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1 **Cardiac and Kidney Benefits of Empagliflozin in Heart Failure Across the**
2 **Spectrum of Kidney Function: Insights from the EMPEROR-Preserved Trial**

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4
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1 **Abstract:**

2

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

7

8 Methods: Patients were categorized by the presence or absence of chronic kidney disease (CKD)
9 at baseline (CKD defined by an estimated glomerular filtration rate [eGFR] $<60\text{ml}/\text{min}/1.73\text{m}^2$ or
10 urine albumin to creatinine ratio [UACR] $>300\text{mg}/\text{g}$). The primary and key secondary outcomes
11 were (1) a composite of cardiovascular death or first HF hospitalization (primary outcome); (2)
12 total number of HF hospitalization, (3) eGFR slope; and a prespecified exploratory composite
13 kidney outcome including a sustained $\geq 40\%$ decline in eGFR, chronic dialysis or renal
14 transplant. The median follow-up was 26.2 months.

15

16 Results: 5,988 patients were randomized to empagliflozin or placebo, of whom 3,198 (53.5%)
17 had CKD. Irrespective of CKD status, empagliflozin reduced the primary outcome (with CKD
18 HR 0.80 [95% CI 0.69, 0.94], and without CKD HR 0.75 [95% CI 0.60 0.95], interaction
19 $P=0.67$) and total (first and recurrent) hospitalizations for HF (with CKD 0.68, [95% CI 0.54,
20 0.86], and without CKD 0.89 [95% CI 0.66, 1.21], interaction $P=0.17$). Empagliflozin slowed the
21 slope of eGFR decline by 1.43 (1.01, 1.85) $\text{ml}/\text{min}/1.73\text{m}^2/\text{year}$ in patients with CKD and 1.31
22 (0.88, 1.74) $\text{ml}/\text{min}/1.73\text{m}^2/\text{year}$ without CKD (interaction $P=0.70$). Empagliflozin did not
23 reduce the pre-specified kidney outcome in patients with or without CKD (with CKD HR 0.97

1 [95% CI 0.71,1.34]; without CKD HR 0.92 [0.58, 1.48], interaction P=0.86) but slowed
2 progression to macroalbuminuria and reduced the risk of acute kidney injury. The effect of
3 empagliflozin on the primary composite outcome and the key secondary outcomes was
4 consistent across 5 baseline eGFR categories (all interaction p-value > 0.05). Empagliflozin was
5 well tolerated independent of CKD status.

6
7 Conclusions: In EMPEROR-Preserved, empagliflozin had a beneficial effect on the key efficacy
8 outcomes in patients with and without CKD. Overall, the benefit and safety of empagliflozin was
9 consistent across a wide range of kidney function spectrum, down to a baseline eGFR of 20
10 ml/min/1.73m².

11
12 Keywords: empagliflozin, glomerular filtration rate, heart failure, renal insufficiency, chronic
13

1 **Introduction**

2

3 Randomized trials have shown that sodium glucose cotransporter -2 inhibitors (SGLT2i) prevent
4 hospitalizations for heart failure (HF) and slow the decline of renal function in patients with type
5 II diabetes (T2D)¹⁻⁸, chronic kidney disease (CKD)^{9,10}, and HF with reduced ejection
6 fraction.^{11,12}

7 While pharmacologic therapies to improve cardiovascular outcomes have been demonstrated
8 across multiple therapeutic classes in patients with HF and reduced ejection fraction, there has
9 been few therapeutic options for those with a preserved ejection fraction.¹³ Recently, in the

10 EMPEROR-Preserved (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with
11 Preserved Ejection Fraction) trial, empagliflozin versus placebo reduced the composite of
12 cardiovascular death or HF hospitalization and total (first and recurrent) hospitalizations for HF,
13 and slowed the progressive decline in kidney function.¹⁴ For the first time, a therapeutic option is
14 now available for patients with HF and preserved ejection fraction.

15

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

1
2 Within EMPEROR-Preserved, patients with an eGFR as low as 20 ml/min/1.73m² were eligible
3 for enrollment; as more than half of the patients had prevalent CKD at baseline, a robust
4 assessment could be conducted regarding the efficacy and safety of empagliflozin on cardiac and
5 kidney outcomes according to the presence of CKD and across a wide range of baseline kidney
6 function. The present analysis reports the prespecified analysis of EMPEROR-Preserved on
7 cardiovascular and kidney outcomes among patients with and without CKD.

8
9 **Methods**

10
11 The design and rationale of the EMPEROR-Preserved trial have been previously published.^{14,21}
12 To summarize, EMPEROR-Preserved was a double-blind placebo-controlled trial that
13 randomized 5,988 patients with symptomatic HF (New York Heart Association [NYHA] of 2 or
14 greater) and a left ventricular ejection fraction (LVEF) of more than 40% to receive
15 empagliflozin (10 mg orally once per day) or matching placebo.
16
17 Randomization was performed with a permuted block design and was stratified by geographic
18 region, diabetes status, estimated glomerular filtration rate (eGFR) of less than 60 ml or 60 ml or
19 more per minute per 1.73 m², and a LVEF of less than 50% or \geq 50% (all measured at
20 screening). The primary outcome and the first two secondary outcomes were included in a
21 hierarchical testing procedure. The primary outcome was analyzed as the time to the first event
22 of the composite of adjudicated cardiovascular death or hospitalization for HF. The first
23 secondary outcome was the occurrence of all adjudicated hospitalizations for HF, including first
24 and recurrent events. The second secondary outcome was the rate of decline in the eGFR during
25 double blind treatment. In the main trial, empagliflozin, versus placebo, reduced the risk of the

1 primary composite outcome: 13.8% in empagliflozin group versus 17.1% in placebo group;
2 hazard ratio, 0.79; 95% confidence interval [CI], 0.69-0.90. Ethics approval was obtained at each
3 study site, and all patients provided informed consent to participate in the study; the registration
4 identifier at ClinicalTrials.gov is NCT03057951.

