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Treatment with sodium-glucose co-transporter-2 inhibitors induces an initial 3–5 ml/min/1.73 m^2 decline in estimated glomerular filtration rate (eGFR). Although considered to be of hemodynamic origin and largely reversible, this 'eGFR dip' may cause concern in clinical practice, which highlights the need to better understand its incidence and clinical implications. In this *post hoc* analysis of the EMPA-REG OUTCOME trial, 6,668 participants randomized to empagliflozin 10 mg, 25 mg or placebo with eGFR available at baseline and week four were categorized by initial eGFR change into three groups; over 10% decline ('eGFR dipper'), over 0 and up to 10% decline ('eGFR intermediate'), no eGFR decline ('eGFR non-dipper'). Baseline characteristics of 'eGFR intermediate' and 'eGFR non-dipper' were generally comparable. An initial 'eGFR dip' was observed in 28.3% of empagliflozin versus 13.4% of placebo-treated participants; odds ratio 2.7 [95% Confidence Interval 2.3–3.0]. In multivariate logistic regression, diuretic use and higher KDIGO risk category at baseline were independently predictive of an 'eGFR dip' in empagliflozin versus placebo. Safety and beneficial treatment effects with empagliflozin on cardiovascular and kidney outcomes were consistent across subgroups based on these predictive factors. The initial 'eGFR dip' did not have a major impact on the treatment effect of empagliflozin on subsequent cardiovascular death, hospitalization for heart failure, and incident or worsening kidney disease. Thus, patients with type 2 diabetes with more advanced kidney disease and/or on diuretic therapy were more likely to experience an 'eGFR dip' of over 10% with empagliflozin, but reduction in cardiovascular and kidney outcomes was not relevantly modified by such 'eGFR dip.'

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Sodium-glucose co-transporter-2 inhibitors (SGLT2i) were developed as glucose-lowering agents but represent a new treatment option for cardiovascular (CV) and kidney disease in patients with type 2 diabetes (T2D). Improvements in CV and kidney outcomes have been observed across several SGLT2i outcomes trials.[1-6] Owing to its renal mechanism of action, SGLT2i is associated with a transient decrease in estimated glomerular filtration rate (eGFR), also termed the 'eGFR dip,' shortly after treatment initiation.[2,7,8] Although considered largely hemodynamic and reversible, this initial 'eGFR dip' has raised concerns in clinical practice, as it may predispose patients to acute kidney injury (AKI). Adverse event (AE) post-marketing reporting on AKI led the U.S. Food and Drug Administration to issue warnings

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for SGLT2i to be used with caution in patients at risk of AKI.[9] However, data from clinical trials[1,3,4,6] and large observational cohorts[10-13] show a reduced AKI risk with SGLT2i.

An initial 'eGFR dip' has been reported with renin-angiotensin-aldosterone system (RAAS) inhibition.[14,15] Until recently, RAAS inhibition was the sole nephroprotective treatment for patients with kidney disease, and it remains widely used. Nevertheless, the predictive value of the 'eGFR dip' associated with RAAS inhibition on CV and kidney outcomes remains controversial.[16-19]

The initial 'eGFR dip' with SGLT2i on top of RAAS inhibition may limit its clinical use, especially in patients within the lower eGFR range. Therefore, its incidence and clinical implications need to be better understood. We characterized EMPA-REG OUTCOME participants with various degrees of initial change in eGFR and investigated whether the initial 'eGFR dip' observed with empagliflozin was influenced by baseline characteristics and/or had an impact on safety and CV and kidney outcomes.

METHODS

The design and methods of the double-blind, placebo-controlled, multinational EMPA-REG OUTCOME trial (ClinicalTrials.gov identifier: NCT01131676) have been described previously.[1] The study population included 7020 treated participants with T2D, established CV disease, and eGFR ≥30 ml/min per 1.73 m^2 (MDRD; modification of diet in kidney disease). Participants were assigned at random to receive empagliflozin 10 mg or 25 mg or placebo (1:1:1) once daily, in addition to standard care. The median duration of treatment was 2.6 years, and the median observation time was 3.1 years. The primary CV outcome and prespecified secondary kidney outcome (defined as incident or worsening nephropathy) have been reported previously.[1,2]

