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1 **Early changes in estimated glomerular filtration rate post-initiation of**
2 **empagliflozin in EMPEROR-Reduced**

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38 **Abstract**

39 *Background:* Sodium glucose co-transporter 2 inhibitors (SGLT2i) may induce an
40 early post-initiation eGFR decrease which does not impact the SGLT2i benefits. The
41 occurrence, characteristics, determinants, and clinical significance of an initial eGFR
42 change among patients with heart failure with reduced ejection fraction (HFrEF)
43 require further study.

44 *Aims:* To describe eGFR change from randomisation to week 4 (as % of change
45 relative to randomisation) and assess its impact in EMPEROR-Reduced.

46 *Methods:* Landmark analyses (week 4) were performed.

47 *Results:* eGFR change was available in 3547 patients out of 3730 (95%). The tertiles
48 of post initiation eGFR % change for empagliflozin were: tertile 1 (T1) $\leq -11.4\%$; T2 $\geq -$
49 11.4% to $\leq -1.0\%$ and T3 $\geq 0.0\%$. The placebo group tertiles were: T1 $\leq -6.5\%$; T2 $\geq -$
50 6.4% to $\leq +3.6\%$; and T3 $\geq +3.6\%$. On average, empagliflozin induced a leftward
51 distributional shift of initial eGFR changes of $-2.5 \text{ ml/min/1.73m}^2$ vs. placebo. In the
52 empagliflozin group, after covariate adjustment, the risk of cardiovascular and renal
53 outcomes did not differ between patients in whom early post treatment initiation
54 eGFR decreased (T1) and patients in whom it increased (T3). However, in the
55 placebo group, patients in whom early post treatment initiation eGFR decreased (T1)
56 had a higher risk of sustained worsening kidney function and all-cause mortality
57 compared to patients in whom eGFR increased (T3): HR 2.38, 95%CI 1.25-4.55 and
58 HR 1.37, 95%CI 1.01-1.85, respectively.

59 *Conclusion:* A mild eGFR decrease may expected after the initiation of empagliflozin,
60 it is not associated with untoward kidney safety concerns, and it may indicate that

61 the drug is having its intended effects that improve HF outcomes. Clinicians should
62 not be concerned with early eGFR changes post-initiation of empagliflozin.

63

64 *Key-words:* estimated glomerular filtration rate; heart failure with reduced ejection
65 fraction; empagliflozin; outcomes.

66

67

68 **Introduction**

69 Sodium glucose co-transporter 2 inhibitors (SGLT2i) reduce major cardiovascular
70 events, particularly heart failure hospitalizations (HHF), and improve kidney
71 outcomes in patients with type 2 diabetes (T2D), chronic kidney disease (CKD), and
72 heart failure with a reduced ejection fraction (HFrEF).¹ Additionally, in heart failure
73 with reduced ejection fraction, treatment with SGLT2i, over a period of between one
74 to two years, slows the rate of decline in estimated glomerular filtration rate (eGFR)
75 compared with placebo, as assessed by the difference in eGFR slopes from week 4
76 after treatment initiation.²⁻⁴ However, SGLT2i may induce an initial eGFR decrease,
77 which may result from an acute reduction in intraglomerular pressure.⁵⁻⁸
78 Despite some biological understanding of the effect of SGLT2i in the kidneys,
79 particularly the hemodynamic mechanisms are rather complex. Clinicians may feel
80 concerned when they see an eGFR decrease early after SGLT2i initiation, and out of
81 risk aversion, they may be tempted to stop or withhold treatment. This behavior is
82 also very common when clinicians are faced with an early decrease after initiation of
83 a renin angiotensin aldosterone system inhibitor.⁹

84 In patients with T2D enrolled in the Empagliflozin Cardiovascular Outcome Event
85 Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) and in the
86 Canagliflozin and Renal Events in Diabetes With Established Nephropathy Clinical
87 Evaluation (CREDENCE) trials, the clinical benefit of empagliflozin and canagliflozin,
88 respectively, compared with placebo, was not impacted by the initial eGFR
89 decrease.¹⁰ In patients with HFrEF enrolled in the Study to Evaluate the Effect of
90 Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death
91 in Patients With Chronic Heart Failure (DAPA-HF), the eGFR decrease after initiation
92 of dapagliflozin was of small magnitude, on average, and associated with better

93 outcomes among patients randomized to dapagliflozin, but not among those
94 randomized to placebo.¹¹ The impact of the initial eGFR decrease may be different in
95 T2D and in HFrEF, because the latter may be more susceptible to rapid changes in
96 volume status and kidney function.¹²

97 In the present study, we aim to describe the occurrence, characteristics,
98 determinants, and prognostic significance of eGFR change in the early post-
99 treatment initiation period, in patients with HFrEF enrolled in the EMPagliflozin
100 outcomE tRial in Patients With chrONic heaRt Failure With Reduced Ejection
101 Fraction (E
102 MPEROR-Reduced) trial.

103

104 **Methods**

105 The EMPEROR-Reduced trial was a randomized, double-blind, parallel-group,
106 placebo-controlled and event-driven study, whose design has been described
107 previously.¹³ In short, participants were men or women with chronic heart failure
108 (functional class II, III or IV) with a left ventricular ejection fraction $\leq 40\%$, who were
109 receiving background treatment for heart failure. Patients with an ejection fraction
110 $\leq 30\%$ were preferentially enrolled by requiring those with a higher ejection fraction to
111 have been hospitalized for HF within 12 months or to have markedly increased levels
112 of N-terminal prohormone B-type natriuretic peptide (NT-pro BNP), i.e., >1000 pg/ml
113 or >2500 pg/ml in those with an ejection fraction of 31-35% or 36-40%, respectively;
114 these thresholds were doubled in patients with atrial fibrillation.

115 The Ethics Committee of each of the 520 sites in 20 countries approved the protocol
116 and all patients gave written informed consent.

117 **Randomization**

118 Patients were randomized double-blind (in a 1:1 ratio) to receive placebo or
119 empagliflozin 10 mg daily, in addition to their usual therapy. Patients were
120 periodically assessed at study visits for major outcomes, symptoms and functional
121 capacity related to heart failure, initiation, vital signs, and biomarkers (including
122 eGFR), and adverse events.

123 All randomized patients were followed for the occurrence of prespecified outcomes
124 for the entire duration of the trial, regardless of whether the study participants were
125 taking their study medications or adhered to the schedule of study visits.

