

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

Faiez Zannad, João Pedro Ferreira, John Gregson, Bettina Johanna Kraus, Michaela Mattheus, Sibylle Jenny Hauske, Javed Butler, Gerasimos Filippatos, Christoph Wanner, Stefan D Anker, et al.

#### ▶ To cite this version:

Faiez Zannad, João Pedro Ferreira, John Gregson, Bettina Johanna Kraus, Michaela Mattheus, et al.. Early changes in estimated glomerular filtration rate post-initiation of empagliflozin in EMPEROR-Reduced. European Journal of Heart Failure, 2022, 24 (10), pp.1829-1839. 10.1002/ejhf.2578. hal-03813870

# HAL Id: hal-03813870 https://hal.univ-lorraine.fr/hal-03813870

Submitted on 13 Oct 2022

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

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

- Faiez Zannad, MD, PhD<sup>1\*</sup>; João Pedro Ferreira, MD, PhD<sup>1.2</sup>; John Gregson, PhD<sup>3</sup>;
- 4 Bettina Johanna Kraus, MD<sup>4,6</sup>; Michaela Mattheus, MSc<sup>7</sup>; Sibylle Jenny Hauske,
- 5 MD<sup>4,5</sup>; Javed Butler, MD MPH MBA<sup>8</sup>; Gerasimos Filippatos, MD, PhD<sup>9</sup>; Christoph
- Wanner, MD<sup>10</sup>; Stefan D. Anker, MD, PhD<sup>11</sup>; Stuart J. Pocock, PhD<sup>3</sup>; Milton Packer,
- 7 MD<sup>12,13</sup> for the EMPEROR-Reduced Trial Committees and Investigators

<sup>1</sup>Université de Lorraine, Inserm, Center d'Investigations Cliniques, - Plurithématique

10 14-33, and Inserm U1116, CHRU, F-CRIN INI-CRCT (Cardiovascular and Renal

11 Clinical Trialists), Nancy, France; <sup>2</sup>Cardiovascular Research and Development

12 Center, Department of Surgery and Physiology, Faculty of Medicine of the University

of Porto, Porto, Portugal; <sup>3</sup>Department of Medical Statistics, London School of

14 Hygiene and Tropical Medicine, London, UK; <sup>4</sup>Boehringer Ingelheim International

15 GmbH, Ingelheim, Germany; <sup>5</sup>Vth Department of Medicine, University Medical

16 Center Mannheim, University of Heidelberg, Heidelberg, Germany; <sup>6</sup>Comprehensive

17 Heart Failure Center, University of Würzburg, Würzburg, Germany; <sup>7</sup>Biostatistics,

Boehringer Ingelheim Pharma GmbH & Co KG, Ingelheim; <sup>8</sup>Department of Medicine,

University of Mississippi School of Medicine, Jackson, MS, USA; <sup>9</sup>National and

20 Kapodistrian University of Athens School of Medicine, Athens, Greece; <sup>10</sup>Würzburg

21 University Clinic, Würzburg, Germany; <sup>11</sup>Department of Cardiology (CVK), and Berlin

22 Institute of Health Center for Regenerative Therapies, German Center for

23 Cardiovascular Research Partner Site Berlin, Charité Universitätsmedizin, Berlin,

24 Germany; <sup>12</sup>Baylor Heart and Vascular Institute, Baylor University Medical Center,

Dallas TX USA; <sup>13</sup>Imperial College, London UK

## 27 \*Corresponding Author

- 28 Professor Faiez Zannad
- 29 Center d'Investigation Clinique 1433 module Plurithématique
- 30 CHRU Nancy Hopitaux de Brabois
- 31 Institut Lorrain du Coeur et des Vaisseaux Louis Mathieu
- 4 rue du Morvan, 54500 Vandoeuvre les Nancy
- 33 Tel: +33 (0) 3 83 15 73 15
- 34 Fax: +33 (0) 3 83 15 73 24
- 35 Email: f.zannad@chru-nancy.fr

37 **Word count:** 3142/3500

#### Abstract

- 39 Background: Sodium glucose co-transporter 2 inhibitors (SGLT2i) may induce an
- early post-initiation eGFR decrease which does not impact the SGLT2i benefits. The
- occurrence, characteristics, determinants, and clinical significance of an initial eGFR
- 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
- 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) ≤-11.4%; T2 ≥-
- 49 11.4% to ≤-1.0% and T3 ≥0.0%. The placebo group tertiles were: T1 ≤-6.5%; T2 ≥-
- 50 6.4% to ≤+3.6%; and T3 ≥+3.6%. On average, empagliflozin induced a leftward
- distributional shift of initial eGFR changes of -2.5 ml/min/1.73m<sup>2</sup> vs. placebo. In the
- 52 empagliflozin group, after covariate adjustment, the risk of cardiovascular and renal
- outcomes did not differ between patients in whom early post treatment initiation
- 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
- 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,
- it is not associated with untoward kidney safety concerns, and it may indicate that

- the drug is having its intended effects that improve HF outcomes. Clinicians should
- not be concerned with early eGFR changes post-initiation of empagliflozin.
- 64 Key-words: estimated glomerular filtration rate; heart failure with reduced ejection
- 65 fraction; empagliflozin; outcomes.

68

69

70

71

72

73

74

75

76

77

78

79

80

81

82

83

84

85

86

87

88

89

90

91

92

Introduction

Sodium glucose co-transporter 2 inhibitors (SGLT2i) reduce major cardiovascular events, particularly heart failure hospitalizations (HHF), and improve kidney outcomes in patients with type 2 diabetes (T2D), chronic kidney disease (CKD), and heart failure with a reduced ejection fraction (HFrEF). Additionally, in heart failure with reduced ejection fraction, treatment with SGLT2i, over a period of between one to two years, slows the rate of decline in estimated glomerular filtration rate (eGFR) compared with placebo, as assessed by the difference in eGFR slopes from week 4 after treatment initiation.<sup>2-4</sup> However, SGLT2i may induce an initial eGFR decrease, which may result from an acute reduction in intraglomerular pressure. 5-8 Despite some biological understanding of the effect of SGLT2i in the kidneys. particularly the hemodynamic mechanisms are rather complex. Clinicians may feel concerned when they see an eGFR decrease early after SGLT2i initiation, and out of risk aversion, they may be tempted to stop or withhold treatment. This behavior is also very common when clinicians are faced with an early decrease after initiation of a renin angiotensin aldosterone system inhibitor.9 In patients with T2D enrolled in the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) and in the Canagliflozin and Renal Events in Diabetes With Established Nephropathy Clinical Evaluation (CREDENCE) trials, the clinical benefit of empagliflozin and canagliflozin, respectively, compared with placebo, was not impacted by the initial eGFR decrease. 10 In patients with HFrEF enrolled in the Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients With Chronic Heart Failure (DAPA-HF), the eGFR decrease after initiation of dapagliflozin was of small magnitude, on average, and associated with better

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

In the present study, we aim to describe the occurrence, characteristics, determinants, and prognostic significance of eGFR change in the early post-treatment initiation period, in patients with HFrEF enrolled in the EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Reduced Ejection Fraction (E

MPEROR-Reduced) trial.

