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# Early changes in estimated glomerular filtration rate post-initiation of empagliflozin in EMPEROR-Preserved

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## Aims

Renal function (estimated glomerular filtration rate [eGFR]) changes early after the introduction of empagliflozin have not been described in heart failure with preserved ejection fraction (HFpEF). The aim of this study was to describe early eGFR changes, assess its determinants and its clinical impact on cardiovascular and renal outcomes in patients with HFpEF enrolled in EMPEROR-Preserved.

## Methods and results

Estimated glomerular filtration rate changes (absolute and relative) from randomization to week 4 were calculated and landmark analyses performed. Initial eGFR change was available in 5836 patients (97.5% of the population). Empagliflozin induced a mean eGFR change of  $-3.2$  ml/min/1.73 m<sup>2</sup> versus placebo from baseline to week 4. After week 4, in the empagliflozin group, the risk of the primary outcome (composite of heart failure hospitalization or cardiovascular death), cardiovascular, all-cause mortality and sustained  $\geq 50\%$  eGFR decrease or end-stage renal disease (ESRD) did not differ by eGFR change levels. In contrast, in the placebo group, patients included in the tertile with most profound eGFR decrease (i.e.  $\geq 5.1\%$  from baseline) had a higher risk of the primary outcome (hazard ratio [HR] 1.46, 95% confidence interval [CI] 1.17–1.82), cardiovascular mortality (HR 1.38, 95% CI 1.01–1.89) and sustained  $\geq 50\%$  eGFR decrease or ESRD (HR 2.20, 95% CI 1.20–4.04) versus tertile with eGFR increase.

## Conclusion

An initial relatively small eGFR decrease may be expected after empagliflozin initiation. Such small eGFR decrease was not associated with adverse cardiovascular outcomes with empagliflozin. In contrast, eGFR decrease was associated with poor cardiovascular outcomes with placebo.

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## Graphical Abstract

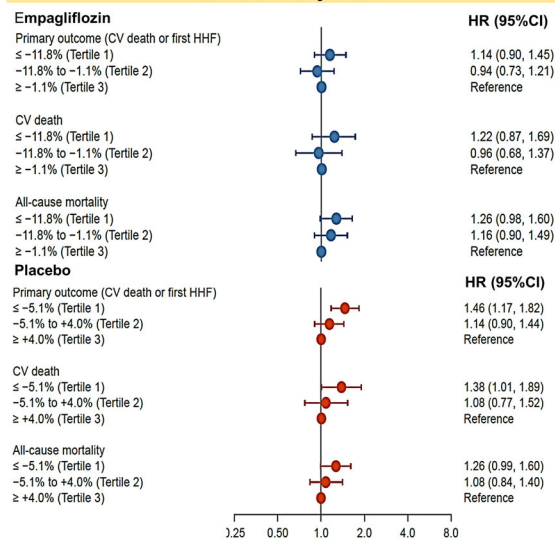
## Early changes in eGFR post-initiation of empagliflozin in patients with HFpEF

**Objective:** To describe early eGFR changes, assess its determinants and clinical impact in in patients with HFpEF

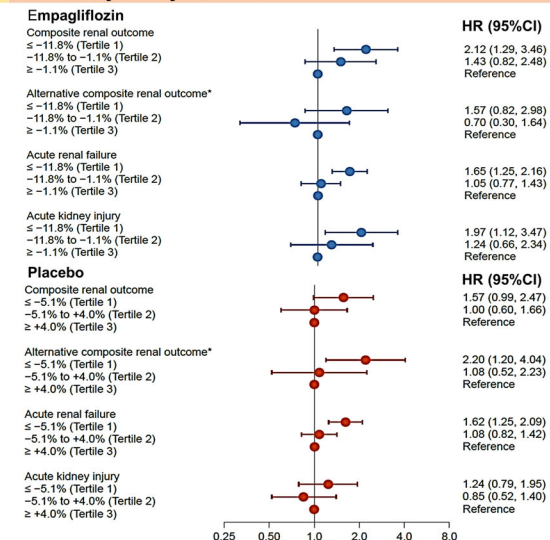
**Methods:** Patients with LVEF >40% & available %eGFR change from randomization to week 4 (N = 5836)  
% eGFR change categorized into tertiles in placebo and empagliflozin group  
Landmark analysis of Cardiovascular, mortality and kidney outcomes

**Results:** Placebo corrected mean initial eGFR change of -3.2 ml/min/1.73m<sup>2</sup> at week 4 with empagliflozin

## Association of initial % eGFR changes with cardiovascular and mortality outcome



## Association of initial % eGFR changes with kidney outcomes and kidney safety outcome



**Conclusion:** A small ( $\approx 3$  ml/min/1.73m<sup>2</sup>) eGFR decrease may be expected during the first month after initiation of empagliflozin compared to placebo. Such small eGFR decrease was not associated with adverse cardiovascular outcomes with empagliflozin. In contrast, eGFR decrease was associated with poor cardiovascular outcomes with placebo

Composite renal endpoint: need for chronic dialysis or renal transplant or a sustained  $\geq 40\%$  decrease in eGFR or a sustained eGFR  $< 15$  mL/min/1.73m<sup>2</sup> (if the baseline eGFR was  $\geq 30$  mL/min/1.73m<sup>2</sup>)  
\* Alternative composite renal end-point based on the definition of DAPA-HF trial: (i.e., a sustained decline in eGFR  $\geq 50\%$  from baseline, end-stage renal disease (defined as a sustained  $\geq 30$  days) eGFR of  $< 15$  mL/min/1.73m<sup>2</sup> or eGFR of  $< 10$  mL/min/1.73m<sup>2</sup> (if the baseline eGFR was  $< 30$  mL/min/1.73m<sup>2</sup>), sustained dialysis, or renal transplantation, or renal death)

Early changes in estimated glomerular filtration rate (eGFR) post-initiation of empagliflozin in patients with heart failure with preserved ejection fraction (HFpEF). CI, confidence interval; CV, cardiovascular; HHF, hospitalization for heart failure; HR, hazard ratio; LVEF, left ventricular ejection fraction.