126 A total of 3730 patients were included and followed for a median of 16 months.

127 **Trial Endpoints**

128 The primary endpoint was the composite of adjudicated cardiovascular death or
129 hospitalization for heart failure, analysed as time to first event. Cardiovascular death,
130 all-cause mortality, and a composite renal endpoint, defined by the need for chronic
131 dialysis or renal transplant or a sustained $\geq 40\%$ decrease in eGFR or a sustained
132 eGFR < 15 mL/min/1.73m² (if the baseline eGFR was ≥ 30 mL/min/1.73m²) or < 10
133 mL/min/1.73m² (if the baseline eGFR was < 30 mL/min/1.73m²) were also analysed.

134 The pre-specified safety assessed in this analysis focused on adverse events of
135 special interest, defined following the Medical Dictionary for Regulatory Activities
136 (MedDRA): acute kidney injury (based on the reporting of the preferred term “acute
137 kidney injury”), and acute renal failure (based on the narrow Standardized MedDRA
138 Query [SMQ] 20000003, “acute renal failure”, based on 19 preferred terms [MedDRA
139 version 23.0]) obtained up until 7 days following discontinuation of the study
140 medication.

141 **Statistical Analysis**

142 For this analysis, 3547 out of 3730 (95%) patients who received at least one dose of
143 the study drug and had eGFR values available both at randomization (last available
144 measurement before first study drug intake) and week 4 (obtained on-treatment)
145 were included. The 4-week measurement was the first time point at which eGFR
146 measurements were available following randomization. We categorized the percent
147 (%) eGFR change in the early post-randomization period from randomization value
148 to week 4 ($\text{eGFR at week 4} - \text{eGFR at randomization} / \text{eGFR at randomization} * 100$)
149 into tertiles in each treatment group separately. We described and compared
150 the patients' baseline characteristics across these tertiles. As the initial eGFR
151 change was computed from randomization to week 4, we used landmark analyses
152 (with landmark at week 4) to study the associations of % eGFR change with
153 outcomes. Thereby only patients without an event prior to the week 4 eGFR
154 measurement and still at risk for the event of interest from that measurement
155 onwards were included in the analysis of an endpoint event. We used Cox
156 proportional hazards models to calculate hazard ratios comparing the tertiles of %
157 eGFR changes within each treatment group for each of the primary outcome, CV
158 death and all-cause death after adjusting for the corresponding EMPEROR-Reduced
159 risk score.¹⁴ An equivalent model was used to investigate safety outcomes including
160 adjustment for the EMPEROR-Reduced mortality risk score.¹⁴ Additionally, we
161 analyzed eGFR changes as a continuous covariate and tested treatment-by-eGFR
162 changes interaction across the continuous spectrum of eGFR change, adjusting for
163 the EMPEROR-Reduced risk models as above described. Sensitivity analysis to
164 assess the risk associated with eGFR decreases >20% and >30% were also
165 performed. We estimated adjusted mean absolute eGFR change from randomization
166 obtained on-treatment at various time points over follow-up by treatment group using

167 a mixed model for repeated measures with an unstructured variance covariance
168 matrix and adjustment for baseline age, sex, geographical region, diabetes, left
169 ventricular ejection fraction, last projected visit based on dates of randomization and
170 trial closure, treatment-by-visit interaction and randomization eGFR-by-visit
171 interaction in all patients who received at least one dose of the study drug. This
172 analysis was repeated within each treatment group to compare the tertiles of %
173 eGFR changes (replacing term for treatment-by-visit interaction with tertile-by-visit
174 interaction). Among a subset of patients with available eGFR 30 days after treatment
175 discontinuation we estimated the eGFR change from randomization to the last value
176 on treatment, and after treatment discontinuation (i.e., follow-up) using an analysis of
177 covariance with adjustment for the same baseline covariates including eGFR at
178 randomization. This analysis was repeated within each treatment group to compare
179 the tertiles of % eGFR changes (replacing term for treatment with tertile). Equivalent
180 models were also used to estimate changes in serum creatinine during follow-up.
181 Finally, we assessed the consistency of the treatment effect on eGFR changes at
182 week 4 across several baseline subgroups using a mixed model for repeated
183 measures with adjustment for baseline age, sex, geographical region, and left
184 ventricular ejection fraction, last projected visit based on dates of randomization and
185 trial closure, subgroup-by-treatment-by-visit interaction and randomization eGFR-by-
186 visit interaction. P values and 95% confidence intervals presented in this report have
187 not been adjusted for multiplicity. All analyses were performed using SAS, version
188 9.4 (SAS Institute).

189

190 **Results**

191 **eGFR change post-initiation and baseline characteristics**

192 Changes in eGFR from randomization to week 4 occurred both in the empagliflozin
193 and in the placebo groups, with a shift in eGFR change distribution to the left (i.e.,
194 higher decrease) in the empagliflozin group of -2.5, 95%CI -3.1 to -1.9
195 ml/min/1.73m² on average compared to placebo (**Figure 1**).

196 Baseline covariates that modified the effect of empagliflozin on eGFR change from
197 randomization to week 4 were blood pressure at baseline and history of
198 hospitalization for HF in the previous 12 months (**Figure 2**). Patients with higher
199 blood pressure at baseline and no history of HHF in the previous 12 months had
200 larger placebo-corrected mean eGFR decrease from randomization to week 4
201 compared to patients with lower blood pressure and history of HHF, respectively.
202 The remaining baseline characteristics did not significantly modify the association of
203 empagliflozin with eGFR changes. Percentage eGFR changes (mean±SE) from
204 randomization at week 4 were -4.9±0.4% in empagliflozin and -0.8±0.4% in placebo
205 (**Supplemental Figure 1**).

206 The tertiles of % eGFR change in the early post-initiation period for empagliflozin
207 were: tertile 1 (T1) ≤ -11.4%; tertile 2 (T2) ≥ -11.4% to ≤ -1.0% and tertile 3 (T3) ≥
208 0.0%. In the placebo group they were: T1 ≤ -6.5%; T2 ≥ -6.4% to ≤ +3.6%; and T3 ≥
209 +3.6%. Mean % eGFR changes for the tertiles were: -20.8 ± 0.3% (T1), -6.0 ± 0.1%
210 (T2), 11.5 ± 0.7% (T3) in empagliflozin and -16.1 ± 0.4% (T1), -1.3 ± 0.1% (T2), 15.2
211 ± 0.6% (T3) in placebo.