#### **Methods**

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

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

#### Randomization

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 heart failure, initiation, vital signs, and biomarkers (including eGFR), and adverse events.

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

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

### **Trial Endpoints**

The primary endpoint was the composite of adjudicated cardiovascular death or hospitalization for heart failure, 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 ≥40% decrease in eGFR or a sustained eGFR <15 mL/min/1.73m² (if the baseline eGFR was ≥30 mL/min/1.73m²) or <10 mL/min/1.73m² (if the baseline eGFR was <30 mL/min/1.73m²) were also analysed. 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] 20000003, "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**

141

142

143

144

145

146

147

148

149

150

151

152

153

154

155

156

157

158

159

160

161

162

163

164

165

166

For this analysis, 3547 out of 3730 (95%) 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. The 4-week measurement was the first time point at which eGFR measurements were available following randomization. We categorized 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) into tertiles in each treatment group separately. We described and compared the patients' baseline characteristics across these tertiles. As the initial eGFR change was computed from randomization to week 4, we used landmark analyses (with landmark at week 4) to study the associations of % eGFR change with 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 an endpoint event. We used Cox proportional hazards models to calculate hazard ratios comparing the tertiles of % eGFR changes within each treatment group for each of the primary outcome, CV death and all-cause death after adjusting for the corresponding EMPEROR-Reduced risk score. 14 An equivalent model was used to investigate safety outcomes including adjustment for the EMPEROR-Reduced mortality risk score. 14 Additionally, we analyzed eGFR changes as a continuous covariate and tested treatment-by-eGFR changes interaction across the continuous spectrum of eGFR change, adjusting for the EMPEROR-Reduced risk models as above described. Sensitivity analysis to assess the risk associated with eGFR decreases >20% and >30% were also performed. 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 baseline age, sex, geographical region, diabetes, left ventricular ejection fraction, last projected visit based on dates of randomization and trial closure, treatment-by-visit interaction and randomization eGFR-by-visit interaction in all patients who received at least one dose of the study drug. This analysis was repeated within each treatment group to compare the tertiles of % eGFR changes (replacing term for treatment-by-visit interaction with tertile-by-visit interaction). 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 (i.e., follow-up) using an analysis of covariance with adjustment for the same baseline covariates including eGFR at randomization. This analysis was repeated within each treatment group to compare the tertiles of % eGFR changes (replacing term for treatment with tertile). 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, 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-byvisit interaction. P values and 95% confidence intervals presented in this report have not been adjusted for multiplicity. All analyses were performed using SAS, version 9.4 (SAS Institute).

189

190

191

188

167

168

169

170

171

172

173

174

175

176

177

178

179

180

181

182

183

184

185

186

187

#### Results

#### eGFR change post-initiation and baseline characteristics

Changes in eGFR from randomization to week 4 occurred both in the empagliflozin 192 and in the placebo groups, with a shift in eGFR change distribution to the left (i.e., 193 higher decrease) in the empagliflozin group of -2.5, 95%CI -3.1 to -1.9 194 ml/min/1.73m<sup>2</sup> on average compared to placebo (*Figure 1*). 195 Baseline covariates that modified the effect of empagliflozin on eGFR change from 196 randomization to week 4 were blood pressure at baseline and history of 197 hospitalization for HF in the previous 12 months (Figure 2). Patients with higher 198 blood pressure at baseline and no history of HHF in the previous 12 months had 199 larger placebo-corrected mean eGFR decrease from randomization to week 4 200 compared to patients with lower blood pressure and history of HHF, respectively. 201 The remaining baseline characteristics did not significantly modify the association of 202 empagliflozin with eGFR changes. Percentage eGFR changes (mean±SE) from 203 randomization at week 4 were -4.9±0.4% in empagliflozin and -0.8±0.4% in placebo 204 (Supplemental Figure 1). 205 The tertiles of % eGFR change in the early post-initiation period for empagliflozin 206 were: tertile 1 (T1) ≤ -11.4%; tertile 2 (T2) ≥ -11.4% to ≤ -1.0% and tertile 3 (T3) ≥ 207 0.0%. In the placebo group they were: T1  $\leq$  -6.5%; T2  $\geq$  -6.4% to  $\leq$  +3.6%; and T3  $\geq$ 208 +3.6%. Mean % eGFR changes for the tertiles were:  $-20.8 \pm 0.3\%$  (T1),  $-6.0 \pm 0.1\%$ 209 210 (T2),  $11.5 \pm 0.7\%$  (T3) in empagliflozin and  $-16.1 \pm 0.4\%$  (T1),  $-1.3 \pm 0.1\%$  (T2), 15.2± 0.6% (T3) in placebo. 211 The corresponding mean (± SD) serum creatinine increases in T1 were relatively 212 213 small:  $+0.29 \pm 0.21$  mg/dL in the empagliflozin group and  $+0.22 \pm 0.21$  mg/dL in the

placebo group (Supplemental Figure 2).