## Keywords

Estimated glomerular filtration rate changes • Heart failure with preserved ejection fraction • Empagliflozin • Cardiovascular and renal outcomes

## Introduction

Sodium–glucose cotransporter 2 inhibitors (SGLT2i) reduce the risk of hospitalization for heart failure (HHF), and adverse cardiovascular events in patients with type 2 diabetes (T2D), chronic kidney disease (CKD) and heart failure (HF), irrespective of ejection fraction.<sup>1–7</sup> SGLT2i also reduce the decline in estimated glomerular filtration rate (eGFR) compared to placebo over several months to years of use, although an early and transient eGFR decrease (often referred as eGFR ‘dip’) is frequently found after SGLT2i initiation. Such early post-initiation eGFR decrease is reversible and likely related to the haemodynamic effects and changes in intraglomerular pressures induced by SGLT2i. It has not

been found to be associated with adverse outcomes in patients with T2D, CKD and HF with reduced ejection fraction (HFrEF).<sup>8–12</sup>

Patients with HF with preserved ejection fraction (HFpEF) are older, have more comorbidities (including CKD), and receive more medications than those with T2D or HFrEF.<sup>13,14</sup> Therefore, eGFR decrease with SGLT2i in HFpEF may be associated with a different risk than that found in T2D, CKD and HFrEF populations. Therefore, studying the determinants and clinical impact of early eGFR changes in HFpEF is clinically relevant.

In this study, we analysed the pattern and determinants of early eGFR changes according to randomized treatment, and the influence of eGFR changes on cardiovascular and renal outcomes

in patients with HFpEF enrolled in EMPEROR-Preserved.<sup>15,16</sup> The findings of EMPEROR-Preserved are compared with those of EMPEROR-Reduced.<sup>9</sup>

## Methods

The EMPEROR-Preserved trial was a randomized, double-blind, parallel-group, placebo-controlled and event-driven study, whose design has been described previously.<sup>7</sup> Briefly, in EMPEROR-Preserved, participants were men or women with chronic HF (New York Heart Association functional class II–IV) with a left ventricular ejection fraction >40% who had elevated N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels (>300 pg/ml for patients without atrial fibrillation, and >900 pg/ml for patients with atrial fibrillation).

The Ethics Committee of each centre approved the trial, and all patients gave written informed consent.

## Randomization

In EMPEROR-Preserved, patients were randomized double-blind (in a 1:1 ratio) to receive placebo or empagliflozin 10 mg daily, in addition to their usual therapy. Patients were periodically assessed at study visits for major outcomes, symptoms and functional capacity related to HF, initiation or discontinuation of new treatments, vital signs, and biomarkers (including creatinine), and adverse events.

All randomized patients were followed up for occurrence of any pre-specified outcomes for the entire duration of the trial, regardless of whether the study participants were taking their study medications or adhered to the scheduled visits. The median follow-up was 26.2 months.

## Trial endpoints

The primary endpoint was the composite of adjudicated cardiovascular death or HHF, analysed as time to first event. Cardiovascular death, all-cause mortality, and a composite renal endpoint, defined by the need for chronic dialysis or renal transplant or a sustained  $\geq 40\%$  decrease in eGFR or a sustained eGFR <15 ml/min/1.73 m<sup>2</sup> (if the baseline eGFR was  $\geq 30$  ml/min/1.73 m<sup>2</sup>) or <10 ml/min/1.73 m<sup>2</sup> (if the baseline eGFR was <30 ml/min/1.73 m<sup>2</sup>) were also analysed. Additionally, an alternative composite renal endpoint based on the definition of the DAPA-HF trial (i.e. a sustained decline in eGFR  $\geq 50\%$  from baseline, end-stage renal disease [ESRD, defined as a sustained  $\geq 30$  days – eGFR <15 ml/min/1.73 m<sup>2</sup>], or eGFR <10 ml/min/1.73 m<sup>2</sup> [if the baseline eGFR was <30 ml/min/1.73 m<sup>2</sup>], sustained dialysis, or renal transplantation, or renal death) was also analysed.<sup>4</sup> This definition has been used in recent analysis in EMPEROR-Preserved as the conventional definition because it aligns with other large trials assessing SGLT2i.<sup>17,18</sup>

The pre-specified safety assessed in this analysis focused on adverse events of special interest, defined following the Medical Dictionary for Regulatory Activities (MedDRA): acute kidney injury (based on the reporting of the preferred term ‘acute kidney injury’), and acute renal failure (based on the narrow Standardized MedDRA Query [SMQ] 20 000 003, ‘acute renal failure’, based on 19 preferred terms [MedDRA version 23.0]) obtained up until 7 days following discontinuation of the study medication.

## Statistical analysis

Patients who received at least one dose of the study drug and had eGFR values available both at randomization (last available measurement before first study drug intake) and week 4 (obtained on-treatment) were included in this analysis. The 4-week measurement was the first time point at which eGFR measurements were planned to be obtained following randomization. The percent (%) eGFR change in the early post-randomization period from randomization value to week 4 (eGFR at week 4 – eGFR at randomization)/eGFR at randomization\*100) was categorized into tertiles in each treatment group, separately. Patient baseline characteristics were then described by tertiles of % eGFR change within each treatment group. As the initial eGFR change was computed from randomization to week 4, we used landmark analyses (with landmark timepoint at week 4) to study the associations of % eGFR change at week 4 with subsequent outcomes. Thereby only patients without an event prior to the week 4 eGFR measurement and still at risk for the event of interest from that measurement onwards were included in the analysis of the respective endpoint. Cox proportional hazards models were used to calculate hazard ratios (HR) comparing the tertiles of initial % eGFR changes within each treatment group for each of the primary outcome, cardiovascular death, all-cause death, composite renal outcome and safety outcomes after adjusting for the factors from the primary analysis model, i.e. age, sex, baseline left ventricular ejection fraction, region, diabetes at baseline, eGFR at randomization. Additionally, these outcomes were analysed assessing treatment-by-eGFR changes interaction across the continuous spectrum of % eGFR change adjusting for the factors as for the primary analysis model. Sensitivity analyses to assess the risk associated with eGFR decreases >30% were also performed including an evaluation based on tertiles of initial % eGFR change based on pooled treatment groups. We estimated adjusted mean absolute eGFR change from randomization obtained on-treatment at various time points over follow-up by treatment group using a mixed model for repeated measures with an unstructured variance covariance matrix and adjustment for the pre-specified baseline variables age, sex, geographical region, diabetes, left ventricular ejection fraction, last projected visit based on dates of randomization and trial closure, visit according to treatment interaction and randomization eGFR according to visit interaction in all patients who received at least one dose of the study drug. Absolute eGFR changes from randomization were analysed within each treatment group to compare the tertiles of initial % eGFR changes. Among a subset of patients with available eGFR 30 days after treatment discontinuation we estimated the eGFR change from randomization to the last value on treatment, and after treatment discontinuation using an analysis of covariance with adjustment for the same baseline covariates including eGFR at randomization. These eGFR changes were further investigated within each treatment group to compare the tertiles of initial % eGFR changes. Equivalent models were also used to estimate changes in serum creatinine during follow-up. Finally, we assessed the consistency of the treatment effect on eGFR changes at week 4 across several baseline subgroups using a mixed model for repeated measures with adjustment for baseline age, sex, geographical region, diabetes and left ventricular ejection fraction, last projected visit based on dates of randomization and trial closure, subgroup-by-treatment-by-visit interaction, and randomization eGFR-by-visit interaction. A *p*-value of <0.05 was considered statistically significant. *P*-values and 95% confidence intervals (CI) presented in this report have not been adjusted for multiplicity. All analyses were performed using SAS, version 9.4 (SAS Institute, Cary, NC, USA).