212 The corresponding mean (± SD) serum creatinine increases in T1 were relatively
213 small: +0.29 ± 0.21 mg/dL in the empagliflozin group and +0.22 ± 0.21 mg/dL in the
214 placebo group (**Supplemental Figure 2**).

215 The characteristics of the patients across tertiles of eGFR change in empagliflozin
216 and placebo groups are presented in the **Supplemental Table 1**.

217 **eGFR progression at 4 weeks and after**

218 At week 4, empagliflozin-treated patients experienced an eGFR change of -3.5 (95%
219 CI -3.9 to -3.1) compared to -1.0 (95% CI -1.4 to -0.6) in placebo-treated patients
220 (**Figure 3a, left panel**). In the subset of patients with available eGFR values after
221 treatment discontinuation at the end of the trial, eGFR increased in empagliflozin-
222 treated patients but remained similar to the last “on-treatment” value in placebo-
223 treated patients (**Figure 3a, right panel**).

224 In empagliflozin-treated patients, among those with the steepest decrease at week 4
225 (T1: $\leq -11.4\%$ change), eGFR increased throughout the follow-up, while among
226 those in whom eGFR increased at week 4 (T3: $\geq 0.0\%$ change), eGFR decreased
227 throughout the follow-up, and remained stable in T2, suggesting a “regression to the
228 mean” phenomenon (**Figure 3b, left panel**). After treatment discontinuation, eGFR
229 increased across all tertiles (**Figure 3b, right panel**).

230 In placebo-treated patients with the largest eGFR decrease at week 4 (T1: $\leq -6.5\%$
231 change), eGFR recovered slightly at week 52 and then decreased subsequently. In
232 the 2 other tertiles, eGFR decreased continuously throughout the follow-up (**Figure**
233 **3c, left panel**). After placebo discontinuation, eGFR remained stable across all
234 tertiles (**Figure 3c, right panel**).

235 **Association of %eGFR changes with subsequent cardiac, renal and mortality** 236 **outcomes**

237 In the empagliflozin group, patients who experienced the steepest eGFR decrease
238 (T1: $\leq -11.4\%$ change) had a similar risk of cardiovascular death or HF

239 hospitalization, cardiovascular death, all-cause mortality, and the kidney composite
240 outcome, compared to patients in whom eGFR increased (T3: $\geq 0.0\%$ change).
241 Patients who experienced modest eGFR decreases with empagliflozin (T2: $> -11.4\%$
242 to -1.0% change) had a lower risk of cardiovascular death or HF hospitalization, and
243 similar risk of the remainder outcomes, compared to patients in whom eGFR
244 increased (T3: $\geq 0.0\%$ change) (**Figure 4a**). In the placebo group, patients who
245 experienced the steepest eGFR decrease (T1: $\leq -6.5\%$ change) had a higher risk of
246 the kidney composite outcome (HR 2.38, 95%CI 1.25-4.55) and all-cause mortality
247 (HR 1.37, 95%CI 1.01-1.85) compared to patients in whom eGFR increased (T3: \geq
248 $+3.6\%$ change). The risk of cardiovascular death or HF hospitalizations and
249 cardiovascular death was similar across tertiles (**Figure 4b**).

250 Analyzing the effect of empagliflozin vs. placebo across the spectrum of %eGFR
251 change, we may observe that empagliflozin reduced the risk of the primary outcome
252 for most patients across the spectrum of eGFR changes (**Figure 5a**). Patients with
253 eGFR decrease seemed to have experienced a greater benefit from treatment with
254 empagliflozin than patients with eGFR increase (treatment-by-eGFR changes
255 interaction $P = 0.082$). A similar pattern to that observed for the primary outcome was
256 observed for the composite renal endpoint (**Figure 5d**). The effect of empagliflozin on
257 cardiovascular death and all-cause mortality was neutral across the eGFR spectrum
258 (**Figures 5b & 5c**), as it was in the overall trial.

259 In the empagliflozin group, 249 patients experienced an eGFR decrease $>20\%$, of
260 whom 45 (18.1%) had a primary outcome event. In the placebo group, 132 patients
261 experienced an eGFR decrease $>20\%$, of whom 28 (21.2%) had a primary outcome
262 event. The risk of subsequent primary outcome events was similar between
263 empagliflozin and placebo groups regardless of an eGFR decrease $>20\%$

264 (interaction $P = 0.64$) (**Figure 6**). In the empagliflozin group, 76 patients experienced
265 an eGFR decrease $>30\%$, of whom 20 (26.3%) had a primary outcome event. In the
266 placebo group, 45 patients experienced an eGFR decrease $>30\%$, of whom 11
267 (24.4%) had a primary outcome event. The risk of subsequent primary outcome
268 events was similar between empagliflozin and placebo groups regardless of an
269 eGFR decrease $>30\%$ (interaction $P = 0.50$) (**Figure 6**). In the empagliflozin group,
270 patients with an eGFR decrease $>30\%$ experienced a similar risk compared to
271 patients with eGFR increase for the primary outcome, HF hospitalization,
272 cardiovascular death, and all-cause mortality (**Supplemental Figure 3a**). In the
273 placebo group, patients with an eGFR decrease $>30\%$ had a tendency for a higher
274 risk of cardiovascular and all-cause death compared to patients with eGFR increase
275 (**Supplemental Figure 3b**). The risk of composite renal outcome and acute renal
276 failure was increased in patients with an eGFR decrease $>30\%$ compared to patients
277 with eGFR increase, regardless of the treatment group (**Supplemental Figures 4a &**
278 **4b**).

279 **Association of % eGFR changes with subsequent safety outcomes within each** 280 **treatment group**

281 In the empagliflozin group compared to patients in whom eGFR increased (T3: \geq
282 0.0% change), patients who experienced the steepest eGFR decrease (T1: $\leq -11.4\%$
283 change) had a similar risk of acute kidney injury and acute renal failure (**Figure 7a**).
284 In the placebo group compared to patients in whom eGFR increased (T3: $\geq +3.6\%$
285 change), patients who experienced the steepest eGFR decrease (T1: $\leq -6.5\%$
286 change) had a higher risk of acute renal failure (adjusted HR 1.58, 95%CI 1.08-
287 2.32). The risk of acute kidney injury was not statistically different across tertiles
288 (**Figure 7b**).