The characteristics of the patients across tertiles of eGFR change in empagliflozin 215 and placebo groups are presented in the **Supplemental Table 1**. 216 eGFR progression at 4 weeks and after 217 At week 4, empagliflozin-treated patients experienced an eGFR change of -3.5 (95%) 218 CI -3.9 to -3.1) compared to -1.0 (95% CI -1.4 to -0.6) in placebo-treated patients 219 220 (Figure 3a, left panel). In the subset of patients with available eGFR values after treatment discontinuation at the end of the trial, eGFR increased in empagliflozin-221 treated patients but remained similar to the last "on-treatment" value in placebo-222 treated patients (*Figure 3a, right panel*). 223 In empagliflozin-treated patients, among those with the steepest decrease at week 4 224 225 (T1: ≤ -11.4% change), eGFR increased throughout the follow-up, while among 226 those in whom eGFR increased at week 4 (T3: ≥ 0.0% change), eGFR decreased throughout the follow-up, and remained stable in T2, suggesting a "regression to the 227 228 mean" phenomenon (*Figure 3b, left panel*). After treatment discontinuation, eGFR increased across all tertiles (*Figure 3b, right panel*). 229 230 In placebo-treated patients with the largest eGFR decrease at week 4 (T1: ≤ -6.5 % change), eGFR recovered slightly at week 52 and then decreased subsequently. In 231 the 2 other tertiles, eGFR decreased continuously throughout the follow-up (*Figure* 232 **3c, left panel**). After placebo discontinuation, eGFR remained stable across all 233 tertiles (*Figure 3c, right panel*). 234 Association of %eGFR changes with subsequent cardiac, renal and mortality 235 outcomes 236 In the empagliflozin group, patients who experienced the steepest eGFR decrease 237 (T1: ≤ -11.4% change) had a similar risk of cardiovascular death or HF 238

hospitalization, cardiovascular death, all-cause mortality, and the kidney composite outcome, compared to patients in whom eGFR increased (T3: ≥ 0.0% change). Patients who experienced modest eGFR decreases with empagliflozin (T2: > -11.4% to -1.0% change) had a lower risk of cardiovascular death or HF hospitalization, and similar risk of the remainder outcomes, compared to patients in whom eGFR increased (T3: ≥ 0.0% change) (*Figure 4a*). In the placebo group, patients who experienced the steepest eGFR decrease (T1: ≤ -6.5% change) had a higher risk of the kidney composite outcome (HR 2.38, 95%CI 1.25-4.55) and all-cause mortality (HR 1.37, 95%CI 1.01-1.85) compared to patients in whom eGFR increased (T3: ≥ +3.6% change). The risk of cardiovascular death or HF hospitalizations and cardiovascular death was similar across tertiles (Figure 4b). Analyzing the effect of empagliflozin vs. placebo across the spectrum of %eGFR change, we may observe that empagliflozin reduced the risk of the primary outcome for most patients across the spectrum of eGFR changes (Figure 5a). Patients with eGFR decrease seemed to have experienced a greater benefit from treatment with empagliflozin than patients with eGFR increase (treatment-by-eGFR changes interaction P =0.082). A similar pattern to that observed for the primary outcome was observed for the composite renal endpoint (*Figure5d*). The effect of empagliflozin on cardiovascular death and all-cause mortality was neutral across the eGFR spectrum (Figures 5b & 5c), as it was in the overall trial. In the empagliflozin group, 249 patients experienced an eGFR decrease >20%, of whom 45 (18.1%) had a primary outcome event. In the placebo group, 132 patients experienced an eGFR decrease >20%, of whom 28 (21.2%) had a primary outcome event. The risk of subsequent primary outcome events was similar between empagliflozin and placebo groups regardless of an eGFR decrease >20%

239

240

241

242

243

244

245

246

247

248

249

250

251

252

253

254

255

256

257

258

259

260

261

262

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

# Association of % eGFR changes with subsequent safety outcomes within each treatment group

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

290

291

292

293

294

295

296

297

298

299

300

301

302

303

304

305

306

307

308

309

310

311

312

313

#### **Discussion**

Our study shows that, in patients with HFrEF enrolled in the EMPEROR-Reduced trial, early post-initiation eGFR changes were common and bidirectional; however, more patients had a mild eGFR decrease (-2.5 ml/min on average) after initiation of empagliflozin than after the initiation of placebo. The initial eGFR decrease was only associated with subsequent higher risk for the kidney composite outcome and allcause mortality, if occurring in the placebo group, and not with empagliflozin. Any post-empagliflozin initiation decrease in eGFR not only did not deprive patients from benefiting from empagliflozin therapy as it suggests that these patients may benefit more than patients who experience eGFR increases >15-20% from baseline. These findings replicate those from DAPA-HF where patients experiencing an early eGFR decrease with dapagliflozin had better outcomes than patients with eGFR decline taking placebo. Large eGFR decreases with SGLT2i were uncommon in both trials. 11 Together, these findings allow to inform clinicians about the impact of eGFR changes after SGLT2i initiation. An initial and mild eGFR decrease after SGLT2i treatment may be expected. It is usually mild (on average <5% change from baseline) and does not deprive patients from benefiting of SGLT2i therapy, emphasizing that clinicians should not stop or withhold treatment solely due to this initial eGFR decrease.2 Under normal conditions the SGLT2 (and SGLT1 to a lesser extent) induces reabsorption of glucose, chloride, and sodium in the proximal tubule of the kidney. Under circumstances where the reabsorption of glucose, chloride, sodium, and fluid is excessive (e.g., CKD and diabetes), a tubuloglomerular feedback mechanism increases eGFR in order to promote restoration of glucose, sodium, and volume

excretion; however, it is currently unknown whether this is true for patients with HFrEF.<sup>15</sup> These compensatory mechanisms lead to tubular growth, hyperfiltration and higher oxygen demand, promoting inflammation, fibrosis, and kidney dysfunction, particularly in patients with diabetes or CKD (who represented nearly 75% of EMPEROR-Reduced patients).<sup>5, 16</sup> In addition, it is possible that inflammation, circulating proinflammatory cytokines and oxidative stress, which are overamplified in heart failure, also contribute to kidney dysfunction. Treatment with SGLT2i may reverse these deleterious mechanisms along with a slight decrease in eGFR within the first few weeks of treatment due to the rapid reversion of hyperfiltration. The mitigation of tubular stress and hyperfiltration will lead to a further decrease in oxygen demand and reactive oxygen species, subsequently reducing inflammation and fibrosis, ultimately leading to eGFR stabilization after the initial decline. 18 In other words, the eGFR decline early after SGLT2i initiation is likely hemodynamic and not structural, which is consistent with the "tubular hypothesis".5 Therefore, the results of this analysis strongly suggest that clinicians reassessing eGFR within 4-8 weeks of SGLT2i initiation (for any other clinical imperative than SGLT2i initiation itself) should expect to observe a slight decrease in eGFR, and be reassured that this does not deprive their patient from benefiting from empagliflozin treatment. As seen in our study, the eGFR decrease with empagliflozin was more pronounced in patients with high blood pressure and those who have not been hospitalized for HF (likely because those with a HF hospitalization received IV diuretics that increased the excretion of sodium). We speculate that these patients might have higher sodium reabsorption as a result of higher sodium avidity.<sup>5, 6, 19</sup>