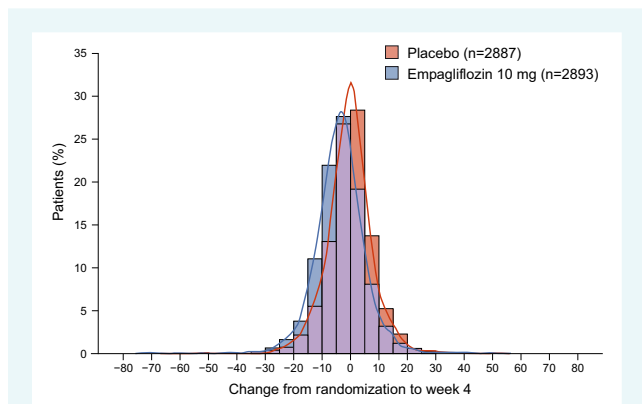
## Results

### Estimated glomerular filtration rate change post-initiation and baseline characteristics in EMPEROR-Preserved

The initial eGFR changes from randomization to on-treatment week 4 were available for 97.5% (5836/5988) patients enrolled in the EMPEROR-Preserved trial. Bidirectional eGFR changes occurred in both empagliflozin and placebo group at week 4 post-randomization, with a mean difference (a higher decrease) of  $-3.2$  (95% CI  $-3.6$  to  $-2.8$ ) ml/min/1.73 m<sup>2</sup> in the empagliflozin group compared to placebo (Figure 1).

The treatment effect of empagliflozin on early eGFR change (from randomization to week 4) differed according to eGFR at randomization, HHF within past 12 months and use of nitrates at baseline (Table 1). Specifically, lower baseline eGFR ( $<30$  ml/min/1.73 m<sup>2</sup>), previous HHF and nitrate use at baseline were associated with smaller placebo-corrected mean eGFR decrease compared to higher baseline eGFR (eGFR  $\geq 30$  ml/min/1.73 m<sup>2</sup>), no previous HHF and no nitrate use at baseline, respectively ( $p$ -trend: 0.005;  $p$ -interaction 0.05 and 0.04, respectively). Patients with lower eGFR at randomization had smaller absolute eGFR decrease at week 4 than patients with higher eGFR at randomization (online supplementary Tables S1–S3). Treatment effect on placebo-corrected eGFR change at week 4 was consistent across the diuretic use (online supplementary Table S3).

Percent eGFR changes (mean  $\pm$  standard error) from randomization to week 4 were  $-5.2 \pm 0.3\%$  in the empagliflozin group and  $+0.1 \pm 0.3\%$  in the placebo group. The tertiles of % eGFR change from randomization to week 4 in the empagliflozin group were: tertile 1 (T1)  $\leq -11.8\%$ ; tertile 2 (T2)  $\geq -11.8\%$  to  $-1.1\%$  and tertile 3 (T3)  $\geq -1.1\%$ . The tertiles for placebo group were: T1  $\leq -5.1\%$ ; T2  $\geq -5.1\%$  to  $4.0\%$ ; and T3  $\geq 4.0\%$ . The characteristics of the patients across tertiles of % eGFR change in the empagliflozin and placebo groups are presented in online supplementary Table S1.



**Figure 1** Distribution of individual estimated glomerular filtration rate (eGFR) change (ml/min/1.73 m<sup>2</sup>) from randomization to week 4 by treatment group. The mean difference in 4-week eGFR change with empagliflozin is  $-3.2$  ml/min/1.73 m<sup>2</sup>.

Overall, adjusted mean  $\pm$  standard error increase in serum creatinine was  $+0.075 \pm 0.004$  mg/dl in the empagliflozin group and  $+0.014 \pm 0.004$  mg/dl in the placebo group. The corresponding adjusted mean  $\pm$  standard error serum creatinine increases in T1 were  $+0.269 \pm 0.006$  mg/dl in the empagliflozin group and  $+0.180 \pm 0.004$  mg/dl in the placebo group (online supplementary Figure S1).

### Estimated glomerular filtration rate progression at week 4 and after

At week 4, patients randomized to empagliflozin had a mean eGFR change from randomization of  $-3.7$  (95% CI  $-4.0$  to  $-3.4$ ) ml/min/1.73 m<sup>2</sup> compared to  $-0.5$  (95% CI  $-0.8$  to  $-0.2$ ) ml/min/1.73 m<sup>2</sup> in patients randomized to placebo (Figure 2A, left panel). From week 12 (the following visit scheduled after week 4) onwards, eGFR decreased more slowly in empagliflozin-treated patients compared to the placebo group (Figure 2A, left panel).

In the empagliflozin group, patients who had eGFR decrease at week 4 (eGFR change T1  $\leq -11.8\%$  and T2  $\geq -11.8\%$  to  $-1.1\%$ ) had partial eGFR recovery at week 12 whereas, in patients who had eGFR change  $\geq -1.1\%$  at week 4 (T3), the eGFR slightly decreased at week 12 (regression to mean phenomenon). Thereafter, eGFR levels remained stable up to week 52 and then gradually decreased throughout the follow-up in all three tertiles (Figure 2B, left panel).

In the placebo group, in patients who had the largest eGFR decrease at week 4 (T1:  $\leq -5.1\%$  change), eGFR recovered marginally at week 12 and subsequently decreased in parallel to T2 and T3; in both the other tertiles, eGFR decreased continuously throughout the follow-up (Figure 2C, left panel).