289

290 **Discussion**

291 Our study shows that, in patients with HFrEF enrolled in the EMPEROR-Reduced
292 trial, early post-initiation eGFR changes were common and bidirectional; however,
293 more patients had a mild eGFR decrease (-2.5 ml/min on average) after initiation of
294 empagliflozin than after the initiation of placebo. The initial eGFR decrease was only
295 associated with subsequent higher risk for the kidney composite outcome and all-
296 cause mortality, if occurring in the placebo group, and not with empagliflozin. Any
297 post-empagliflozin initiation decrease in eGFR not only did not deprive patients from
298 benefiting from empagliflozin therapy as it suggests that these patients may benefit
299 more than patients who experience eGFR increases >15-20% from baseline.

300 These findings replicate those from DAPA-HF where patients experiencing an early
301 eGFR decrease with dapagliflozin had better outcomes than patients with eGFR
302 decline taking placebo. Large eGFR decreases with SGLT2i were uncommon in both
303 trials.¹¹ Together, these findings allow to inform clinicians about the impact of eGFR
304 changes after SGLT2i initiation. An initial and mild eGFR decrease after SGLT2i
305 treatment may be expected. It is usually mild (on average <5% change from
306 baseline) and does not deprive patients from benefiting of SGLT2i therapy,
307 emphasizing that clinicians should not stop or withhold treatment solely due to this
308 initial eGFR decrease.²

309 Under normal conditions the SGLT2 (and SGLT1 to a lesser extent) induces
310 reabsorption of glucose, chloride, and sodium in the proximal tubule of the kidney.
311 Under circumstances where the reabsorption of glucose, chloride, sodium, and fluid
312 is excessive (e.g., CKD and diabetes), a tubuloglomerular feedback mechanism
313 increases eGFR in order to promote restoration of glucose, sodium, and volume

314 excretion; however, it is currently unknown whether this is true for patients with
315 HF_rEF.¹⁵ These compensatory mechanisms lead to tubular growth, hyperfiltration
316 and higher oxygen demand, promoting inflammation, fibrosis, and kidney
317 dysfunction, particularly in patients with diabetes or CKD (who represented nearly
318 75% of EMPEROR-Reduced patients).^{5, 16} In addition, it is possible that
319 inflammation, circulating proinflammatory cytokines and oxidative stress, which are
320 overamplified in heart failure, also contribute to kidney dysfunction.¹⁷ Treatment with
321 SGLT2i may reverse these deleterious mechanisms along with a slight decrease in
322 eGFR within the first few weeks of treatment due to the rapid reversion of
323 hyperfiltration.⁷ The mitigation of tubular stress and hyperfiltration will lead to a
324 further decrease in oxygen demand and reactive oxygen species, subsequently
325 reducing inflammation and fibrosis, ultimately leading to eGFR stabilization after the
326 initial decline.¹⁸ In other words, the eGFR decline early after SGLT2i initiation is likely
327 hemodynamic and not structural, which is consistent with the “tubular hypothesis”.⁵
328 Therefore, the results of this analysis strongly suggest that clinicians reassessing
329 eGFR within 4-8 weeks of SGLT2i initiation (for any other clinical imperative than
330 SGLT2i initiation itself) should expect to observe a slight decrease in eGFR, and be
331 reassured that this does not deprive their patient from benefiting from empagliflozin
332 treatment.

333 As seen in our study, the eGFR decrease with empagliflozin was more pronounced
334 in patients with high blood pressure and those who have not been hospitalized for
335 HF (likely because those with a HF hospitalization received IV diuretics that
336 increased the excretion of sodium). We speculate that these patients might have
337 higher sodium reabsorption as a result of higher sodium avidity.^{5, 6, 19}

338 Similar observations with SGLT2i have been consistently reported in randomized
339 placebo-controlled trials in patients with diabetes, CKD and HFrEF, whereby SGLT2i
340 initiation is more frequently associated with an early eGFR decrease, usually
341 measured 4 weeks post-initiation). Examining eGFR changes, we could describe an
342 overall largely random normally distributed variation of eGFR when measured 4
343 weeks apart. In patients initiated on empagliflozin we could substantiate a leftward
344 shift of the distribution with more patients experiencing an early eGFR decrease than
345 with placebo. Importantly, in contrast to placebo treated patients, and whatever the
346 initial eGFR change, there is a long-term kidney function preservation, as evidenced
347 by a significant slowing of eGFR decline (i.e., eGFR “slope”), and significantly less
348 serious sustained eGFR decline, end stage kidney disease or kidney death .^{2, 4, 20} In
349 addition, discontinuation of empagliflozin, as planned per protocol, at the end of the
350 study, restored eGFR to pre-treatment levels, whereas among patients randomized
351 to placebo eGFR did not change post-discontinuation and remained lower than in the
352 pre-treatment period.

353 Previous reports studying the initial eGFR changes in patients with diabetes
354 randomized to either SGLT2i or placebo did not find an impact of eGFR decrease on
355 the clinical benefit of SGLT2i.¹⁰

356 An initial eGFR decrease can also occur after the initiation of inhibitors of the renin-
357 angiotensin aldosterone system (RAAS), often leading clinicians to withhold or stop
358 RAAS inhibitors, despite their proven benefit in HFrEF regardless of the initial eGFR
359 decrease.⁹ Only with an eGFR decrease of >30% more adverse events were
360 observed and warrant RAAS inhibitor dose adjustment or discontinuation.

361 Interestingly, in our analysis, background RAAS inhibition did not modify the eGFR
362 change following empagliflozin treatment initiation, and occurrence of eGFR

363 decreases of >30% were uncommon in both treatments. While for RAAS inhibitors
364 one may argue that eGFR needs to be re-checked early post-initiation to assess the
365 potential for drug up-titration, for SGLT2 inhibitors this concern does not apply
366 because they do not need up-titration. Our results suggest that eGFR changes post
367 SGLT2i initiation are hemodynamic and without prognostic implications. Therefore,
368 an early eGFR decrease after the initiation of SGLT2i is expected and should not
369 lead clinicians to withhold or stop treatment. We would recommend to not monitor
370 eGFR within the first month post SGLT2i initiation, unless clinically indicated, e.g., for
371 suspected kidney injury.

372 **Limitations**

373 Some limitations should be highlighted in this study. This is a secondary analysis of
374 a randomized trial with the aim of exploring the association between the initial eGFR
375 changes and outcomes per treatment group. While categories of initial eGFR
376 changes were defined based on post-randomization values, patients across the
377 tertiles of %eGFR changes significantly differed with respect to some of their
378 baseline characteristics. The landmark analysis does not allow for a randomized
379 comparison, as patients who died or had experienced an event before the 4-week
380 eGFR measurement were excluded from the analyses and others might have
381 stopped treatment or not have eGFR obtained. We have tried to mitigate these
382 potential biases by covariate adjustment for corresponding EMPEROR-Reduced risk
383 scores, but this by no means replaces randomization. Therefore, these findings
384 should be regarded as hypothesis-generating. In addition, much of the mechanistic
385 speculation we offer is based on pathophysiological knowledge relating to patients
386 with CKD and/or diabetes, which may or may not apply to all patients with HFrEF.