314

315

316

317

318

319

320

321

322

323

324

325

326

327

328

329

330

331

332

333

334

335

336

Similar observations with SGLT2i have been consistently reported in randomized placebo-controlled trials in patients with diabetes, CKD and HFrEF, whereby SGLT2i initiation is more frequently associated with an early eGFR decrease, usually measured 4 weeks post-initiation). Examining eGFR changes, we could describe an overall largely random normally distributed variation of eGFR when measured 4 weeks apart. In patients initiated on empagliflozin we could substantiate a leftward shift of the distribution with more patients experiencing an early eGFR decrease than with placebo. Importantly, in contrast to placebo treated patients, and whatever the initial eGFR change, there is a long-term kidney function preservation, as evidenced by a significant slowing of eGFR decline (i.e., eGFR "slope"), and significantly less serious sustained eGFR decline, end stage kidney disease or kidney death .2, 4, 20 In addition, discontinuation of empagliflozin, as planned per protocol, at the end of the study, restored eGFR to pre-treatment levels, whereas among patients randomized to placebo eGFR did not change post-discontinuation and remained lower than in the pre-treatment period. Previous reports studying the initial eGFR changes in patients with diabetes randomized to either SGLT2i or placebo did not find an impact of eGFR decrease on the clinical benefit of SGLT2i.<sup>10</sup> An initial eGFR decrease can also occur after the initiation of inhibitors of the reninangiotensin aldosterone system (RAAS), often leading clinicians to withhold or stop RAAS inhibitors, despite their proven benefit in HFrEF regardless of the initial eGFR decrease. Only with an eGFR decrease of >30% more adverse events were observed and warrant RAAS inhibitor dose adjustment or discontinuation.

Interestingly, in our analysis, background RAAS inhibition did not modify the eGFR

change following empagliflozin treatment initiation, and occurrence of eGFR

338

339

340

341

342

343

344

345

346

347

348

349

350

351

352

353

354

355

356

357

358

359

360

361

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

#### Limitations

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

## Conclusions

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

**Acknowledgments** 393 Graphical assistance was provided by 7.4 Limited, Oxford, UK and editing support 394 was provided by Envision Pharma Ltd, UK, both supported financially by Boehringer 395 396 Ingelheim. 397 **Funding** 398 The EMPEROR-Reduced trial was funded by Boehringer Ingelheim and Eli Lilly 399 (EMPEROR-Reduced ClinicalTrials.gov number, NCT03057977). 400 401 **Data sharing** 402 Data will be made available upon request in adherence with transparency 403 conventions in medical research and through requests to the corresponding author. 404 The executive committee of EMPEROR has developed a comprehensive analysis 405 plan and numerous prespecified analyses, which will be presented in future scientific 406 meetings and publications. At a later time-point, the full database will be made 407 available in adherence with the transparency policy of the sponsor (available at 408 https://trials.boehringer-ingelheim.com/transparency\_policy.html). 409 410 **Disclosures** 411 412 FZ reports personal fees from Boehringer Ingelheim during the conduct of the study; personal fees from Janssen, Novartis, Boston Scientific, Amgen, CVRx, 413 AstraZeneca, Vifor Fresenius, Cardior, Cereno Pharmaceutical, Applied 414 Therapeutics, Merck, Bayer, and Cellprothera outside the submitted work; and other 415 support from CVCT and Cardiorenal, outside the submitted work. JPF reports 416 consulting fees from Boehringer Ingelheim during the conduct of the study. JG 417

reports personal fees from Boehringer Ingelheim during the conduct of the study.

419	SJH and MM are employees of Boehringer Ingelheim International. BJK is an
420	employee of Boehringer Ingelheim International and the University Hospital of
421	Würzburg, Germany. JB reports consultancy fees from Boehringer Ingelheim during
422	the conduct of the study; and consultancy fees from Abbott, Adrenomed, Amgen,
423	Applied Therapeutics, Array, AstraZeneca, Bayer, BerlinCures, Boehringer
424	Ingelheim, Cardior, CVRx, Foundry, G3 Pharma, Imbria, Impulse Dynamics, Innolife,
425	Janssen, LivaNova, Luitpold, Medtronic, Merck, Novartis, NovoNordisk, Relypsa,
426	Roche, Sanofi, Sequana Medical, V-Wave, and Vifor, outside the submitted work.
427	GF reports receiving payment from Boehringer Ingelheim for being a trial committee
428	member during the conduct of the study and from Medtronic, Vifor, Servier, and
429	Novartis for being a trial committee member outside the submitted work. CW reports
430	personal fees from Boehringer Ingelheim during the conduct of the study; personal
431	fees from Akebia, AstraZeneca, Bayer, FMC, Eli Lilly, GSK, GILEAD, MSD, Sanofi-
432	Genzyme and Vifor Fresenius outside the submitted work; SDA reports grants from
433	Vifor; personal fees from Vifor, Bayer, Boehringer Ingelheim, Novartis, Servier,
434	Impulse Dynamics, Cardiac Dimensions, and Thermo Fisher Scientific; and grants
435	and personal fees from Abbott Vascular, outside the submitted work.
436	SJP reports personal fees from Boehringer Ingelheim during the conduct of the
437	study. MP reports personal fees from Boehringer Ingelheim, during the conduct of
438	the study; personal fees from Abbvie, Actavis, Amgen, Amarin, AstraZeneca,
439	Boehringer Ingelheim, Bristol Myers Squibb, Casana, CSL Behring, Cytokinetics,
440	Johnson & Johnson, Lilly, Moderna, Novartis, ParatusRx, Pfizer, Relypsa,
441	Salamandra, Synthetic Biologics, Theravance, outside the submitted work.