For this *post hoc* analysis, 6668 participants who received ≥1 dose of study drug and had baseline and week 4 eGFR values available were categorized by percent eGFR (equation developed by the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI]) change from baseline at week 4 into 3 categories: >10% decline ('eGFR dipper'), >0% to ≤10% decline ('eGFR intermediate'), and no decline ('eGFR non-dipper'). This pragmatic categorization, using clinically relevant, memorable, and easy-to-apply cutoffs, resulted in 3 similar-sized groups in the empagliflozin treatment arm. For each category, we described baseline characteristics and eGFR change over time for the duration of treatment and after treatment discontinuation. Additional sensitivity analysis was performed for an eGFR decline of >30% from baseline. For all analyses, we compared placebo and pooled empagliflozin (10 mg and 25 mg) groups. Serum creatinine and albumin, and urinary albumin in spot urine, were measured in central laboratories to calculate the urine-albumin-to-creatinine ratio (UACR). Kidney Disease: Improving Global Outcomes (KDIGO) categorization was conducted according to the KDIGO heat map, a 2-dimensional classification system, identifying patients with low eGFR and higher UACR levels, who are at elevated risk of adverse kidney and CV outcomes.[20] For kidney function over time, we used the CKD-EPI creatinine equation. Mixed-model, repeated-measures analysis was used to evaluate changes in eGFR over time, including glycated hemoglobin (HbA1c) level and eGFR (CKD-EPI) at baseline as linear covariates and geographic region, baseline body mass index (BMI), treatment, visit, visit-by-treatment interaction, interaction between baseline HbA1c level and visit, and interaction between baseline eGFR and visit as fixed effects. Changes in eGFR per year (i.e., eGFR slope) were obtained using a random intercept/random coefficient model, as described previously.[21] The model was applied by each 'eGFR dipping' category separately, and only data for participants on treatment were used. Participants who also had eGFR values available after treatment discontinuation where assessed for absolute and percent changes in eGFR between last value on treatment (LVOT) and first value after treatment discontinuation (follow-up).

Baseline characteristics of the 'eGFR intermediate' and 'eGFR non-dipper' groups were generally comparable. Thus, further analyses were performed based on pooled data from these 2 categories to focus on one harmonized 'eGFR dip' event, defined as the occurrence of an 'eGFR dip' >10% from baseline at week 4. Baseline characteristics were evaluated for potential predictive effect of such an initial percent 'eGFR dip' from baseline at week 4 with empagliflozin versus placebo. We used logistic regression with baseline factors, treatment, and interaction of baseline factors with treatment to investigate potential interactions of baseline factors with treatment and hence predictive effects. Following that approach, we applied a multivariate logistic regression model using backward selection and applied significance level of $P < 0.05$ for interaction of each baseline factor and treatment to be retained in the model. Baseline factors with a significance level of $P < 0.1$ for interaction with treatment as determined from the first step were included in the multivariate model. Relevant predictive factors for an 'eGFR dip' event were calculated from the multivariate logistic regression model.

To investigate the association of an 'eGFR dip' from baseline at week 4 with CV-related death, hospitalization for heart failure (HHF), or kidney outcomes after week 4 independent of treatment, we combined empagliflozin and placebo groups and used a Cox proportional hazards model with factors for treatment group, baseline variables of age, sex, BMI, HbA1c, eGFR, region, and 'eGFR dip' at week 4 and with additional adjustment for baseline values and changes from baseline at week 4 in systolic blood pressure (SBP), diastolic blood pressure (DBP), and fasting plasma glucose.

While categorization by actual 'eGFR dipping' after randomization results in loss of randomization and thus does not allow for a comparison of empagliflozin treatment effect in 'eGFR dipper' versus other categories, we assessed the impact of an 'eGFR dip' at week 4 using 2 approaches. We first analyzed the effect of empagliflozin on CV and kidney outcomes across relevant predictive baseline factors for an 'eGFR dip' event. These analyses were performed using a Cox proportional hazards model with factors for treatment, age, sex, baseline BMI, baseline HbA1c, region, subgroup, and treatment-by-subgroup interaction. In addition, we assessed the 'eGFR dip' as potential mediator for the effect of empagliflozin on these outcomes. This analysis was done in accordance with the previously described concept of traditional mediation analysis proposed by Baron and Kenny,[22] and similarly applied for time to occurrence of CV death.[23] We compared the treatment effect of empagliflozin on outcomes from week 4 onward from the analysis using the primary model,[1] with the treatment effect obtained using a model also adjusted for a >10%