### Association of % estimated glomerular filtration rate changes with subsequent cardiac and mortality outcomes in EMPEROR-Preserved

Patients randomized to the empagliflozin group who experienced greater eGFR decrease from randomization to week 4 (i.e. eGFR change T1  $\leq -11.8\%$ ; tertile 2 (T2)  $\geq -11.8\%$  to  $-1.1\%$ ) had a similar risk of the primary outcome, cardiovascular death and all-cause mortality (Figure 3A) as patients with smaller eGFR change (i.e. T3:  $\geq -1.1\%$ ). In the placebo group, patients with the steepest eGFR decrease (i.e. T1  $\leq -5.1\%$  decrease) had a higher risk of the primary outcome (HR 1.46, 95% CI 1.17–1.82) and cardiovascular death (HR 1.38, 95% CI 1.01–1.89), and a tendency towards increased risk of all-cause mortality (HR 1.26, 95% CI 0.99–1.60) as compared to patients with eGFR increase (i.e. T3:  $\geq 4.0\%$ ) (Figure 3B).

In a small subgroup of patients with  $>30\%$  initial eGFR decrease (96 patients in the empagliflozin group and 58 in the placebo group), the risk of the primary outcome was similar to that of patients who had initial eGFR decrease  $\leq 30\%$ , and was consistent across empagliflozin and placebo ( $p$ -interaction = 0.98).

By overall tertiles of the cohort, patients with an eGFR decrease had a similar risk of the primary outcome, cardiovascular death and all-cause mortality compared to patients with eGFR

**Table 1** Effect of empagliflozin on estimated glomerular filtration rate change from randomization to week 4 (ml/min/1.73 m<sup>2</sup>) across baseline subgroups

Variable	Patients (n analysed)	Adjusted mean absolute change in eGFR Empagliflozin vs. placebo (95% CI)	Interaction p-value
Overall mean difference	5780	-3.2 (-3.6, -2.6)	-
Age (years)			
<65	1153	-2.8 (-3.7, -1.8)	0.36
65 to <75	2155	-3.6 (-4.3, -2.9)	
≥75	2472	-3.0 (-3.7, -2.4)	
Sex			0.77
Male	3201	-3.2 (-3.8, -2.7)	
Female	2579	-3.1 (-3.7, -2.5)	
BMI (kg/m <sup>2</sup> )			0.70
<25	1253	-2.9 (-3.8, -2.0)	
25 to <30	1916	-3.4 (-4.1, -2.6)	
≥30	2611	-3.2 (-3.8, -2.6)	
Race			0.54
White	4386	-3.0 (-3.5, -2.5)	
Black/ African-American	245	-3.0 (-5.0, -0.9)	
Asian	802	-3.8 (-4.9, -2.6)	
Other including mixed race	346	-3.9 (-5.6, -2.2)	
Region			0.47
North America	686	-2.5 (-3.8, -1.3)	
Latin America	1460	-3.6 (-4.4, -2.7)	
Europe	2599	-3.1 (-3.7, -2.4)	
Asia	672	-3.8 (-5.1, -2.6)	
Other	363	-2.5 (-4.2, -0.8)	
LVEF (%)			0.82
<50	1905	-3.2 (-4.0, -2.5)	
50 to <60	1983	-3.0 (-3.7, -2.3)	
≥60	1892	-3.3 (-4.1, -2.6)	
NYHA functional class			0.38
II	4731	-3.1 (-3.6, -2.6)	
III/IV	1045	-3.6 (-4.6, -2.6)	
NT-proBNP <sup>a</sup>			0.44
<T1	1932	-3.4 (-4.1, -2.6)	
≥T1 and <T2	1927	-3.4 (-4.1, -2.6)	
≥T2	1912	-2.8 (-3.5, -2.1)	
Cause of HF			0.29
Ischaemic	2050	-2.9 (-3.6, -2.2)	
Non-ischaemic	3729	-3.3 (-3.9, -2.8)	
Time since diagnosis of HF (years)			0.74
≤1	1460	-2.9 (-3.7, -2.0)	
>1 to 5	2607	-3.3 (-3.9, -2.7)	
>5 to 10	1057	-3.5 (-4.5, -2.5)	
>10	656	-2.8 (-4.1, -1.6)	
Heart rate (bpm)			0.47
≤70	3187	-3.3 (-3.9, -2.8)	
>70	2593	-3.0 (-3.6, -2.4)	
History of AF			0.33
No	2739	-3.4 (-4.0, -2.8)	
Yes	3033	-3.0 (-3.6, -2.4)	
History of hypertension			0.91
No	538	-3.1 (-4.5, -1.7)	
Yes	5242	-3.2 (-3.6, -2.7)	

**Table 1 (Continued)**

Variable	Patients (n analysed)	Adjusted mean absolute change in eGFR Empagliflozin vs. placebo (95% CI)	Interaction p-value
HHF within past 12 months			<b>0.0459</b>
No	4471	-3.4 (-3.9, -2.9)	
Yes	1309	-2.4 (-3.3, -1.5)	
Diabetes			0.18
No	2949	-2.9 (-3.5, -2.3)	
Yes	2831	-3.5 (-4.1, -2.9)	
Smoking status			0.51
Never smoked	3031	-3.0 (-3.6, -2.4)	
Ex-smoker	2331	-3.3 (-4.0, -2.7)	
Currently smoker	415	-3.9 (-5.5, -2.3)	
eGFR (ml/min/1.73 m <sup>2</sup> )			<b>0.0016</b> (0.0051 for trend)
≥60	2874	-3.5 (-4.1, -2.9)	
45 to <60	1508	-3.3 (-4.2, -2.5)	
30 to <45	1073	-3.1 (-4.0, -2.1)	
<30	325	0.2 (-1.6, 2.0)	
UACR (mg/g)			0.91
<30	3367	-3.2 (-3.7, -2.6)	
30 to ≤300	1786	-3.2 (-3.9, -2.4)	
>300	604	-3.5 (-4.8, -2.2)	
Anaemia			>0.99
Yes	1239	-3.2 (-4.1, -2.3)	
No	4541	-3.2 (-3.6, -2.7)	
ACEi/ARB use			0.42
No	1230	-2.8 (-3.8, -1.9)	
Yes	4550	-3.3 (-3.7, -2.8)	
ACEi/ARB/ARNi use			0.17
No	1112	-2.6 (-3.5, -1.6)	
Yes	4668	-3.3 (-3.8, -2.9)	
Beta-blocker use			0.61
No		-2.9 (-4.0, -1.8)	
Yes	4991	-3.2 (-3.7, -2.8)	
Thiazide or low ceiling-diuretic use			0.53
No	4576	-3.1 (-3.6, -2.6)	
Yes	1204	-3.4 (-4.4, -2.5)	
MRA use			0.68
No	3608	-3.1 (-3.7, -2.6)	
Yes	2172	-3.3 (-4.0, -2.6)	
Cardiac glycoside use			0.76
No	5240	-3.2 (-3.6, -2.8)	
Yes	540	-3.0 (-4.4, -1.6)	
Loop or high-ceiling diuretic use			0.15
No	1868	-3.6 (-4.4, -2.9)	
Yes	3912	-3.0 (-3.5, -2.5)	
Loop or high-ceiling diuretic dose			0.28
Low	2955	-2.8 (-3.4, -2.2)	
Medium	550	-3.3 (-4.7, -1.9)	
High	313	-2.8 (-4.6, -1.0)	
CCB use			0.43
No	4013	-3.1 (-3.6, -2.6)	
Yes	1767	-3.4 (-4.2, -2.7)	