## **Author Contributions**

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

#### References

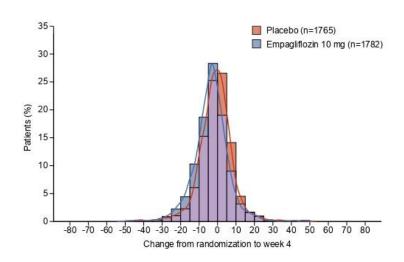
- 452 (1) Zelniker, T. A.; Wiviott, S. D.; Raz, I.; Im, K.; Goodrich, E. L.; Bonaca, M. P.;
- Mosenzon, O.; Kato, E. T.; Cahn, A.; Furtado, R. H. M.; et al. SGLT2 inhibitors for
- primary and secondary prevention of cardiovascular and renal outcomes in type 2
- diabetes: a systematic review and meta-analysis of cardiovascular outcome trials.
- 456 Lancet **2019**, 393 (10166), 31-39. DOI: 10.1016/s0140-6736(18)32590-x From NLM.
- Zannad, F.; Ferreira, J. P.; Pocock, S. J.; Anker, S. D.; Butler, J.; Filippatos, G.;
- Brueckmann, M.; Ofstad, A. P.; Pfarr, E.; Jamal, W.; et al. SGLT2 inhibitors in
- patients with heart failure with reduced ejection fraction: a meta-analysis of the
- 460 EMPEROR-Reduced and DAPA-HF trials. Lancet 2020. DOI: 10.1016/s0140-
- 461 6736(20)31824-9 From NLM. McGuire, D. K.; Shih, W. J.; Cosentino, F.;
- Charbonnel, B.; Cherney, D. Z. I.; Dagogo-Jack, S.; Pratley, R.; Greenberg, M.;
- Wang, S.; Huyck, S.; et al. Association of SGLT2 Inhibitors With Cardiovascular and
- Kidney Outcomes in Patients With Type 2 Diabetes: A Meta-analysis. *JAMA Cardiol*
- **2020**. DOI: 10.1001/jamacardio.2020.4511 From NLM. Ferreira, J. P.; Oliveira, A.
- 466 C.; Saraiva, F. A.; Vasques-Nóvoa, F.; Leite-Moreira, A. Sodium-glucose co-
- transporter inhibitors in insulin-treated diabetes: a meta-analysis. *Eur J Endocrinol*
- 468 **2021**. DOI: 10.1530/eje-20-1484 From NLM.
- 469 (2) Packer, M.; Anker, S. D.; Butler, J.; Filippatos, G.; Pocock, S. J.; Carson, P.;
- Januzzi, J.; Verma, S.; Tsutsui, H.; Brueckmann, M.; et al. Cardiovascular and Renal
- Outcomes with Empagliflozin in Heart Failure. *N Engl J Med* **2020**. DOI:
- 472 10.1056/NEJMoa2022190 From NLM.
- 473 (3) Zannad, F.; Ferreira, J. P.; Pocock, S. J.; Zeller, C.; Anker, S. D.; Butler, J.;
- 474 Filippatos, G.; Hauske, S. J.; Brueckmann, M.; Pfarr, E.; et al. Cardiac and Kidney
- Benefits of Empagliflozin in Heart Failure Across the Spectrum of Kidney Function:
- Insights from the EMPEROR-Reduced Trial. *Circulation* **2020**. DOI:
- 10.1161/circulationaha.120.051685 From NLM. McMurray, J. J. V.; Solomon, S. D.;
- Inzucchi, S. E.; Kober, L.; Kosiborod, M. N.; Martinez, F. A.; Ponikowski, P.;
- Sabatine, M. S.; Anand, I. S.; Belohlavek, J.; et al. Dapagliflozin in Patients with
- Heart Failure and Reduced Ejection Fraction. *N Engl J Med* **2019**. DOI:
- 481 10.1056/NEJMoa1911303 From NLM.
- 482 (4) Jhund, P. S.; Solomon, S. D.; Docherty, K. F.; Heerspink, H. J. L.; Anand, I. S.;
- Böhm, M.; Chopra, V.; de Boer, R. A.; Desai, A. S.; Ge, J.; et al. Efficacy of
- Dapagliflozin on Renal Function and Outcomes in Patients with Heart Failure with
- Reduced Ejection Fraction: Results of DAPA-HF. Circulation 2020. DOI:
- 486 10.1161/circulationaha.120.050391 From NLM.
- 487 (5) Vallon, V.; Thomson, S. C. The tubular hypothesis of nephron filtration and
- diabetic kidney disease. *Nat Rev Nephrol* **2020**, *16* (6), 317-336. DOI:
- 489 10.1038/s41581-020-0256-y From NLM.
- 490 (6) Thomson, S. C.; Rieg, T.; Miracle, C.; Mansoury, H.; Whaley, J.; Vallon, V.;
- Singh, P. Acute and chronic effects of SGLT2 blockade on glomerular and tubular
- function in the early diabetic rat. Am J Physiol Regul Integr Comp Physiol 2012, 302
- 493 (1), R75-83. DOI: 10.1152/ajpregu.00357.2011 From NLM.
- 494 (7) Kidokoro, K.; Cherney, D. Z. I.; Bozovic, A.; Nagasu, H.; Satoh, M.; Kanda, E.;
- Sasaki, T.; Kashihara, N. Evaluation of Glomerular Hemodynamic Function by
- Empagliflozin in Diabetic Mice Using In Vivo Imaging. Circulation 2019, 140 (4), 303-
- 497 315. DOI: 10.1161/circulationaha.118.037418 From NLM.
- 498 (8) Vallon, V.; Traynor, T.; Barajas, L.; Huang, Y. G.; Briggs, J. P.; Schnermann, J.
- 499 Feedback control of glomerular vascular tone in neuronal nitric oxide synthase