387

388 **Conclusions**

389 A mild eGFR decrease may expected after the initiation of empagliflozin, it is not
390 associated with untoward kidney safety concerns, and it may indicate that the drug is
391 having its intended effects that improve HF outcomes. Clinicians should not be
392 concerned with early eGFR changes post-initiation of empagliflozin.

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401

402 **Data sharing**

403 Data will be made available upon request in adherence with transparency
404 conventions in medical research and through requests to the corresponding author.

405 The executive committee of EMPEROR has developed a comprehensive analysis
406 plan and numerous prespecified analyses, which will be presented in future scientific
407 meetings and publications. At a later time-point, the full database will be made
408 available in adherence with the transparency policy of the sponsor (available at
409 https://trials.boehringer-ingelheim.com/transparency_policy.html).

410

411 **Disclosures**

412 FZ reports personal fees from Boehringer Ingelheim during the conduct of the study;
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442

443 **Author Contributions**

444 All authors contributed to the conceptualization of this analysis. The sponsor
445 representatives (BJK and MM) were responsible for project administration and
446 supervision of study conduct. MM (an employee of Boehringer Ingelheim) did the
447 statistical analysis. FZ and MM have accessed and verified the underlying data. FZ
448 drafted the first version of the manuscript and subsequent revisions. All the other
449 authors read and edited the manuscript. All authors approved the final version and
450 the decision to submit the manuscript.

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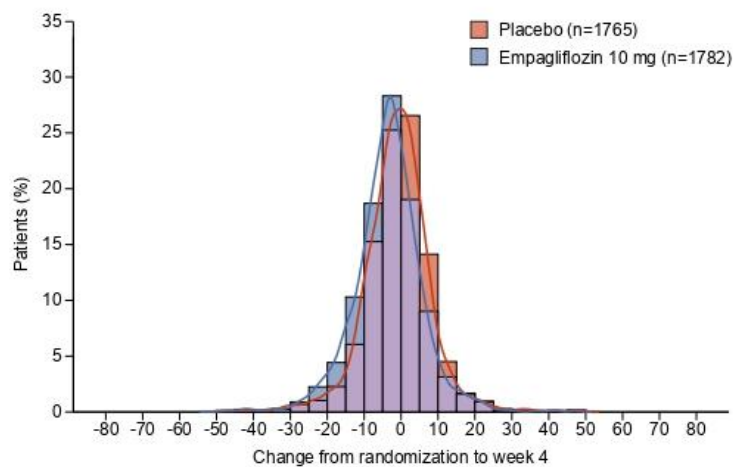
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595

596 **Figure 1.** Distribution of individual eGFR change (mL/min/1.73m²) from
597 randomization to week 4 by treatment group.

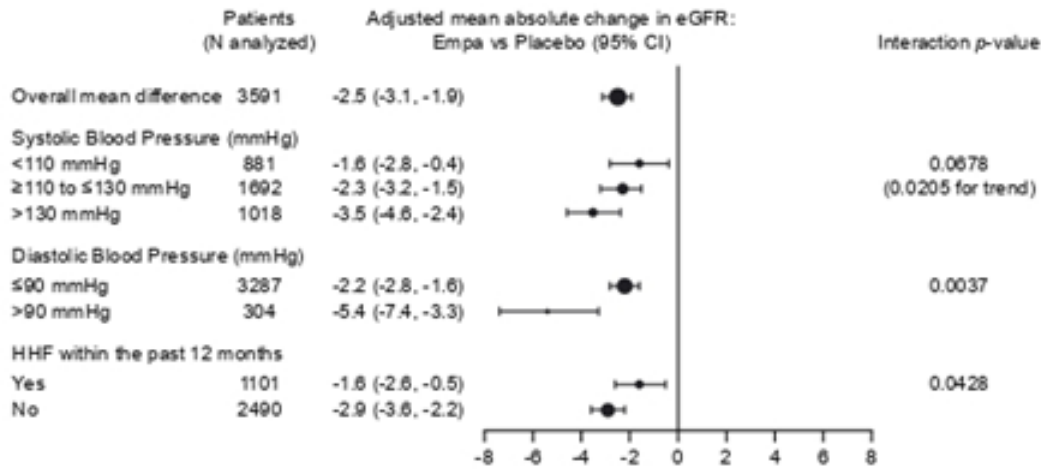


598

599 Legend: The mean difference in 4-week eGFR change with empagliflozin is -

600 2.5mL/min/1.73m².

601 **Figure 2.** Baseline covariates with modified effect of empagliflozin on eGFR change
 602 from randomization to week 4.