**Table 1 (Continued)**

Variable	Patients (n analysed)	Adjusted mean absolute change in eGFR Empagliflozin vs. placebo (95% CI)	Interaction p-value
Nitrate use			<b>0.0422</b>
No	5063	−3.3 (−3.8, −2.9)	
Yes	717	−2.0 (−3.2, −0.8)	
Ivabradine use			0.90
No	5711	−3.2 (−3.6, −2.8)	
Yes	69	−2.9 (−6.8, 1.0)	
Statin use			0.62
No	1784	−3.0 (−3.8, −2.3)	
Yes	3996	−3.3 (−3.8, −2.8)	
Anti-platelet use			0.39
No	3040	−3.4 (−3.9, −2.8)	
Yes	2740	−3.0 (−3.6, −2.4)	
Anti-coagulant use			0.75
No	2966	−3.1 (−3.7, −2.5)	
Yes	2814	−3.2 (−3.9, −2.6)	

Note: Bold values represent statistically significant interaction p-value ( $p < 0.05$ ).

The numbers represent the difference in adjusted mean changes from baseline in the eGFR between empagliflozin versus placebo.

ACEi, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor–neprilysin inhibitor; BMI, body mass index; CCB, calcium channel blocker; CI, confidence interval; eGFR, estimated glomerular filtration rate; HF, heart failure; HHF, hospitalization for heart failure; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; UACR, urine albumin to creatinine ratio.

On-treatment data were analysed with the use of a mixed model for repeated measures that included age and baseline LVEF as linear covariate and sex, region, baseline diabetes status, last projected visit based on dates of randomization and trial closure, randomization eGFR according to visit and subgroup-by-visit-by-treatment interaction as fixed effects.

<sup>a</sup>NT-proBNP tertiles for patients with history of AF or atrial flutter T1: 1006 (pg/ml), T2: 1778 (pg/ml); NT-proBNP tertiles for patients without history of AF or atrial flutter T1: 442 (pg/ml), T2: 889 (pg/ml).

increase  $\geq 1.8\%$  in both empagliflozin and placebo groups (online supplementary Figure S2).

### Association of % estimated glomerular filtration rate changes with subsequent kidney outcomes and safety outcomes within each treatment group in EMPEROR-Preserved

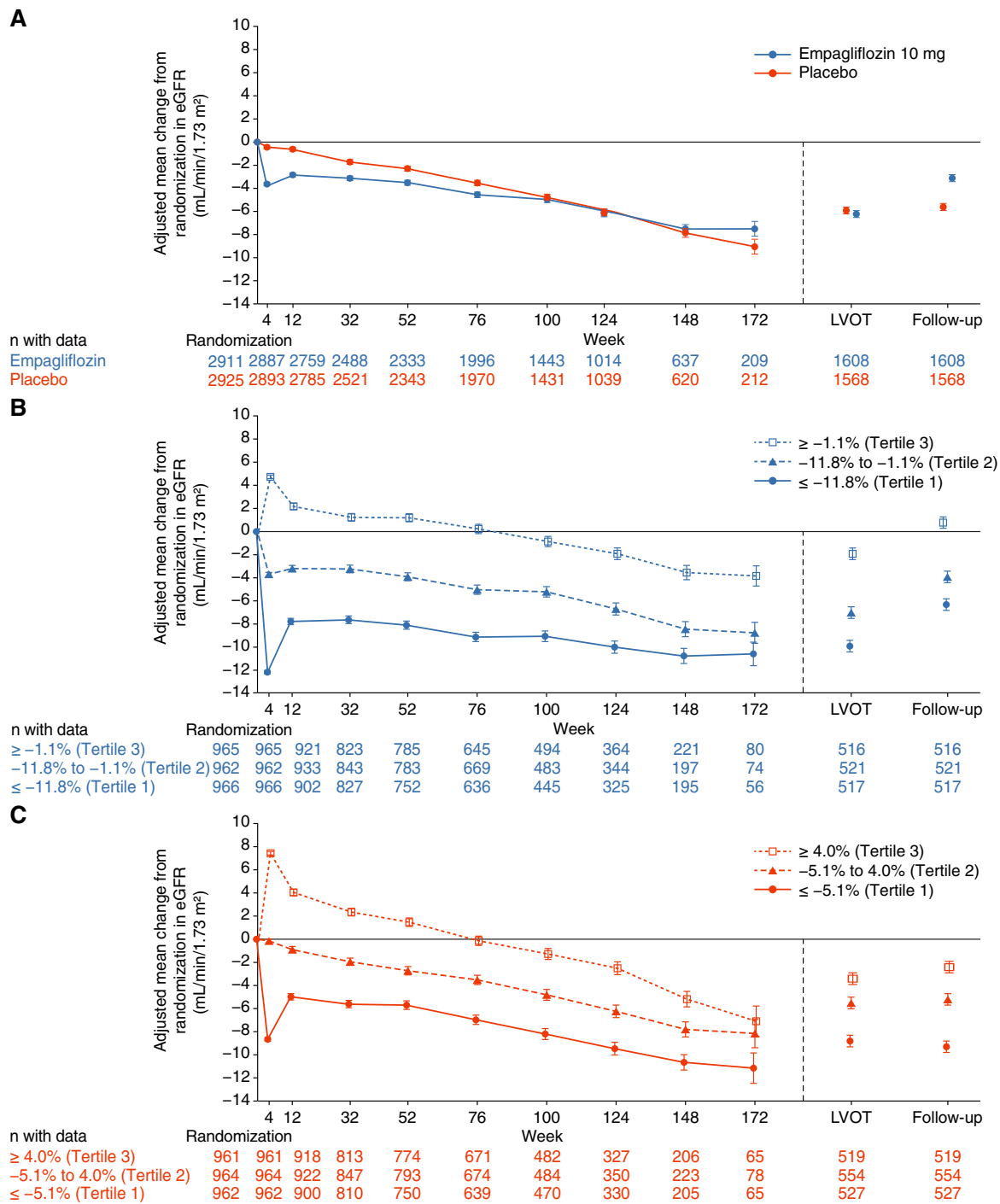
In the empagliflozin group, patients with steepest decrease in eGFR (i.e. T1  $\leq -11.8\%$ ) experienced an increased risk of the composite renal outcome incorporating a  $\geq 40\%$  sustained eGFR decline from baseline in the definition (HR 2.12, 95% CI 1.29–3.46), but presented a similar risk of alternative renal outcome using a  $\geq 50\%$  sustained eGFR decline from baseline in the definition (HR 1.57, 95% CI 0.82–2.98) (Figure 4A). In contrast, in the placebo group, patients with steeper eGFR decrease had similar risk of the composite renal outcome incorporating a  $\geq 40\%$  sustained eGFR decline from baseline but higher risk of experiencing alternative renal outcome using a  $\geq 50\%$  sustained eGFR decline from baseline in the definition (Figure 4B). Investigator-reported renal safety outcomes are also presented in Figure 4 and online supplementary Figure S3.