5
6 **Baseline categorization of kidney impairment**

7
8 For the prespecified subgroup analyses, patients were categorized by the presence or absence of
9 CKD at baseline. Prevalent CKD at baseline was defined by the presence of an eGFR <60
10 ml/min/1.73m² (as measured by the CKD-EPI equation) or urine albumin-to-creatinine ratio
11 (UACR) > 300 mg/g. Conversely, no CKD was defined by an eGFR ≥60 ml/min/1.73m² and
12 UACR ≤300 mg/g. We evaluated the treatment effect on all three of the hierarchically-ranked
13 outcomes and on several cardio-kidney outcomes within the following patients: (1) presence or
14 absence of baseline CKD; and (2) five baseline eGFR categories (<30, 30-<45, 45-<60, 60-<90,
15 and ≥90 ml/min/1.73m²).

16
17 **Kidney endpoint definition**

18
19 The pre-specified composite kidney outcome was defined as time to first occurrence of chronic
20 dialysis, kidney transplant, sustained reduction of ≥40% eGFR or sustained eGFR <15
21 mL/min/1.73 m² if baseline eGFR was > 30 mL/min/1.73m² or <10 mL/min/1.73 m² for patients
22 with baseline eGFR < 30 mL/min/1.73 m².

23 Further, to better align with definitions used in other trials, we explored alternative definitions.

24 These include i) sustained reduction of ≥40% eGFR, end stage kidney disease (ESKD) or renal
25 death, ii) sustained reduction of ≥50% eGFR or ESKD, iii) sustained reduction of ≥50% eGFR,
26 ESKD or renal death, and iv) sustained reduction of 57% eGFR or ESKD and v) sustained

1 reduction of 57% eGFR, ESKD or renal death. A blinded independent external Clinical Event
2 Committee (CEC) adjudicated all fatal events. Non-CV death were categorised into several
3 categories (i.e. infections, malignancies, other non-CV causes, trauma, gastrointestinal,
4 pulmonary, neurological, haemorrhage, non-CV procedure or surgery, hepatobiliary causes,
5 suicide, pancreatic causes). The category ‘Renal cause’ was used for ‘renal death’.

6
7 **Statistical Analyses**
8

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

21
22 The slope model, the MMRM, and the ANCOVA model included baseline eGFR and the
23 covariates of the Cox model. To assess the consistency of effects across CKD subgroups,
24 subgroup-by-treatment interaction terms were added to the models. Adverse event analyses were

1 based on patients with events occurring during the on-treatment period (including 7 days after
2 last drug consumption by the patient). SAS® Version 9.4 was used for all analyses.

3
4

5 **Results**

6
7 **Patient characteristics**
8

9 Among the 5,976 patients in the trial, who could be classified according to CKD categories
10 (99.8% of trial population), 3,198 (53.5%) had prevalent CKD at baseline (**Table 1**). Compared
11 with patients without CKD, those with CKD were older (74.2 vs. 69.2 years), had a longer
12 duration of HF (mean time since diagnosis: 4.6 vs 4.1 years), were more likely to have a
13 hospitalization for HF in the past 12 months (24.9 vs. 20.5%), and were more likely to have
14 diabetes (52.3 vs. 45.3%). Furthermore, compared to those without CKD, those with CKD were
15 less likely to be treated with an ACEi or ARBs (76.9 vs. 80.5%). Compared to those without
16 CKD, as expected and reflective of the subgroup definition for prevalent CKD, baseline eGFR
17 was lower for patients with CKD (mean: 46.3 vs. 77.1 ml/min/1.73m²), and UACR was higher
18 (median: 32 vs. 15 mg/g). The baseline characteristics in the placebo and empagliflozin groups
19 were well balanced in patients with and without CKD as described in Supplemental Table 1. The
20 patient characteristics across the 5 eGFR categories are presented in Supplemental Table 2.

21
22

22 **Primary and key secondary endpoints**

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

26

1 Compared to placebo, empagliflozin reduced the primary outcome of time-to-first cardiovascular
2 death or hospitalization for HF irrespective of CKD status (**Figure 1 and Supplementary**
3 **Figure 1**): HR 0.80 (95% CI 0.69-0.94) in patients with CKD and HR 0.75 (95% CI 0.60-0.95)
4 in patients without CKD; interaction P =0.67. Empagliflozin reduced the key secondary endpoint
5 of total (first and recurrent) HF hospitalizations irrespective of CKD status: HR 0.68 (95% CI
6 0.54, 0.86) in patients with CKD and HR 0.89 (95% CI 0.66, 1.21) in patients without CKD;
7 interaction P =0.17 (**Figure 1**). Empagliflozin reduced the absolute difference in the slope of
8 decline in eGFR irrespective of CKD: 1.43 (95% CI 1.01, 1.85) ml/min/1.73m²/year in patients
9 with CKD and 1.31 (95% CI 0.88, 1.74) ml/min/1.73m²/year in patients without CKD;
10 interaction P =0.70 (**Table 3**). Results were consistent across eGFR and UACR categories
11 (**Table 3**). The change of eGFR over time for patients with and without CKD is shown in **Figure**
12 **2**. An early eGFR decrease ("dip") was only observed in the empagliflozin-treated arms.
13 Following this "dip", stabilization of the eGFR trajectories was observed in the empagliflozin-
14 treated groups; in patients with CKD, eGFR was similar after week 76 in empagliflozin versus
15 placebo; in patients without CKD, the placebo arm had a greater decline in eGFR until the end of
16 the study (**Figure 2**).

17

18 In a subset of 3,170 patients (1,573 with CKD and 1,597 without CKD), that had CKD
19 categorization and measurements of eGFR at baseline and 30 days after discontinuation of
20 treatment, empagliflozin reduced the decline in eGFR from baseline to 30 days after drug
21 discontinuation by 2.4 (95% CI 1.3, 3.5) ml/min/1.73m² in patients with CKD and by 2.4 (95%
22 CI 1.2, 3.5) ml/min/1.73m² in patients without CKD; interaction P =0.97 (**Table 4**).