603

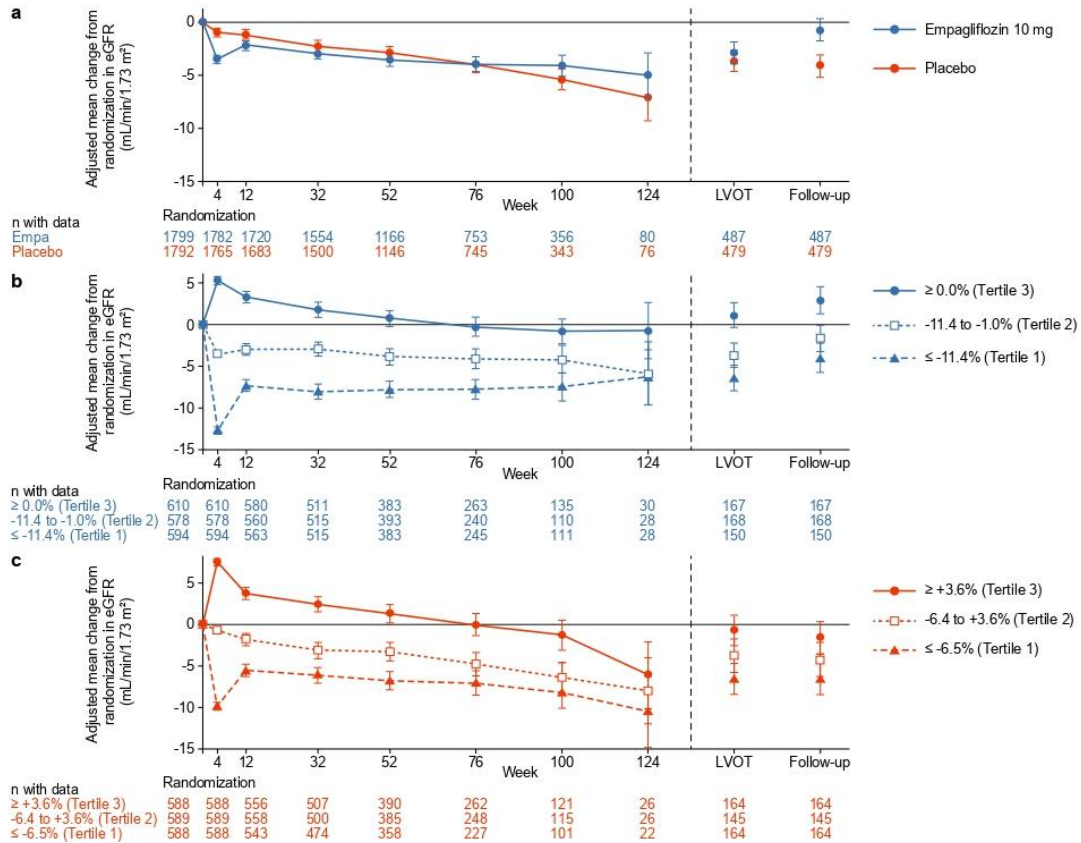
604 Legend: ACEi, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB,
 605 angiotensin receptor blocker; ARNi, angiotensin receptor neprilysin inhibitor; BMI,
 606 body mass index; CCB, calcium channel blocker; CI, confidence interval; CRT,
 607 cardiac resynchronization therapy; CRT-D, cardiac resynchronisation therapy with
 608 defibrillator; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration
 609 rate; HF, heart failure; ICD, implantable cardioverter defibrillator; LVEF, left
 610 ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-
 611 proBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart
 612 Association; SBP, systolic blood pressure; UACR, urine albumin to creatinine ratio.
 613 The numbers represent the difference in adjusted mean changes from baseline in
 614 the eGFR.

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

620 Caption: SBP, DBP, and prior HHF within 12 months, were the only 3 variables
621 associated with eGFR change in the empagliflozin group vs. the placebo group i.e.,
622 with variable by treatment interaction $P < 0.05$ at week 4.

623 Baseline variables with homogeneous treatment effect of empagliflozin vs placebo
624 on eGFR change at week 4 were: age, sex, BMI, race, region, LVEF, NYHA
625 functional class, NT-proBNP, cause of HF, time since diagnosis of HF, heart rate,
626 history of AF, history of hypertension, diabetes status, smoking status, eGFR,
627 UACR, anemia, ACEi/ARB use, ARNi use, beta-blocker use, thiazide or low-ceiling
628 diuretic use, MRA use, cardiac glycosides use, loop diuretic use, loop diuretic dose,
629 CCB use, nitrate use, ivabradine use, statin use, antiplatelet use, anticoagulant use,
630 ICD or CRT-D use, CRT use, and HF physiology.

631 **Figure 3.** Change in eGFR from randomization a) by treatment group; b) by tertiles
 632 of % eGFR change at week 4 within the empagliflozin group; c) by tertiles of %
 633 eGFR change at week 4 within the placebo group.



634
635

636 Legend: Left side: The on-treatment data were analyzed with the use of a mixed
 637 model for repeated measures based on patients who received at least one dose of a
 638 study drug and had a baseline and postbaseline measurement (a) and a week 4
 639 measurement (b, c).

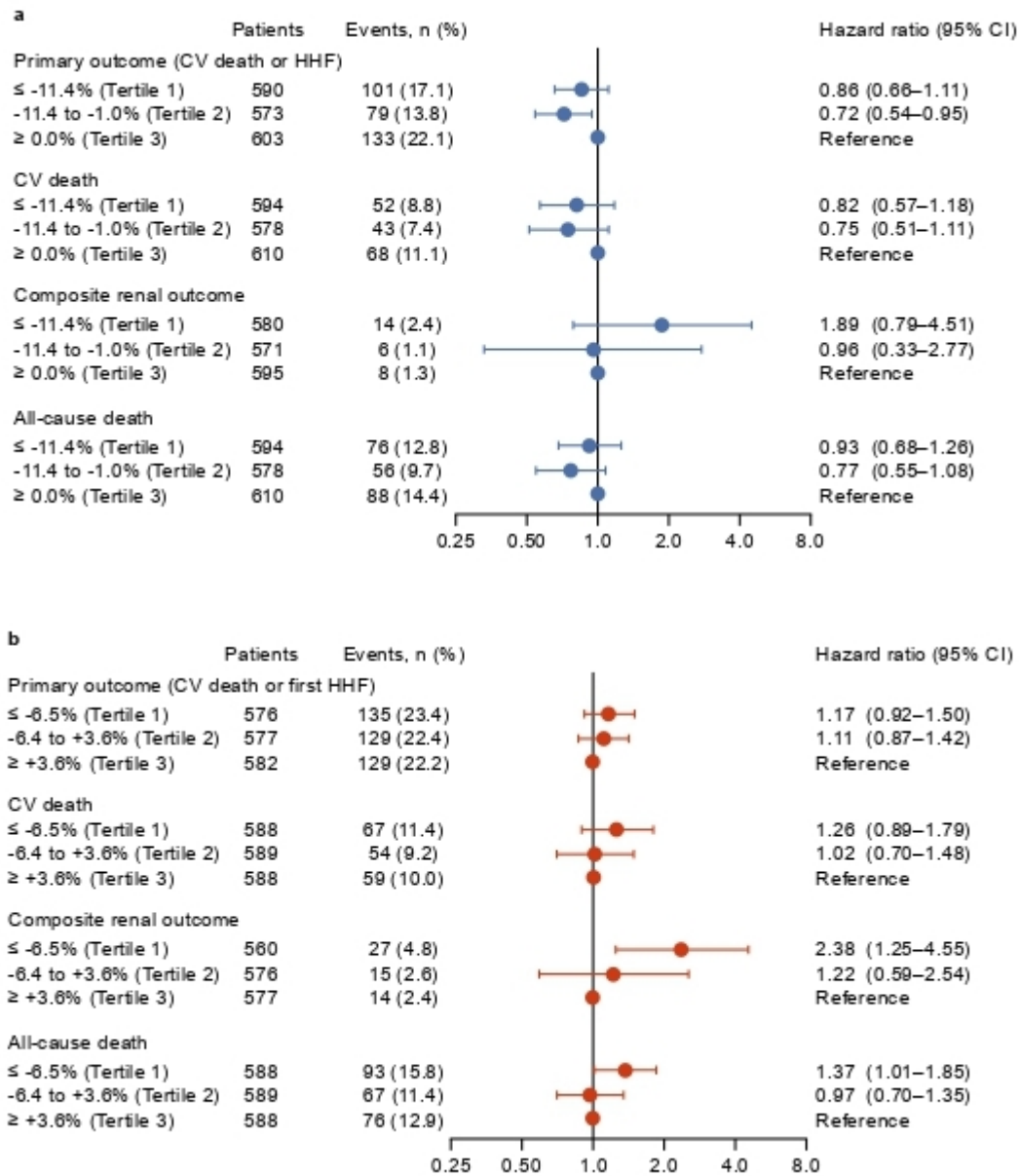
640 Right side: The LVOT and FUP change from randomization are based on an
 641 analysis of a covariance model in patients who underwent measurements at
 642 baseline, LVOT and FUP (a) and week 4 (b, c).