In the small subgroup of patients with an eGFR decrease  $> 30\%$ , 9 (10%) patients in the empagliflozin group and 3 (5.2%) patients in the placebo group had composite renal outcome (online supplementary Figure S3). The effects of empagliflozin compared to placebo across the spectrum of continuous % eGFR early changes are presented in online supplementary Figure S4. The risk for the kidney endpoints decreased in the range of 2–4% across both treatment groups per 1-unit higher in eGFR (ml/min/1.73 m<sup>2</sup>) at randomization (online supplementary Table S4).<sup>24</sup>

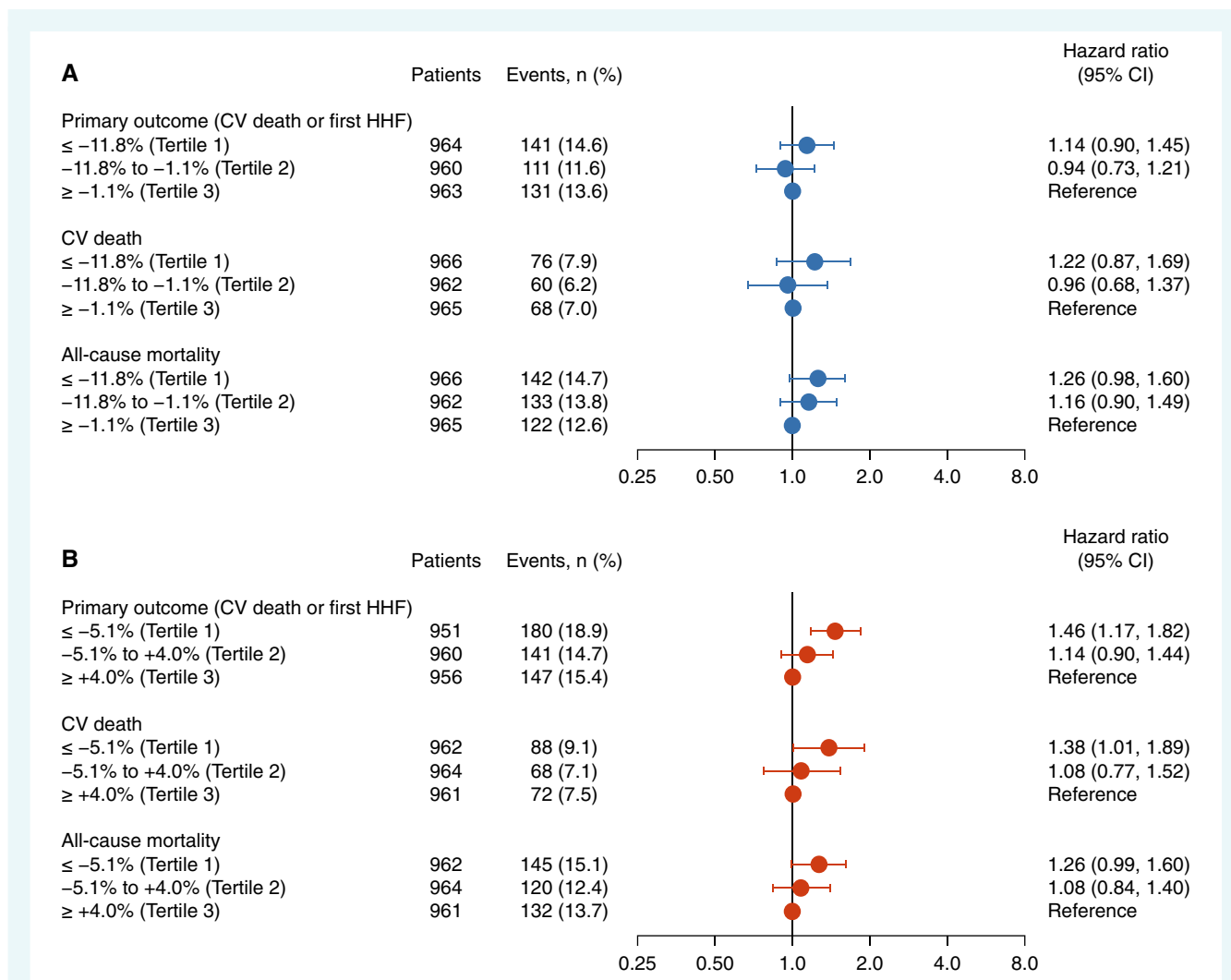
### Discussion

In this study, we observed that mild early (from randomization to week 4) eGFR changes were common in both treatment groups. Among patients who experienced a more profound decrease in eGFR (i.e.  $\leq -11.8\%$ ) post-empagliflozin initiation, no increase in the risk of the primary outcome, HHF, mortality or alternative renal composite outcome (with sustained decline in eGFR  $\geq 50\%$  from baseline or ESRD) was observed compared to patients with smaller eGFR changes (i.e.  $\geq -1.1\%$ ). In contrast, in the placebo group, an initial eGFR decrease ( $\leq -5.1\%$  change) was associated with increased risk of cardiovascular and renal outcomes, and mortality compared to patients with an eGFR increase  $\geq 4.0\%$  (Graphical Abstract).