23

1 Event rates by eGFR categories across outcomes are presented in **Figure 3**. The effect of
2 empagliflozin on the primary composite outcome and the key secondary
3 outcomes across the 5 eGFR categories, is shown in **Figure 3**. Overall, baseline kidney
4 function did not influence the impact of empagliflozin on the primary endpoint, total
5 hospitalizations for heart failure, or other outcomes (all trend p-values > 0.05; **Figure 3**).

6
7 **Additional kidney outcomes**
8

9 The pre-specified composite kidney outcome (of a greater than 40% sustained decline in eGFR,
10 chronic dialysis or kidney transplant or sustained eGFR <15 ml/min/1.73 m² [for patients with
11 baseline eGFR ≥30] or sustained eGFR <10 (for patients with baseline eGFR <30)) was not
12 reduced in patients with and without CKD: HR 0.97 (95% CI 0.71,1.34) in patients with CKD
13 and HR 0.92 (95% CI 0.58, 1.48) in patients without
14 CKD; interaction P =0.86 (**Figure 4**). The results were consistent across eGFR categories
15 (**Figure 5**) and across alternative definitions of kidney outcomes (**Supplementary Figure 2**).

16
17 Investigator reported acute kidney injury was less frequent in the empagliflozin group (HR 0.73
18 [95% CI 0.56, 0.95], p-value 0.0193), both in patients with CKD and without CKD: HR 0.76
19 (95% CI 0.56, 1.02) with CKD and HR 0.66 (95% CI 0.38, 1.15) without CKD; interaction
20 P=0.67. Furthermore, empagliflozin reduced progression to macroalbuminuria (HR 0.82 [95% CI
21 0.68, 0.98], p-value 0.0264) in patients who at baseline were normo/microalbuminuric: HR 0.80
22 (95% CI 0.63, 1.01) with CKD and HR 0.84 (95% CI 0.64, 1.10) without CKD; interaction p =
23 0.77 (**Figure 4 and Supplemental Figure 3**).

24

1
2 **Adverse Events by CKD status at baseline**

3
4 Compared to those without CKD, patients in the empagliflozin group with CKD were more
5 likely to have adverse events including symptomatic hypotension (8.1 vs. 4.8%), hyperkalemia
6 (8.1 vs. 4.1%), volume depletion (14.4 vs. 9.0%), and urinary tract infection (11.0 vs. 8.6%)
7 (**Table 5**). However, empagliflozin appeared to be well tolerated and frequencies of adverse
8 events were similar between those randomized to empagliflozin versus placebo regardless of
9 CKD status (**Table 5**).

10
11 **Discussion**
12

13 This prespecified study of the EMPEROR-Preserved trial evaluated the effect of empagliflozin
14 versus placebo in HF patients with prevalent CKD at baseline on the primary outcome, key
15 secondary outcomes, and kidney outcomes. Our study has the following key findings: 1)
16 empagliflozin reduced the risk of the primary outcome of the composite of cardiovascular death
17 or hospitalization for HF, the key secondary outcome of total hospitalizations for HF, and of
18 eGFR slope, in patients with and without CKD; 2) the benefit across the primary and key
19 secondary outcomes was consistent across the spectrum of eGFR; 3) empagliflozin reduced the
20 reporting of acute kidney injury and slowed progression to macroalbuminuria overall and across
21 CKD and eGFR categories; and 4) empagliflozin was well-tolerated in patients with and without
22 CKD.

23
24 Overall, among patients with T2D, HF with reduced ejection fraction, CKD, and Acute HF,
25 SGLT2i have demonstrated broad clinical benefit.^{1,22-241,22-24} These findings also extended to

1 subgroups of those with CKD among patients with T2D²⁵ or in HF with reduced ejection
2 fraction.^{20,26} A pooled meta-analysis of the DAPA-HF (Dapagliflozin and Adverse Events in
3 Chronic Heart Failure and a Reduced Ejection Fraction) and EMPEROR-Reduced trial have
4 demonstrated efficacy of the SGLT2i dapagliflozin and empagliflozin to reduce the risk of the
5 composite of cardiovascular death or first hospitalization for HF in patients with eGFR < 60
6 ml/min/1.73m² (HR 0.77, 95% CI 0.86, 0.88) and those with eGFR ≥ 60 ml/min/1.73m² (HR
7 0.72, 95% CI 0.62, 0.82).²³ However, a detailed analysis of the benefit of SGLT2i across CKD
8 populations in patients with HFpEF, including evaluation of eGFR slopes, has not been
9 conducted. The present findings further expand on the existing literature by demonstrating that
10 among patients with HF with LVEF greater than 40%, in those with and without CKD,
11 empagliflozin reduces the risk of cardiovascular death or hospitalization for HF and reduces the
12 decline in eGFR slopes.

13
14 Real-world registries clearly indicate an increase in the risk of cardiovascular outcomes in
15 patients with HF and preserved ejection fraction associated with worse baseline eGFR.^{16,17,16,17}
16 Until recently, there were limited therapeutic options for patients with HF and preserved ejection
17 fraction with reduced eGFR. The EMPEROR-Preserved trial recruited patients with eGFR as
18 low as 20 ml/min/1.73m² aligning with the EMPEROR-Reduced trial eGFR exclusion criteria.¹¹
19 The DAPA-HF trial excluded patients with eGFR < 30 ml/min/1.73m² while the DELIVER trial
20 (Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction
21 Heart Failure) excluded patients with eGFR < 25 ml/min/1.73m². The EMPEROR-Preserved
22 trial had a similar proportion of patients with eGFR < 60 ml/min/1.73m² (50%) when compared
23 to EMPEROR-Reduced (48%)²⁰, DAPA-HF (41%)²⁶, and DELIVER (49.9%).²⁷ The present

1 results highlight the efficacy of empagliflozin in reducing the risk of the primary and key
2 secondary outcomes across the spectrum of eGFR categories, even in those with baseline eGFR
3 ranging from 20-30 ml/min/1.73m². Given the large proportion of patients with reduced eGFR in
4 those with HF and preserved ejection fraction, our results support a treatment strategy with
5 empagliflozin in patients who would have limited therapeutic options.