- 500 knockout mice. *J Am Soc Nephrol* **2001**, *12* (8), 1599-1606. From NLM. Ziyadeh, F.
- N.; Hoffman, B. B.; Han, D. C.; Iglesias-De La Cruz, M. C.; Hong, S. W.; Isono, M.;
- Chen, S.; McGowan, T. A.; Sharma, K. Long-term prevention of renal insufficiency,
- 503 excess matrix gene expression, and glomerular mesangial matrix expansion by
- treatment with monoclonal antitransforming growth factor-beta antibody in db/db
- diabetic mice. *Proc Natl Acad Sci U S A* **2000**, *97* (14), 8015-8020. DOI:
- 506 10.1073/pnas.120055097 From NLM.
- 507 (9) Beldhuis, I. E.; Streng, K. W.; Ter Maaten, J. M.; Voors, A. A.; van der Meer, P.;
- Rossignol, P.; McMurray, J. J.; Damman, K. Renin-Angiotensin System Inhibition,
- 509 Worsening Renal Function, and Outcome in Heart Failure Patients With Reduced
- and Preserved Ejection Fraction: A Meta-Analysis of Published Study Data.
- 511 *Circulation. Heart failure* **2017**, *10* (2). DOI: 10.1161/circheartfailure.116.003588
- 512 From NLM.
- (10) Oshima, M.; Jardine, M. J.; Agarwal, R.; Bakris, G.; Cannon, C. P.; Charytan, D.
- M.; de Zeeuw, D.; Edwards, R.; Greene, T.; Levin, A.; et al. Insights from
- 515 CREDENCE trial indicate an acute drop in estimated glomerular filtration rate during
- treatment with canagliflozin with implications for clinical practice. Kidney Int 2021, 99
- 517 (4), 999-1009. DOI: 10.1016/j.kint.2020.10.042 From NLM. Kraus, B. J.; Weir, M. R.;
- Bakris, G. L.; Mattheus, M.; Cherney, D. Z. I.; Sattar, N.; Heerspink, H. J. L.; Ritter,
- 519 I.; von Eynatten, M.; Zinman, B.; et al. Characterization and implications of the initial
- 520 estimated glomerular filtration rate 'dip' upon sodium-glucose cotransporter-2
- inhibition with empagliflozin in the EMPA-REG OUTCOME trial. Kidney Int 2021, 99
- 522 (3), 750-762. DOI: 10.1016/j.kint.2020.10.031 From NLM.
- 523 (11) Adamson, C.; Docherty, K. F.; Heerspink, H. J. L.; de Boer, R. A.; Damman, K.;
- Inzucchi, S. E.; Køber, L.; Kosiborod, M. N.; Martinez, F. A.; Petrie, M. C.; et al. Initial
- 525 Decline ("dip") in Estimated Glomerular Filtration Rate Following Initiation of
- Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction: Insights
- from DAPA-HF. Circulation **2022**. DOI: 10.1161/circulationaha.121.058910 From
- 528 NLM
- 529 (12) Packer, M.; Anker, S. D.; Butler, J.; Filippatos, G. S.; Ferreira, J. P.; Pocock, S.;
- Carson, P. E.; Anand, I. S.; Doehner, W.; Haass, M.; et al. Effect of Empagliflozin on
- the Clinical Stability of Patients with Heart Failure and a Reduced Ejection Fraction:
- The EMPEROR-Reduced Trial. *Circulation* **2020**. DOI:
- 10.1161/circulationaha.120.051783 From NLM. Packer, M.; Anker, S. D.; Butler, J.;
- Filippatos, G.; Ferreira, J. P.; Pocock, S. J.; Sattar, N.; Brueckmann, M.; Jamal, W.;
- Cotton, D.; et al. Empagliflozin in Patients With Heart Failure, Reduced Ejection
- Fraction, and Volume Overload: EMPEROR-Reduced Trial. *J Am Coll Cardiol* **2021**,
- 537 77 (11), 1381-1392. DOI: 10.1016/j.jacc.2021.01.033 From NLM.
- (13) Packer, M.; Butler, J.; Filippatos, G. S.; Jamal, W.; Salsali, A.; Schnee, J.;
- Kimura, K.; Zeller, C.; George, J.; Brueckmann, M.; et al. Evaluation of the effect of
- sodium-glucose co-transporter 2 inhibition with empagliflozin on morbidity and
- mortality of patients with chronic heart failure and a reduced ejection fraction:
- rationale for and design of the EMPEROR-Reduced trial. Eur J Heart Fail 2019, 21
- 543 (10), 1270-1278. DOI: 10.1002/ejhf.1536 From NLM.
- (14) Pocock, S. J.; Ferreira, J. P.; Gregson, J.; Anker, S. D.; Butler, J.; Filippatos, G.;
- Gollop, N. D.; Iwata, T.; Brueckmann, M.; Januzzi, J. L., Jr; et al. Novel biomarker-
- driven prognostic models to predict morbidity and mortality in chronic heart failure:
- the EMPEROR-Reduced trial. *European Heart Journal* **2021**. DOI:
- 548 10.1093/eurheartj/ehab579 (acccessed 9/21/2021).
- 549 (15) Hallow, K. M.; Gebremichael, Y.; Helmlinger, G.; Vallon, V. Primary proximal
- tubule hyperreabsorption and impaired tubular transport counterregulation determine

```
glomerular hyperfiltration in diabetes: a modeling analysis. Am J Physiol Renal
```