**Figure 2** Change in estimated glomerular filtration rate (eGFR) from randomization (A) by treatment group; (B) by tertiles of % eGFR change at week 4 within the empagliflozin group; (C) by tertiles of % eGFR change at week 4 within the placebo group. Left side: on-treatment data were analysed with the use of a mixed model for repeated measures based on patients who received at least one dose of a study drug and had a baseline and post-baseline measurement (A) and a week 4 measurement (B,C). Right side: the last value on treatment (LVOT) and follow-up change from randomization are based on an analysis of a covariance model in patients who underwent measurements at baseline, LVOT and follow-up (A) and week 4 (B,C). Empagliflozin: Tertile 1 ≤ -11.8%; Tertile 2 ≥ -11.8% to ≤ -1.1% and Tertile 3 ≥ -1.1%. Placebo: Tertile 1 ≤ -5.1%; Tertile 2 ≥ -5.1% to ≤ +4.0%; and Tertile 3 ≥ +4.0%.

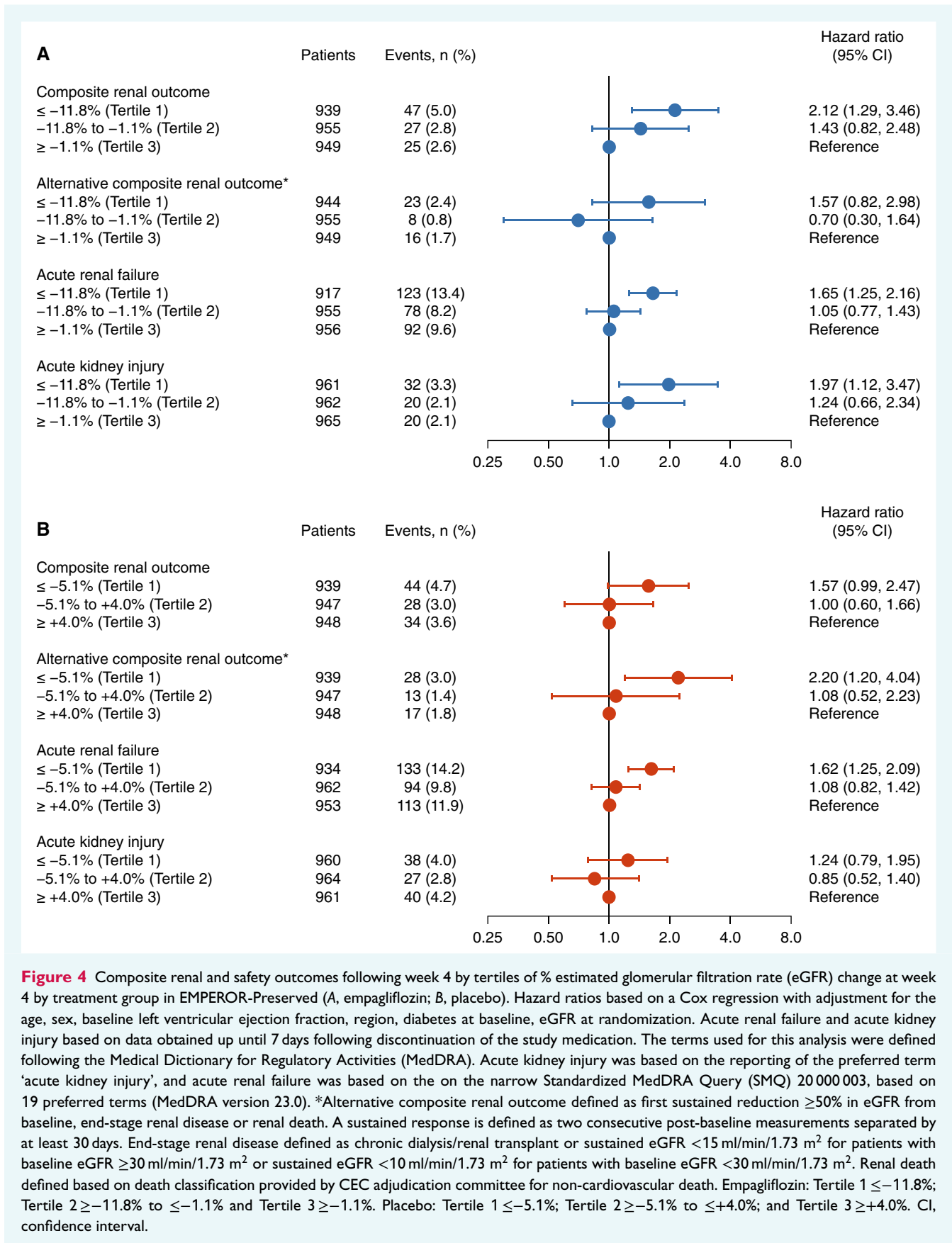


**Figure 3** Primary, cardiovascular (CV) and mortality outcomes following week 4 by tertiles of % estimated glomerular filtration rate (eGFR) change at week 4 by treatment group in EMPEROR-Preserved (A, empagliflozin; B, placebo). Hazard ratios based on a Cox regression model with adjustment for age, sex, baseline left ventricular ejection fraction, region, diabetes at baseline, eGFR at randomization. EMPEROR-Preserved: Tertile 1 ≤-8.8; Tertile 2 ≥-8.8% to ≤+1.8% and Tertile 3 ≥+1.8%. CI, confidence interval; HHF, hospitalization for heart failure.

The magnitude and pattern of initial eGFR changes (at 4 weeks) seen in EMPEROR-Preserved were similar to the findings in EMPEROR-Reduced<sup>9</sup>; the variation in the eGFR changes followed a nearly normal distribution and patients randomized to empagliflozin had a higher mean eGFR decrease post-initiation compared to placebo (absolute placebo corrected mean change -3.2 and -2.5 ml/min/1.73 m<sup>2</sup> in EMPEROR-Preserved and EMPEROR-Reduced, respectively) which recovered partially over the next few weeks. Similar to the findings of EMPEROR-Reduced, moderate to large initial eGFR decrease (T1 ≤-11.8% and T2 ≥-11.8% to ≤-1.1% change) with empagliflozin treatment did not adversely affect cardiovascular or mortality outcomes in HFpEF.<sup>9</sup>