6
7 The kidney-protective effects of SGLT2i have previously been shown in patients with type 2
8 diabetes and chronic kidney disease in the CREDENCE trial^{9,10,10} and in patients irrespective of
9 diabetic status in the DAPA-CKD trial.¹⁰ The EMPEROR-Preserved trial demonstrated that
10 empagliflozin significantly reduced the rate of decline in eGFR – a prespecified outcome that
11 was explored within the hierarchical testing model for the trial – and slowed the progression to
12 macroalbuminuria. Such results align with the data from previously published randomized trials
13 of SGLT2i in patients with T2D² and HF.^{20,26} However, empagliflozin did not reduce the risk of
14 major renal outcomes in those with or without CKD, consistent with the findings from the
15 overall trial. This is in contrast to the effect in EMPEROR-Reduced, whereby empagliflozin
16 reduced the risk of major renal outcomes (which was defined in the same way in EMPEROR-
17 Preserved) in patients with and without CKD: HR 0.53, 95%CI 0.31-0.91 with CKD and HR
18 0.46, 95% CI 0.22-0.99 without CKD.²⁰ There was a greater eGFR decline in participants
19 without baseline CKD (**Figure 2, Table 3**), a finding noted also within the EMPEROR-Reduced
20 trial. With lower baseline values for eGFR in patients with prevalent CKD, the magnitude of
21 benefit on eGFR slope with empagliflozin was proportionally similar in patients with and
22 without CKD. In EMPEROR-Preserved, there was no statistically significant difference in the
23 effect of empagliflozin versus placebo on the eGFR slope by prevalent baseline CKD. Whilst in

1 both treatment arms, participants with higher baseline eGFR have larger absolute decline, loss in
2 eGFR are likely to be more clinically meaningful in patients with CKD in whom even smaller
3 decline in eGFR indicates more earlier progression towards end-stage kidney disease. Overall,
4 the incidence of renal events was relatively small and lower in EMPEROR-Preserved than
5 EMPEROR-Reduced in patients with CKD (2.87 vs 3.77 per 100-patient years respectively) and
6 without CKD (1.52 vs. 2.27 per 100-patient years respectively). The manuscript evaluating data
7 from EMPEROR-Reduced identified a (nominally) significant treatment effect when evaluating
8 baseline eGFR interaction for the effect of empagliflozin on eGFR slope. This was identified
9 whether the analysis categorized patients by CKD or by 5 eGFR subgroups. However, these
10 analyses are model-dependent and are based on absolute differences. Our analysis did not
11 indicate a significant interaction of the treatment effect with baseline eGFR. The differences
12 between the two trials may have arisen due to differences in trial inclusion criteria, duration of
13 follow-up, comorbidity burden which may influence risk of progression of CKD, or chance (due
14 to multiple hypothesis testing). Longer follow-up may have uncovered whether slowing both, the
15 eGFR decline and progression to macroalbuminuria, would have translated into a difference in
16 renal outcomes over time.

17

18 The proposed mechanisms of action of SGLT2i on glomerular function remains unclear.
19 Potentially, the initial drop in the eGFR with initiation of SGLT2i is related to the hemodynamic
20 effect of diminishment of proximal nephron sodium reabsorption resulting in a restoration of
21 tubuloglomerular feedback and a decrease in intraglomerular hydrostatic pressures.^{28,29} However,
22 animal models evaluating gene knock out of SGLT2 suggests that the hemodynamic effect may
23 not be related to longer term renal protection.^{30,31} Emerging evidence suggests that a critical

1 determinant of injury in the diabetic kidney is through oxidative and endoplasmic reticulum
2 stress; such stress impacts glomerular podocytes and renal tubules by dysregulating autophagy
3 processes which increases susceptibility to injury.^{32,33} SGLT2i may be able to reduce oxidative
4 stress by inducing a state of nutrient and oxygen deprivation by increasing sirtuin-1 (SIRT1),
5 AMP-activated protein kinase (AMPK), and hypoxia-inducible factors (HIF-1 α and HIF-2 α)
6 which can exert renoprotective effects through the promotion of autophagic flux in addition to
7 direct effects on sodium transport and inflammasome activation.³³⁻³⁵ The impact of SGLT2i on
8 albuminuria has been extensively described and may be related to a variety of mechanisms.^{36,37}
9 Animal models suggest that SGLT2i may reduce albuminuria through direct effects on the
10 kidney; for instance, in diabetic mice, SGLT2i reduced albuminuria by ameliorating
11 intraglomerular hypertension in addition to tubulointerstitial fibrosis, which are the major
12 contributors to chronic kidney damage.³⁸⁻⁴⁰ Whether such mechanisms are dominant among
13 patients with HF and preserved ejection fractions warrants further exploration. The results of the
14 DELIVER trial will provide further insights into the intersection of kidney outcomes with
15 SGLT2i in HFpEF populations.

16

17 Overall, the likelihood of serious adverse events was numerically lower in the EMPEROR-
18 Preserved trial compared to the EMPEROR-Reduced trial as reflected by the placebo event rate
19 of serious adverse events in patients with and without CKD: 49.5 vs. 61.2 per 100 patient-years
20 with CKD and 29.9 vs. 48.6 per 100 patient-years without CKD. Consistent with the result of the
21 EMPEROR-Reduced trial, patients with CKD in EMPEROR-Preserved had a greater likelihood
22 of adverse events compared to those without CKD. This likely represents a frail physiologic
23 phenotype that increases the risk of adverse outcomes even among placebo-treated patients with

1 CKD compared to those without CKD. Of note, in totality serious adverse events were lower in
2 the empagliflozin-treated groups in both patients with and without CKD; furthermore, adverse
3 events leading to drug discontinuation were balanced between treatment groups in those with and
4 without CKD. And acute kidney injury was reported less frequently in the empagliflozin group,
5 regardless of baseline CKD status. These results highlight the overall safety and tolerability of
6 empagliflozin across the spectrum of HF.