643 Empagliflozin: Tertile 1 ≤ -11.4%; Tertile 2 ≥ -11.4% to ≤ -1.0% and Tertile 3 ≥ 0.0%

644 Placebo: Tertile 1 ≤ -6.5%; Tertile 2 ≥ -6.4% to ≤ +3.6%; and Tertile 3 ≥ +3.6%.

645 Corresponding mean eGFR changes per year (annualized slopes): empagliflozin: T1
646 +2.35mL/min/1.73m², T2 -0.47mL/min/1.73m² and T3 -3.52 mL/min/1.73m²; placebo:
647 T1 +1.14mL/min/1.73m², T2 -2.95mL/min/1.73m² and T3 -4.93 mL/min/1.73m².

648 **Figure 4.** Primary, composite renal and mortality outcomes following week 4 by
 649 tertiles of %eGFR change at Week 4 by treatment group (a, empagliflozin; b,
 650 placebo).



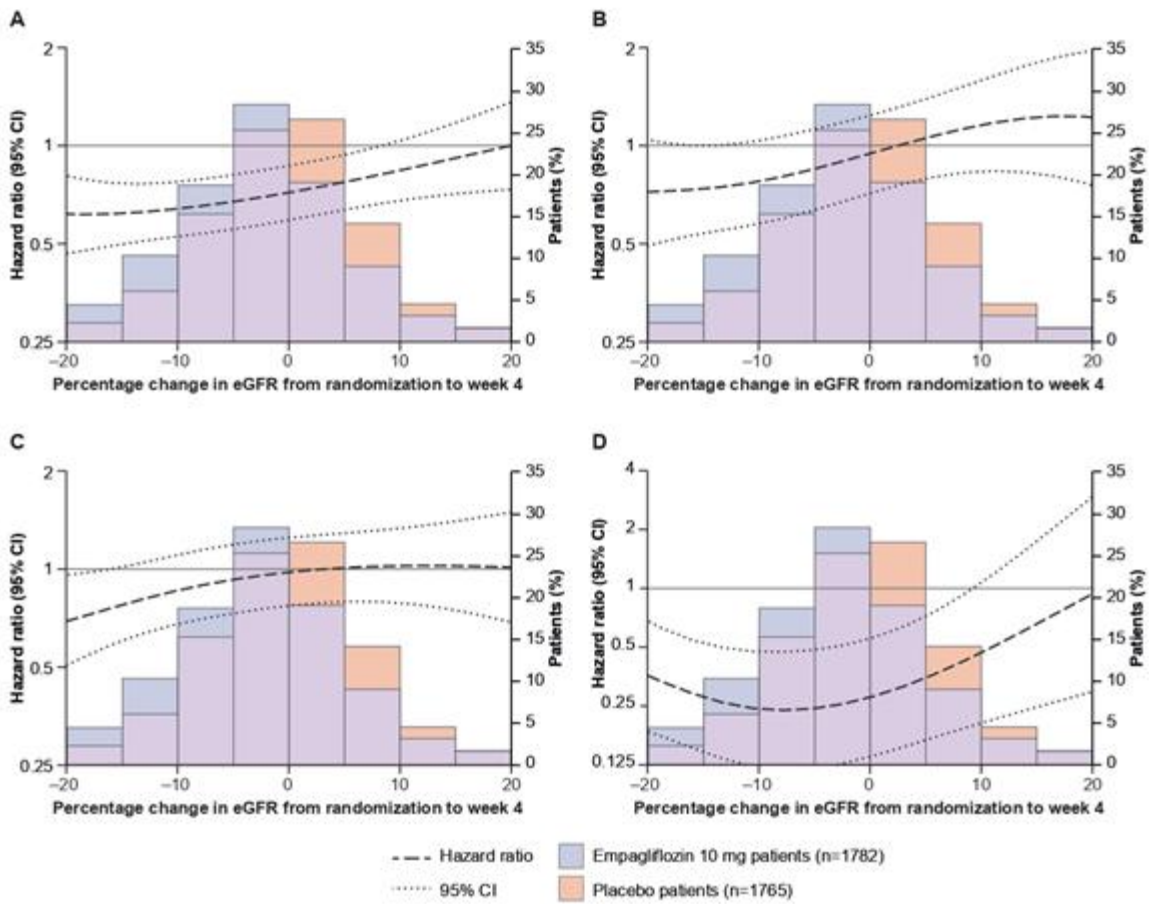
651

652 Legend: Hazard ratios based on a Cox regression model with adjustment for the
 653 EMPEROR-Reduced risk score for the primary outcome, CV death, mortality (latter
 654 is used for composite renal outcome and all-cause death).

655 Empagliflozin: Tertile 1 ≤ -11.4%; Tertile 2 ≥ -11.4% to ≤ -1.0% and Tertile 3 ≥ 0.0%

656 Placebo: Tertile 1 ≤ -6.5%; Tertile 2 ≥ -6.4% to ≤ +3.6%; and Tertile 3 ≥ +3.6%.

657 **Figure 5.** Effect of empagliflozin versus placebo across the spectrum of eGFR
 658 change.