An initial eGFR decrease of ≥11.8% after SGLT2i initiation was not associated with higher risk of poor renal outcome with sustained ≥50% eGFR decrease – a conventional definition

used in a previous meta-analysis of EMPEROR-Reduced and DAPA-HF<sup>19</sup> and post hoc analysis of EMPEROR trials.<sup>17,18</sup> In contrast, a high risk of cardiovascular, renal and mortality outcomes was observed among patients with eGFR decrease (≤-5.1%) in the placebo group. The increase in mean serum creatinine observed in patients with steep eGFR decreases in EMPEROR-Preserved (+0.27 ± 0.01 mg/dl) was quantitatively similar to serum creatinine increases observed in DAPA-HF (0.21 ± 0.16 mg/dl) and EMPEROR-Reduced (0.29 ± 0.21 mg/dl).<sup>8,9</sup> It should be noted that an increase of ≥0.3 mg/dl in serum creatinine on patient level is one of the criteria for defining acute kidney injury/worsening renal function in clinical settings and research. A mean serum creatinine increase with empagliflozin may have contributed towards the number of acute kidney injury events reported. However, this increase in serum creatinine after SGLT2i initiation is most likely subsequent to haemodynamic changes<sup>20,21</sup> and not irreversible



**Figure 4** Composite renal and safety outcomes following week 4 by tertiles of % estimated glomerular filtration rate (eGFR) change at week 4 by treatment group in EMPEROR-Preserved (A, empagliflozin; B, placebo). Hazard ratios based on a Cox regression with adjustment for the age, sex, baseline left ventricular ejection fraction, region, diabetes at baseline, eGFR at randomization. Acute renal failure and acute kidney injury based on data obtained up until 7 days following discontinuation of the study medication. The terms used for this analysis were defined following the Medical Dictionary for Regulatory Activities (MedDRA). Acute kidney injury was based on the reporting of the preferred term 'acute kidney injury', and acute renal failure was based on the on the narrow Standardized MedDRA Query (SMQ) 20 000 003, based on 19 preferred terms (MedDRA version 23.0). \*Alternative composite renal outcome defined as first sustained reduction  $\geq 50\%$  in eGFR from baseline, end-stage renal disease or renal death. A sustained response is defined as two consecutive post-baseline measurements separated by at least 30 days. End-stage renal disease defined as chronic dialysis/renal transplant or sustained eGFR  $< 15$  ml/min/1.73 m<sup>2</sup> for patients with baseline eGFR  $\geq 30$  ml/min/1.73 m<sup>2</sup> or sustained eGFR  $< 10$  ml/min/1.73 m<sup>2</sup> for patients with baseline eGFR  $< 30$  ml/min/1.73 m<sup>2</sup>. Renal death defined based on death classification provided by CEC adjudication committee for non-cardiovascular death. Empagliflozin: Tertile 1  $\leq -11.8\%$ ; Tertile 2  $\geq -11.8\%$  to  $\leq -1.1\%$  and Tertile 3  $\geq -1.1\%$ . Placebo: Tertile 1  $\leq -5.1\%$ ; Tertile 2  $\geq -5.1\%$  to  $\leq +4.0\%$ ; and Tertile 3  $\geq +4.0\%$ . CI, confidence interval.

kidney injury.<sup>22</sup> We are of opinion that systematic monitoring of eGFR may not be necessary after 4 weeks of SGLT2i. Clinicians may monitor eGFR as per their standard monitoring protocols for renal function in HFpEF.

We observed that the absolute placebo-corrected eGFR changes in empagliflozin remains approximately 3 ml/min/1.73 m<sup>2</sup> in patients receiving concomitant medications such as angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, diuretics and mineralocorticoid receptor antagonists, suggesting the concomitant initiation of empagliflozin on top of these commonly used cardiovascular drugs does not induce additional eGFR decline. A previously published DAPA-HF report suggested that diabetes was associated with larger early eGFR decrease (*p*-interaction = 0.004).<sup>8</sup> Although the renoprotective effects of SGLT2i might differ by diabetes status,<sup>23</sup> the early placebo-corrected eGFR decrease with empagliflozin was similar in HF patients regardless of the presence of diabetes in both EMPEROR-Reduced and EMPEROR-Preserved trials.

However, lower baseline eGFR and previous history of HHF were associated with a lower risk of steeper eGFR decrease with empagliflozin. Similar findings were observed in a post-hoc analysis of EMPEROR-Reduced and CREDENCE where previous HHF were associated with lower likelihood of eGFR decrease with SGLT2i.<sup>9,10</sup> Importantly, the placebo-corrected absolute eGFR change was minimal (0.2, 95% CI -1.6 to +2.0 change) in patients with low renal function reserve (eGFR <30ml/min/1.73m<sup>2</sup>). These results are in line with the results of a post-hoc analysis of DAPA-CKD, where patients with more advanced CKD had a smaller eGFR dip after 2 weeks of dapagliflozin initiation.<sup>24</sup> Yet, advanced CKD did not adversely impact outcomes in patients receiving empagliflozin.<sup>25</sup> The most likely explanation of minimal eGFR dip is non-activation of tubuloglomerular feedback in advanced CKD after SGLT2i. Because in advanced CKD, the total solute load filtering through the glomerulus is smaller compared to normal or diabetic kidneys.<sup>26</sup> Hence, the SGLT2i induced small increase in sodium reaching macula densa does not activate tubuloglomerular feedback and a smaller response on eGFR decrease.<sup>26</sup> Moreover, in advanced CKD, several pathologies such as intrarenal arterial stiffening and arteriosclerosis may cause loss of autoregulation in glomerular arterioles causing attenuation of tubuloglomerular feedback.<sup>27</sup> Overall, these findings suggest that low baseline renal function is not associated with steep eGFR decrease and should not be considered as a contraindication for SGLT2i as they continue to provide cardiovascular benefits in these patients.

## Limitations

Our study has some limitations. First, this is a secondary analysis of a randomized trial that explores the association of initial eGFR decrease in each treatment arm with outcomes. We conducted within-treatment group analysis. Hence, comparison of tertiles of the empagliflozin group with that of the placebo group was not possible. Second, baseline characteristics of the patients across the tertiles of % eGFR changes within each treatment group were significantly different. Hence, patients within certain categories of % eGFR changes are not comparable within each treatment group

and between empagliflozin and placebo in terms of their baseline characteristics. Therefore, these findings should be regarded as hypothesis-generating. Third, we do not know if eGFR changes at week 4 were associated with study drug discontinuation. Lastly, as occurrence of eGFR decreases of >30% was uncommon in both treatments, also outcomes were very rare, therefore comparisons made with this group should be interpreted with caution.

## Conclusion

In HFpEF, an initial relatively small and not clinically meaningful eGFR decrease ( $\approx 3$  ml/min/1.73 m<sup>2</sup>) may be expected after empagliflozin initiation. Such small eGFR decrease was not associated with adverse cardiovascular outcomes with empagliflozin. In contrast, eGFR decrease was associated with poor cardiovascular outcomes with placebo.

## Supplementary Information

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

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