7

8 **Limitations**

9

10 Several limitations of this analysis warrant noting. While this was a prespecified analysis, the
11 EMPEROR-Preserved trial was not powered to assess the effect of empagliflozin in subgroups
12 such as CKD. In addition, the trial was not sufficiently powered to evaluate adverse renal
13 outcomes across subgroups of patients with and without CKD, nor primary and key secondary
14 outcomes in further CKD subgroups such as the 5 categories of eGFR. The definition of acute
15 kidney injury was based on MedRA coded reporting of investigator-reported adverse events and
16 therefore may have some heterogeneity in reporting across trial sites. Our results must be kept
17 within context that our statistical analysis plan had prespecified that the slope of eGFR decline
18 was analyzed based on on-treatment data whereby baseline and other off-treatment data were not
19 included in the model.

20

21 **Conclusion**

22

1 In the EMPEROR-Preserved trial, empagliflozin reduced the key efficacy outcomes of time-to-
2 first cardiovascular death or hospitalization HF, total (first and recurrent) HF hospitalizations,
3 and slowed the rate of eGFR decline and the progression to macroalbuminuria, in patients with
4 and without CKD. These results were consistent across a broad kidney function spectrum. These
5 benefits on clinical outcomes in addition to the well tolerated and consistent safety profile
6 provide further evidence for the benefit of empagliflozin in patients with HF and preserved
7 ejection fraction independent of CKD. These results are consistent across the broad spectrum of
8 eGFR including those with severe kidney function impairment down to an eGFR of 20
9 ml/min/1.73m². Further studies are needed to explore the potential reasons why limited benefit
10 was observed with regards to the risk of renal outcomes in patients with or without CKD.

11

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20

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3

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5

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11 **Data sharing statement**

12 To ensure independent interpretation of clinical study results and enable authors to fulfil their
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14 access to relevant clinical study data. In adherence with the Boehringer Ingelheim Policy on
15 Transparency and Publication of Clinical Study Data, scientific and medical researchers can
16 request access to clinical study data after publication of the primary manuscript and secondary
17 analyses in peer-reviewed journals and regulatory and reimbursement activities are completed,
18 normally within 1 year after the marketing application has been granted by major Regulatory
19 Authorities. Researchers should use the <https://vivli.org/> link to request access to study data and
20 visit <https://www.mystudywindow.com/msw/datasharing> for further information.

21

22

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7 **Legends**

8 Figure 1: Primary and Key Secondary Outcomes by CKD status at baseline.

9 Figure 2: eGFR over time by CKD status at baseline.

10 Figure 3: Primary and key secondary outcomes by eGFR categories

11 Figure 4: Kidney outcomes by CKD status at baseline.

12 Figure 5: Kidney outcomes by eGFR categories

13

14

1 **Table 1. Baseline characteristics of the patients by CKD 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 classification			<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, beats/min	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			
Ischemic	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*	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†	95 (3.4)	126 (3.9)	0.2878
Heart failure medication			
ACE inhibitor	1212 (43.6)	1192 (37.3)	<0.0001
ARB‡	1030 (37.1)	1282 (40.1)	0.0172
ARNI	65 (2.3)	68 (2.1)	0.5768
Diuretics§	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

2
3 Data are n (%) or mean ± SD for randomized patients, unless otherwise stated. ACE indicates angiotensin-
4 converting enzyme; ARB, angiotensin-receptor blocker; ARNI, angiotensin-receptor neprilysin inhibitor; BMI, body
5 mass index; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration
6 equation; eGFR, estimated glomerular filtration rate; HHF, hospitalization for heart failure; IQR, interquartile range;
7 LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-pro BNP, N-terminal pro-
8 natriuretic brain peptide; NYHA, New York Heart Association; and UACR, urine albumin-to-creatinine ratio.

1 *Atrial fibrillation/flutter reported in any electrocardiogram before treatment intake or history of atrial
 2 fibrillation/flutter reported as medical history.
 3 †Implantable cardioverter defibrillator with or without cardiac resynchronization therapy.
 4 ‡Excluding valsartan when taken with sacubitril.
 5 §Diuretics other than MRAs
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8 **Table 2. Event Rates by CKD status at baseline.**
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	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*	75 (4.6)	2.82	33 (2.4)	1.37	74 (4.7)	2.87	37 (2.6)	1.52

10
 11 Data for randomized patients. CKD indicates chronic kidney disease; CKD-EPI, Chronic Kidney Disease
 12 Epidemiology Collaboration equation; CV, cardiovascular; eGFR, estimated glomerular filtration rate (mL/min/1.73
 13 m² by CKD-EPI); and HHF, hospitalization for heart failure.
 14 *Composite exploratory endpoint included chronic dialysis or renal transplant or sustained reduction of ≥40% in
 15 eGFR or sustained eGFR <15 ml/min/1.73 m² (for patients with baseline eGFR ≥30) or sustained eGFR <10 (for
 16 patients with baseline eGFR <30).
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Table 3. eGFR Slope analyses by CKD status at baseline.

Slope of change in eGFR, mL/min/1.73 m ² per year*	Empagliflozin (mean±SE)	Placebo (mean±SE)	Absolute difference (95% CI)	P value	P value for interaction/Trend**
All patients (N=5836)*	-1.25±0.11	-2.62±0.11	1.36 (1.06, 1.66)	<0.001	
By prevalent CKD status [†]					
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, 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	

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CI indicates confidence interval; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration equation; eGFR, estimated glomerular filtration rate; and UACR, urine albumin-to-creatinine ratio.

*Data for the treated set of patients from random coefficient model; intercept and slope allowed to vary randomly between patients.

** interaction test for prevalent CKD, trend test for eGFR and UACR subgroups

[†]Prevalent CKD defined as eGFR (CKD-EPI) <60 mL/min/1.73 m² or UACR >300 mg/g.

1 **Table 4. Change of eGFR From Baseline to Follow up (30 Days After Treatment**
 2 **Discontinuation) by CKD Status and eGFR and UACR Categories at Baseline**

Total change in eGFR from baseline to follow up (30 days after treatment discontinuation), 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†					
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, 3.0)	0.2583	
<30 (n=107)	2.8±1.5	0.9±1.6	1.9 (-2.4, 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 indicates confidence interval; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration equation; eGFR, estimated glomerular filtration rate; and UACR, urine albumin-to-creatinine ratio.

