLT2i on albuminuria has been extensively described and may be related to a variety of mechanisms.[37,38] Animal models suggest that SGLT2i may reduce albuminuria through direct effects on the kidney; for instance, in diabetic mice, SGLT2i reduced albuminuria by ameliorating intraglomerular hypertension in addition to tubulointerstitial fibrosis, which are the major contributors to chronic kidney damage.[39–41] Whether such mechanisms are dominant among patients with HF and preserved ejection fraction warrants further exploration. The results of the DELIVER trial will provide further insights into the intersection of kidney outcomes with SGLT2i in HF with preserved ejection fraction populations.

Overall, the likelihood of serious adverse events was numerically lower in the EMPEROR-Preserved trial compared to the EMPEROR-Reduced trial as reflected by the placebo event rate of serious adverse events in patients with and without CKD (49.5 vs. 61.2 per 100 patient-years with CKD and 29.9 vs. 48.6 per 100 patient-years without CKD). Consistent with the result of the EMPEROR-Reduced trial, patients with CKD in EMPEROR-Preserved had a greater likelihood of adverse events compared to those without CKD. This likely represents a frail physiologic phenotype that increases the risk of adverse outcomes even among placebo-treated patients with CKD compared to those without CKD. Of note, in totality serious adverse events were lower in the empagliflozin-treated groups in both patients with and without CKD; furthermore, adverse events leading to drug discontinuation were balanced between treatment groups in those with and without CKD. And acute kidney injury was reported less frequently in the empagliflozin group, regardless of baseline CKD status. These results highlight the overall safety and tolerability of empagliflozin across the spectrum of HF.

Limitations

Several limitations of this analysis warrant noting. While this was a pre-specified analysis, the EMPEROR-Preserved trial was not powered to assess the effect of empagliflozin in subgroups such as CKD. In addition, the trial was not sufficiently powered to evaluate adverse renal outcomes across subgroups of patients with and without CKD, nor primary and key secondary outcomes in further CKD subgroups such as the five categories of eGFR. The definition of acute kidney injury was based on Medical Dictionary for Regulatory Activities (MedRA) coded reporting of investigator-reported adverse events and therefore may have some heterogeneity in reporting across trial sites. Our results must be kept within context that our statistical analysis plan had pre-specified that the slope of eGFR decline was analysed based on on-treatment data whereby

baseline and other off-treatment data were not included in the model.

Conclusion

In the EMPEROR-Preserved trial, empagliflozin reduced the key efficacy outcomes of time-to-first cardiovascular death or hospitalization HF, total (first and recurrent) HF hospitalizations, and slowed the rate of eGFR decline and the progression to macroalbuminuria, in patients with and without CKD. These results were consistent across a broad kidney function spectrum. These benefits on clinical outcomes in addition to the well-tolerated and consistent safety profile provide further evidence for the benefit of empagliflozin in patients with HF and preserved ejection fraction independent of CKD. These results are consistent across the broad spectrum of eGFR including those with severe kidney function impairment down to an eGFR of 20 ml/min/1.73 m^2. Further studies are needed to explore the potential reasons why limited benefit was observed with regard to the risk of renal outcomes in patients with or without CKD.

Supplementary Information

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

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