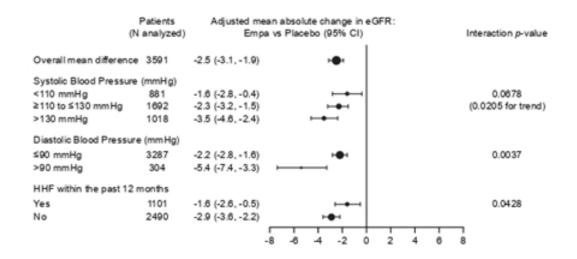
- 552 *Physiol* **2017**, 312 (5), F819-f835. DOI: 10.1152/ajprenal.00497.2016 From NLM.
- 553 (16) Vallon, V. Do tubular changes in the diabetic kidney affect the susceptibility to
- acute kidney injury? *Nephron Clin Pract* **2014**, *127* (1-4), 133-138. DOI:
- 555 10.1159/000363554 From NLM.
- 556 (17) Heerspink, H. J. L.; Perco, P.; Mulder, S.; Leierer, J.; Hansen, M. K.; Heinzel,
- A.; Mayer, G. Canagliflozin reduces inflammation and fibrosis biomarkers: a potential
- mechanism of action for beneficial effects of SGLT2 inhibitors in diabetic kidney
- disease. Diabetologia 2019, 62 (7), 1154-1166. DOI: 10.1007/s00125-019-4859-4
- 560 From NLM. Kim, S. R.; Lee, S. G.; Kim, S. H.; Kim, J. H.; Choi, E.; Cho, W.; Rim, J.
- H.; Hwang, I.; Lee, C. J.; Lee, M.; et al. SGLT2 inhibition modulates NLRP3
- inflammasome activity via ketones and insulin in diabetes with cardiovascular
- disease. *Nat Commun* **2020**, *11* (1), 2127. DOI: 10.1038/s41467-020-15983-6 From
- NLM. Sukhanov, S.; Higashi, Y.; Yoshida, T.; Mummidi, S.; Aroor, A. R.; Jeffrey
- Russell, J.; Bender, S. B.; DeMarco, V. G.; Chandrasekar, B. The SGLT2 inhibitor
- 566 Empagliflozin attenuates interleukin-17A-induced human aortic smooth muscle cell
- proliferation and migration by targeting TRAF3IP2/ROS/NLRP3/Caspase-1-
- dependent IL-1β and IL-18 secretion. *Cell Signal* **2021**, 77, 109825. DOI:
- 569 10.1016/j.cellsig.2020.109825 From NLM.
- 570 (18) Song, P.; Huang, W.; Onishi, A.; Patel, R.; Kim, Y. C.; van Ginkel, C.; Fu, Y.;
- 571 Freeman, B.; Koepsell, H.; Thomson, S.; et al. Knockout of Na(+)-glucose
- 572 cotransporter SGLT1 mitigates diabetes-induced upregulation of nitric oxide
- 573 synthase NOS1 in the macula densa and glomerular hyperfiltration. *Am J Physiol*
- 574 Renal Physiol **2019**, 317 (1), F207-f217. DOI: 10.1152/ajprenal.00120.2019 From
- NLM. Layton, A. T.; Vallon, V.; Edwards, A. Modeling oxygen consumption in the
- proximal tubule: effects of NHE and SGLT2 inhibition. *Am J Physiol Renal Physiol*
- **2015**, 308 (12), F1343-1357. DOI: 10.1152/ajprenal.00007.2015 From NLM.
- 578 (19) Cherney, D. Z.; Perkins, B. A.; Soleymanlou, N.; Maione, M.; Lai, V.; Lee, A.;
- Fagan, N. M.; Woerle, H. J.; Johansen, O. E.; Broedl, U. C.; et al. Renal
- 580 hemodynamic effect of sodium-glucose cotransporter 2 inhibition in patients with
- type 1 diabetes mellitus. *Circulation* **2014**, *129* (5), 587-597. DOI:
- 582 10.1161/circulationaha.113.005081 From NLM.
- 583 (20) Wanner, C.; Inzucchi, S. E.; Lachin, J. M.; Fitchett, D.; von Eynatten, M.;
- Mattheus, M.; Johansen, O. E.; Woerle, H. J.; Broedl, U. C.; Zinman, B.
- 585 Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes. *N Engl J Med*
- **2016**, 375 (4), 323-334. DOI: 10.1056/NEJMoa1515920 From NLM. Perkovic, V.;
- Jardine, M. J.; Neal, B.; Bompoint, S.; Heerspink, H. J. L.; Charytan, D. M.; Edwards,
- R.; Agarwal, R.; Bakris, G.; Bull, S.; et al. Canagliflozin and Renal Outcomes in Type
- 2 Diabetes and Nephropathy. *N Engl J Med* **2019**, *380* (24), 2295-2306. DOI:
- 590 10.1056/NEJMoa1811744 From NLM. Heerspink, H. J. L.; Stefánsson, B. V.;
- Correa-Rotter, R.; Chertow, G. M.; Greene, T.; Hou, F. F.; Mann, J. F. E.; McMurray,
- J. J. V.; Lindberg, M.; Rossing, P.; et al. Dapagliflozin in Patients with Chronic
- 593 Kidney Disease. *N Engl J Med* **2020**, 383 (15), 1436-1446. DOI:
- 594 10.1056/NEJMoa2024816 From NLM.

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



Legend: The mean difference in 4-week eGFR change with empagliflozin is - 2.5mL/min/1.73m<sup>2</sup>.

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



604

605

606

607

608

609

610

611

612

613

614

615

616

617

618

619

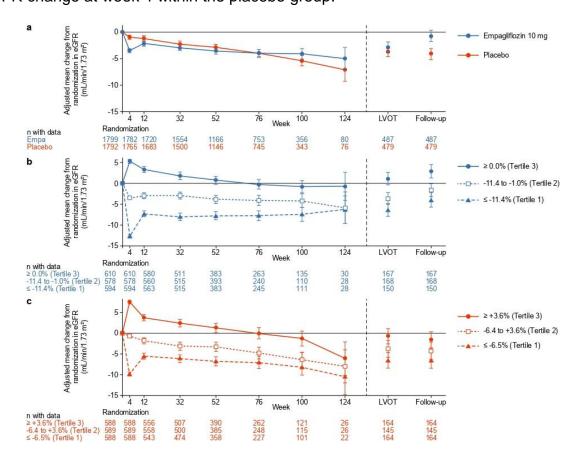
601

602

Legend: 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; CRT, cardiac resynchronization therapy; CRT-D, cardiac resynchronisation therapy with defibrillator; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HF, heart failure; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NTproBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure; UACR, urine albumin to creatinine ratio. The numbers represent the difference in adjusted mean changes from baseline in the eGFR. The on-treatment data were analysed with the use of a mixed model for repeated measures that included age and baseline eGFR as linear covariates and sex, region, baseline LVEF, baseline diabetes status, last projected visit based on dates of randomization and trial closure, baseline eGFR according to visit and subgroup-byvisit-by-treatment interaction as fixed effects.