*Data for patients with baseline data, on-treatment and data of approx. 30 days after treatment discontinuation, without open label SGLT2i use between treatment discontinuation and follow-up measurement . †Prevalent CKD defined as eGFR (CKD-EPI) <60 mL/min/1.73 m² or UACR >300 mg/g

** interaction test for prevalent CKD, trend test for eGFR and UACR subgroups

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1 **Table 5: Adverse Events by CKD 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
Hyperkalemia				
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 hypoglycemia*				
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

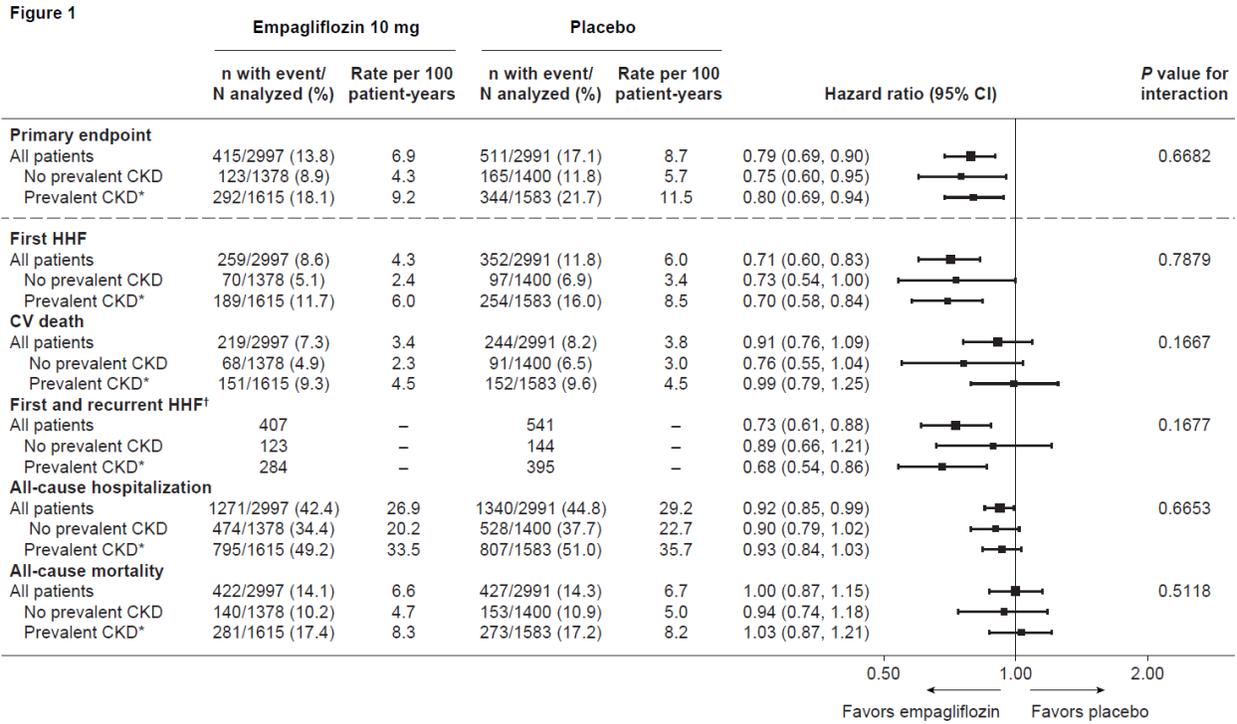
Data are AEs in the treated set of patients classified using MedDRA version 23.0. Prevalent CKD defined as eGFR (CKD-EPI) <60 mL/min/1.73 m² or UACR >300 mg/g. AE indicates adverse event; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration equation; eGFR, estimated glomerular filtration rate; MedDRA, Medical Dictionary for Regulatory Activities; and UACR, urine albumin-to-creatinine ratio.

*Plasma glucose ≤70 mg/dL or requiring assistance.

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1 **Figure 1: Primary and Key Secondary Outcomes by CKD status at baseline.**

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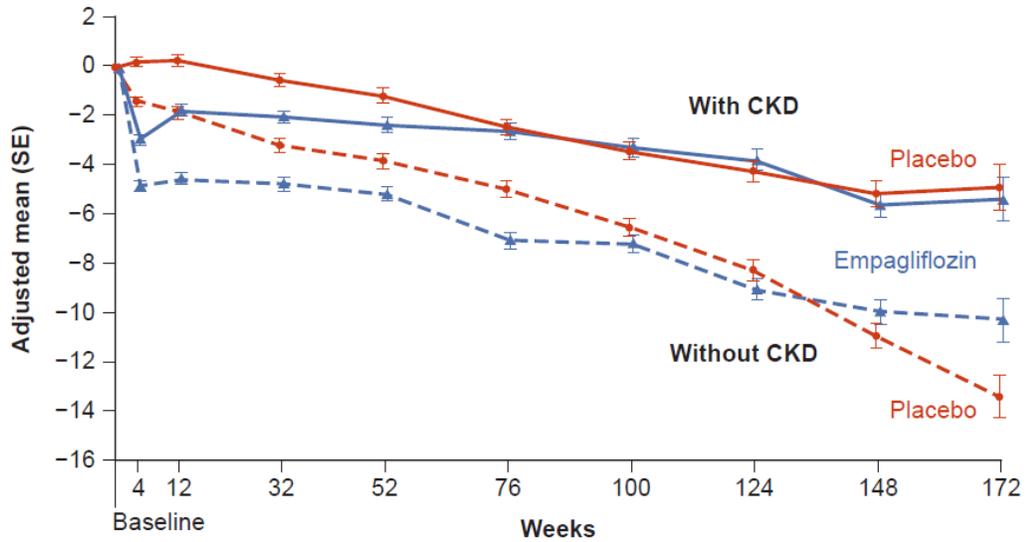


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Data for randomized patients; hazard ratio and 95% CI from Cox proportional hazards model unless otherwise noted. CI indicates confidence interval; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration equation; CV, cardiovascular; estimated glomerular filtration; HHF, hospitalization for heart failure; and UACR, urine albumin-to-creatinine ratio. *Prevalent CKD defined as eGFR (CKD-EPI) <60 ml/min/1.73 m² or UACR >300 mg/g. †Evaluated using a joint frailty model together with CV death.