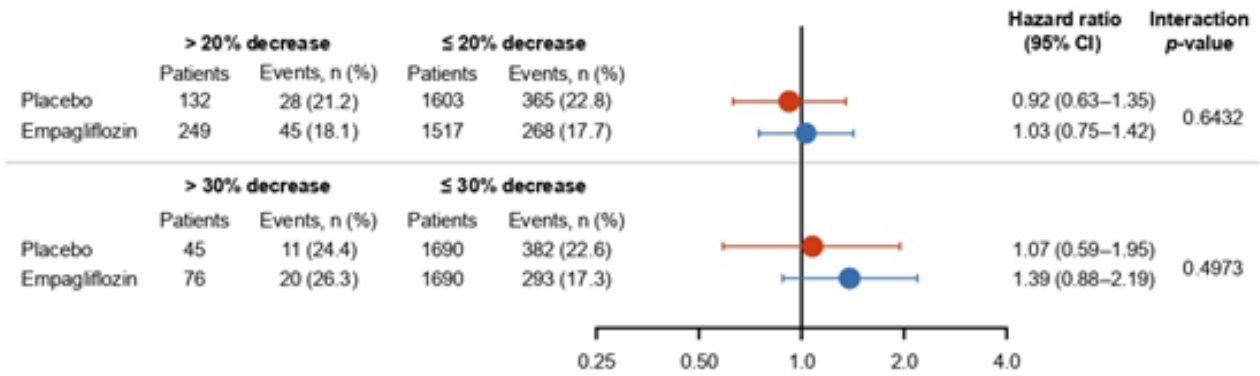
659

660 Legend: a) primary composite outcome of cardiovascular death or heart failure
 661 hospitalization; b) cardiovascular mortality; c) all-cause mortality; d) composite renal
 662 endpoint.

663 %eGFR change-by-treatment interaction p-values for the endpoints (all adjusted for
 664 EMPEROR-Reduced risk score): a) primary outcome interaction P =0.082; b)
 665 cardiovascular mortality interaction P =0.089; c) all-cause mortality interaction P
 666 =0.55; d) renal composite interaction P <0.0001.

667

668 **Figure 6.** Risk of subsequent primary outcome events with week 4 eGFR decrease



669 >20% and >30% from baseline

670

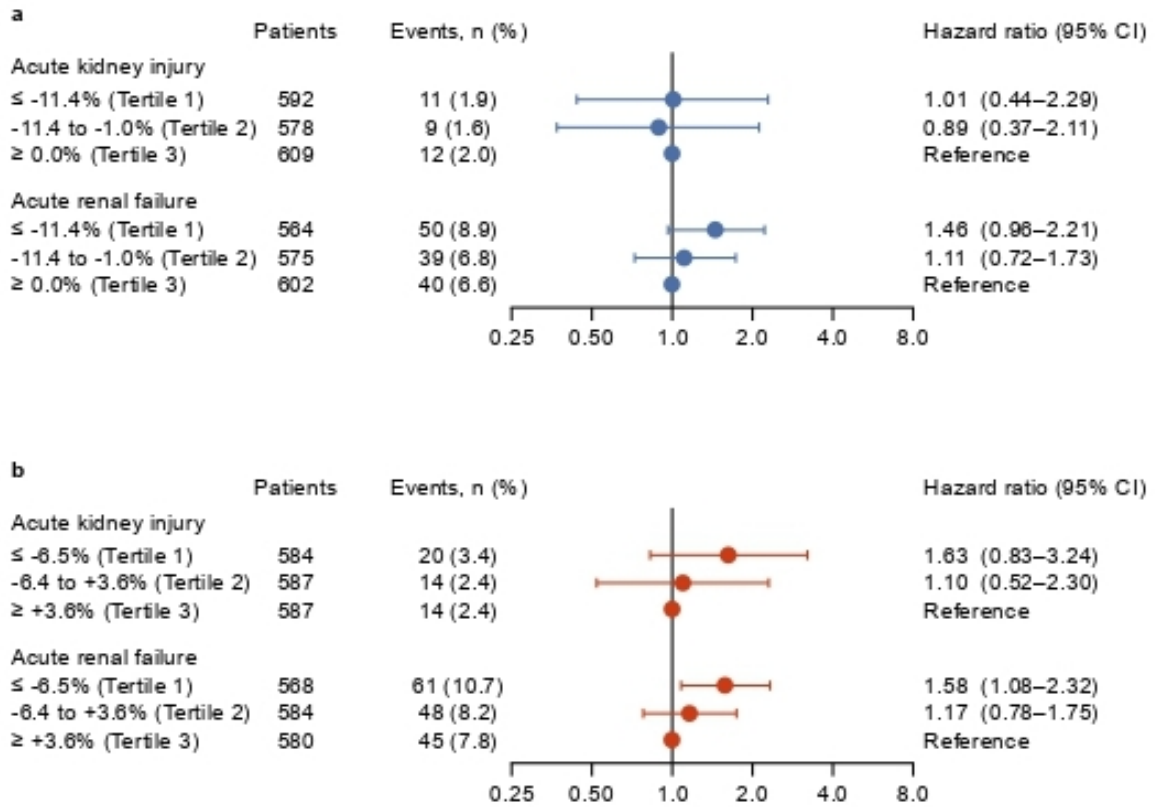
671 Legend: The risk of subsequent primary outcome events was similar between

672 empagliflozin and placebo groups regardless of an eGFR decrease >20%

673 (interaction P =0.64) or an eGFR decrease >30% (interaction P =0.50).

674

675 **Figure 7.** Kidney safety outcomes following week 4 by tertiles of %eGFR change at
 676 Week 4 by treatment group.



677

678 Legend: a, empagliflozin; b, placebo.

679 Hazard ratios based on a Cox regression with adjustment for the EMPEROR-

680 Reduced all-cause mortality risk score. Based on data obtained up until 7 days

681 following discontinuation of the study medication. The terms used for this analysis

682 were defined following the Medical Dictionary for Regulatory Activities (MedDRA).

683 Acute kidney injury was based on the reporting of the preferred term “acute kidney

684 injury”, and acute renal failure was based on the on the narrow Standardized

685 MedDRA Query (SMQ) 20000003, based on 19 preferred terms (MedDRA version

686 23.0).

687 Empagliflozin: Tertile 1 ≤ -11.4%; Tertile 2 ≥ -11.4% to ≤ -1.0% and Tertile 3 ≥ 0.0%

688 Placebo: Tertile 1 ≤ -6.5%; Tertile 2 ≥ -6.4% to ≤ +3.6%; and Tertile 3 ≥ +3.6%.