620 Caption: SBP, DBP, and prior HHF within 12 months, were the only 3 variables associated with eGFR change in the empagliflozin group vs. the placebo group i.e., 621 with variable by treatment interaction P < 0.05 at week 4. 622 623 Baseline variables with homogeneous treatment effect of empagliflozin vs placebo on eGFR change at week 4 were: age, sex, BMI, race, region, LVEF, NYHA 624 functional class, NT-proBNP, cause of HF, time since diagnosis of HF, heart rate, 625 history of AF, history of hypertension, diabetes status, smoking status, eGFR, 626 UACR, anemia, ACEi/ARB use, ARNi use, beta-blocker use, thiazide or low-ceiling 627 628 diuretic use, MRA use, cardiac glycosides use, loop diuretic use, loop diuretic dose, CCB use, nitrate use, ivabradine use, statin use, antiplatelet use, anticoagulant use, 629 ICD or CRT-D use, CRT use, and HF physiology. 630

**Figure 3.** Change in 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.



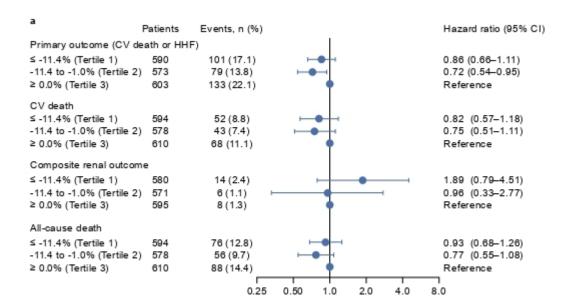
Legend: Left side: The on-treatment data were analyzed with the use of a mixed model for repeated measures based on patients who received at least one dose of a study drug and had a baseline and postbaseline measurement (a) and a week 4 measurement (b, c).

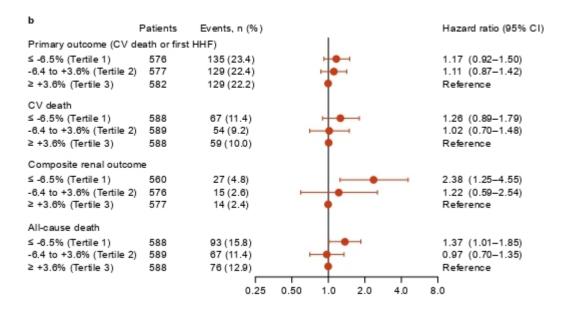
Right side: The LVOT and FUP change from randomization are based on an analysis of a covariance model in patients who underwent measurements at baseline, LVOT and FUP (a) and week 4 (b, c).

Empagliflozin: Tertile  $1 \le -11.4\%$ ; Tertile  $2 \ge -11.4\%$  to  $\le -1.0\%$  and Tertile  $3 \ge 0.0\%$ Placebo: Tertile  $1 \le -6.5\%$ ; Tertile  $2 \ge -6.4\%$  to  $\le +3.6\%$ ; and Tertile  $3 \ge +3.6\%$ .

- 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:
- T1 +1.14mL/min/1.73m², T2 -2.95mL/min/1.73m² and T3 -4.93 mL/min/1.73m².

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

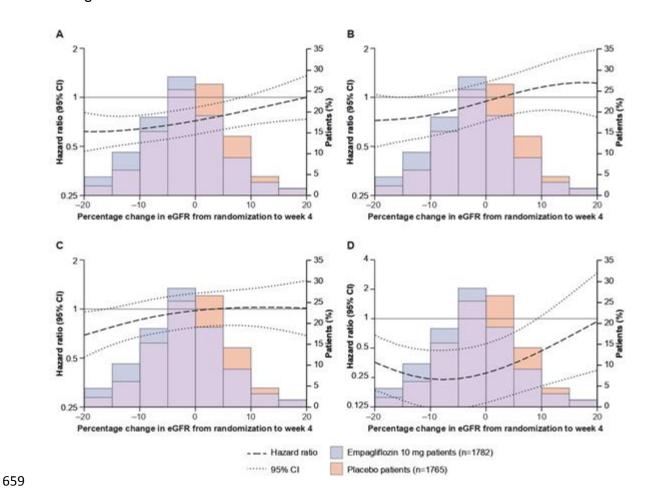




Legend: Hazard ratios based on a Cox regression model with adjustment for the EMPEROR-Reduced risk score for the primary outcome, CV death, mortality (latter is used for composite renal outcome and all-cause death). Empagliflozin: Tertile  $1 \le -11.4\%$ ; Tertile  $2 \ge -11.4\%$  to  $\le -1.0\%$  and Tertile  $3 \ge 0.0\%$ 

Placebo: Tertile  $1 \le -6.5\%$ ; Tertile  $2 \ge -6.4\%$  to  $\le +3.6\%$ ; and Tertile  $3 \ge +3.6\%$ .

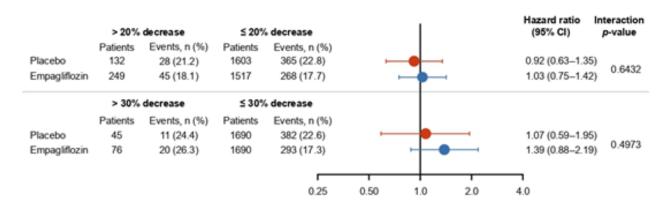
**Figure 5**. Effect of empagliflozin versus placebo across the spectrum of eGFR change.



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

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

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



>20% and >30% from baseline

668

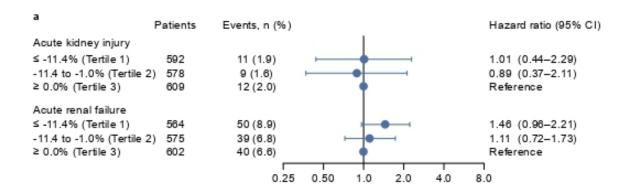
669

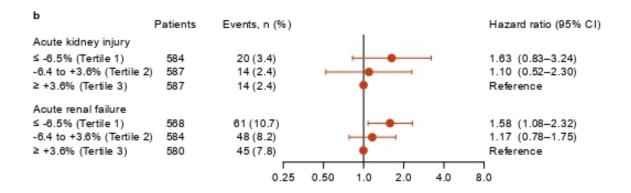
670

674

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).

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





Legend: a, empagliflozin; b, placebo.

Hazard ratios based on a Cox regression with adjustment for the EMPEROR-Reduced all-cause mortality risk score. 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) 20000003, based on 19 preferred terms (MedDRA version 23.0). Empagliflozin: Tertile  $1 \le -11.4\%$ ; Tertile  $2 \ge -11.4\%$  to  $\le -1.0\%$  and Tertile  $3 \ge 0.0\%$  Placebo: Tertile  $1 \le -6.5\%$ ; Tertile  $2 \ge -6.4\%$  to  $\le +3.6\%$ ; and Tertile  $3 \ge +3.6\%$ .