1 **Figure 2: eGFR change from baseline over time by CKD status at baseline.**

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Patients at risk		Baseline	4	12	32	52	76	100	124	148	172
With CKD											
Placebo	1539	1527	1451	1300	1199	1012	716	498	304	98	
Empagliflozin 10 mg	1581	1561	1490	1343	1230	1030	723	514	305	101	
Without CKD											
Placebo	1366	1354	1302	1184	1131	981	724	514	331	111	
Empagliflozin 10 mg	1341	1329	1293	1175	1110	938	706	525	315	111	

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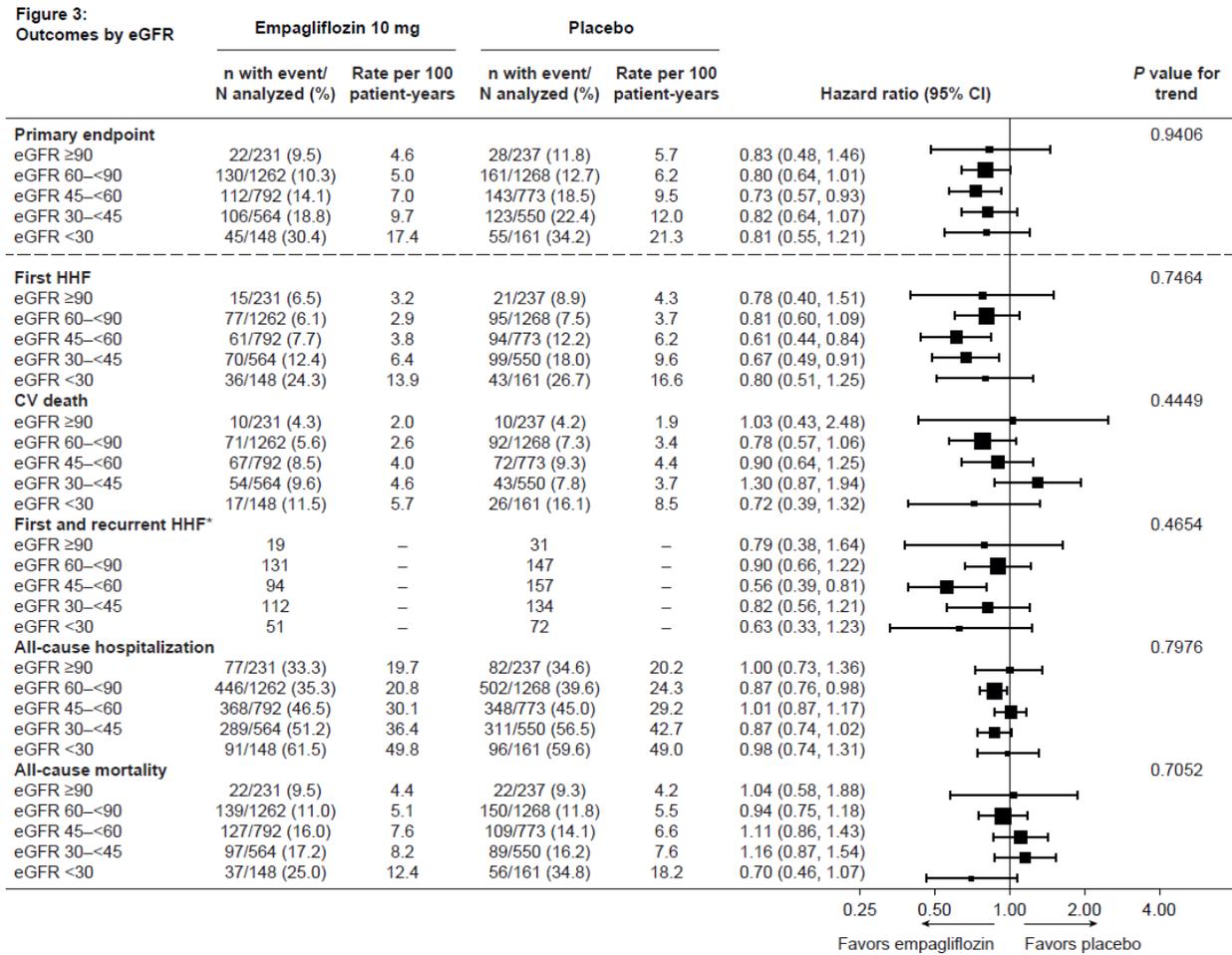
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5 Data for treated patients from a mixed model for repeated measures based on on-treatment data.
 6 CKD defined as eGFR (CKD-EPI) <60 ml/min/1.73 m² or UACR >300 mg/g. CKD indicates
 7 chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration
 8 equation; eGFR, estimated glomerular filtration rate; and UACR, urine albumin-to-creatinine
 9 ratio.

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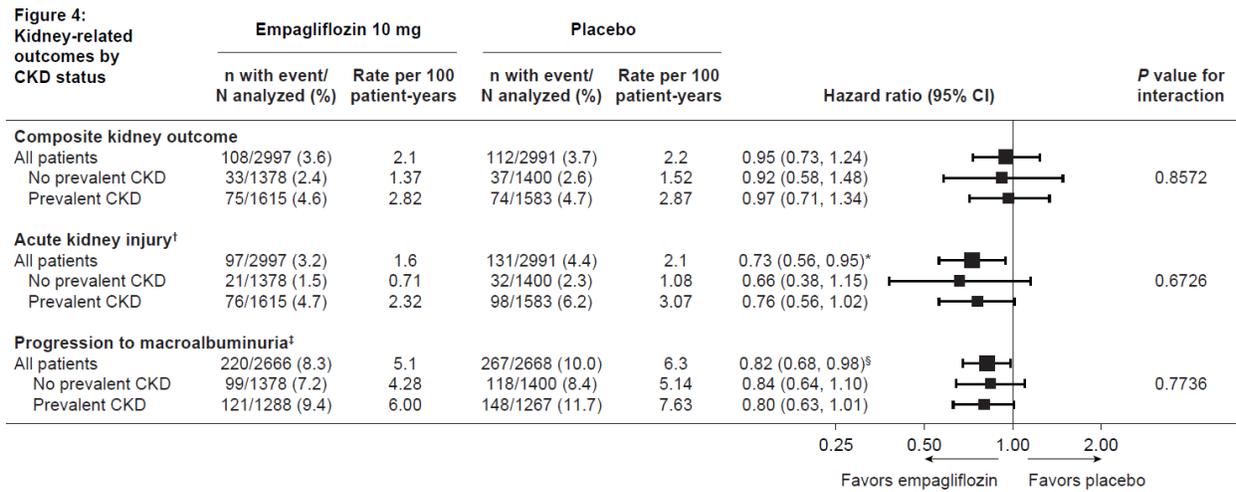
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1 **Figure 3: Primary and key secondary outcomes by eGFR categories**
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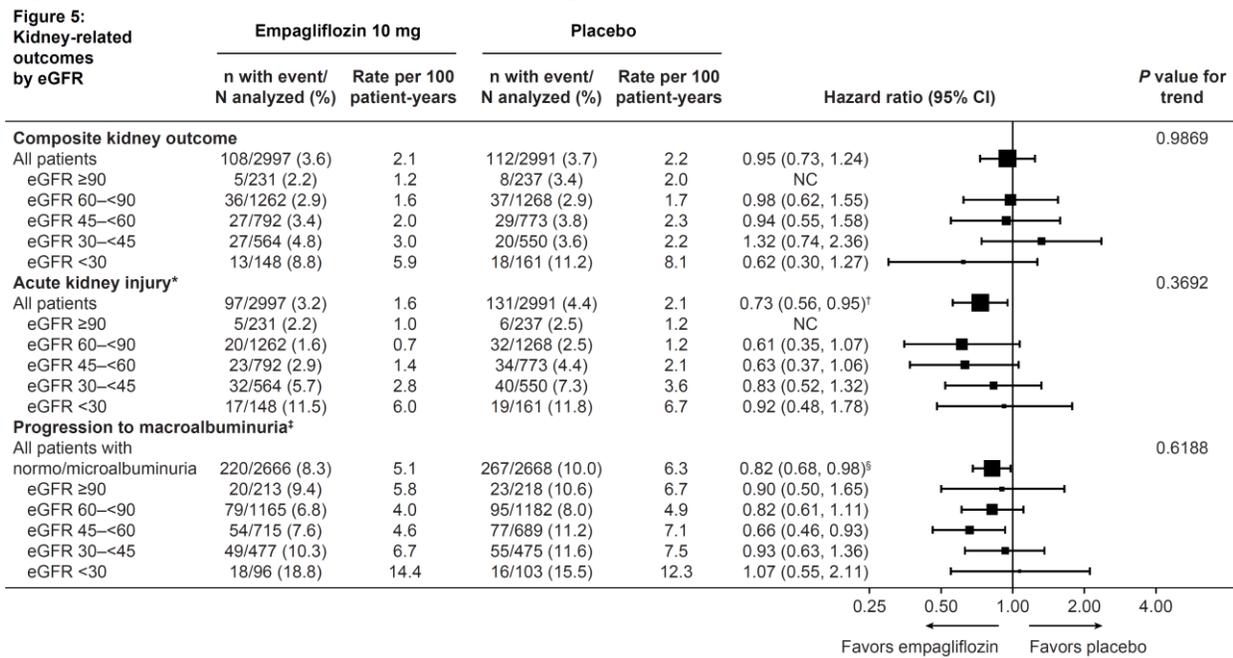
3 Data for randomized patients; hazard ratio and 95% CI from Cox proportional hazards model
 4 unless otherwise noted. CI indicates confidence interval; CV, cardiovascular; eGFR, estimated
 5 glomerular filtration rate; and HHF, hospitalization for heart failure. *Evaluated using a joint
 6 frailty model together with CV death.
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1 **Figure 4: Kidney outcomes by CKD status at baseline.**
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 4 Data for randomized patients; hazard ratio and 95% CI from Cox proportional hazards model.
 5 Prevalent CKD defined as eGFR (CKD-EPI) <60 ml/min/1.73 m² or UACR >300 mg/g. The
 6 composite kidney outcome was an exploratory endpoint that included chronic dialysis or kidney
 7 transplant or sustained reduction of ≥40% in eGFR or sustained eGFR (CKD-EPI) <15
 8 ml/min/1.73 m² (for patients with baseline eGFR ≥30) or sustained eGFR <10 (for patients with
 9 baseline eGFR <30). CI indicates confidence interval; CKD, chronic kidney disease; CKD-EPI,
 10 Chronic Kidney Disease Epidemiology Collaboration equation; MedDRA, Medical Dictionary
 11 for Regulatory Activities; and UACR, urine albumin-to-creatinine ratio. *P value: 0.0193. †Acute
 12 kidney injury based on MedDRA preferred term based on investigator-reported adverse events.
 13 ‡UACR >300 mg/g in patients with baseline UACR ≤300 mg/g. §P value: 0.0264.
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1 **Figure 5: Kidney outcomes by eGFR categories**



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Data for randomized patients; hazard ratio and 95% 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 $\geq 40\%$ in eGFR or sustained eGFR (CKD-EPI) < 15 ml/min/1.73 m² (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. CI indicates confidence interval; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration equation; MedDRA, Medical Dictionary for Regulatory Activities; NC, not calculated; and UACR, urine albumin-to-creatinine ratio. * Acute kidney injury based on MedDRA preferred term based on investigator-reported adverse events. [†] P value: 0.0193. [‡] UACR > 300 mg/g in patients with baseline UACR ≤ 300 mg/g. [§] P value: 0.0264.