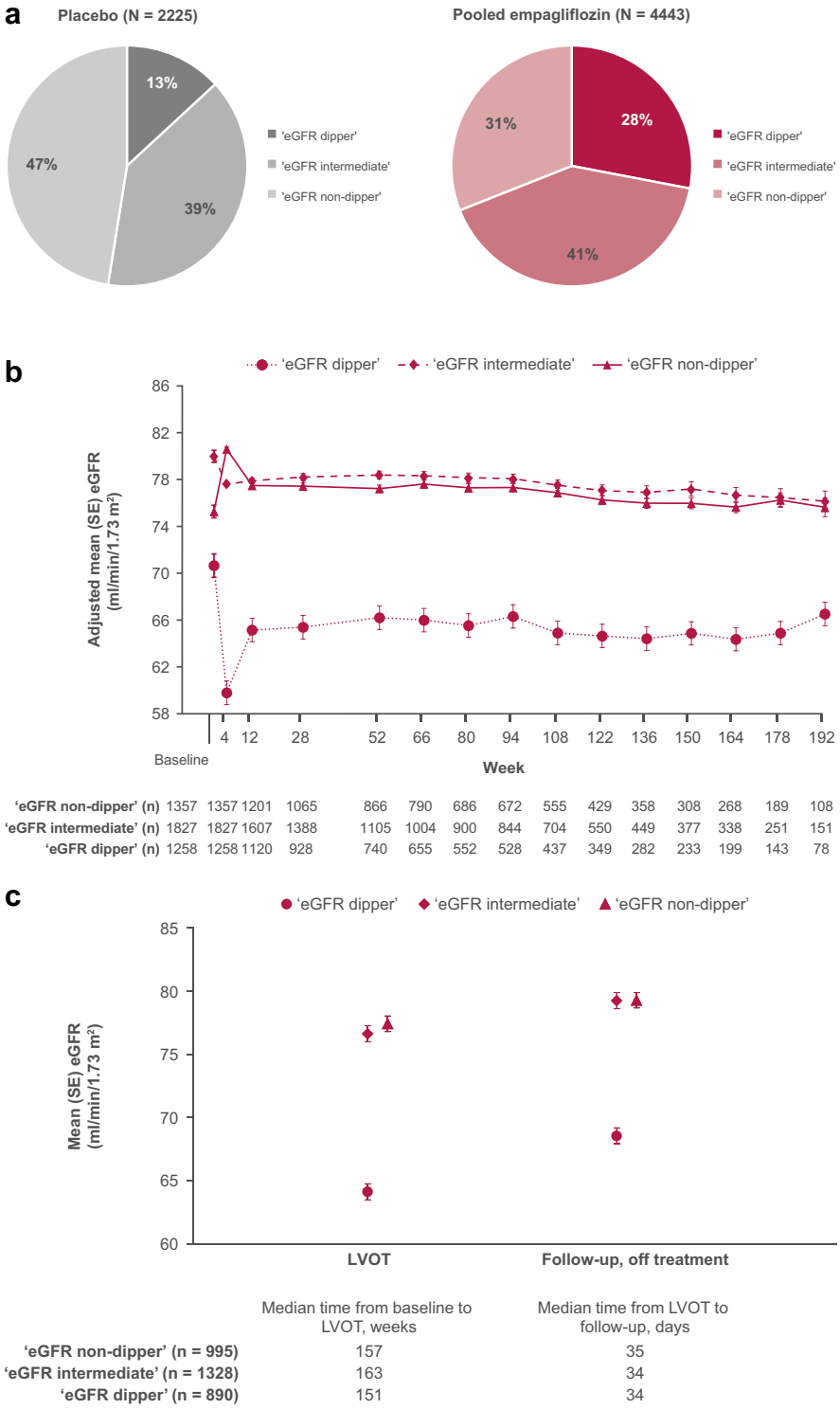


Figure 1 | Percentage of participants by 'estimated glomerular filtration rate (eGFR) dipping' category (a), eGFR over time per 'eGFR dipping' category in empagliflozin-treated participants (b), and mean eGFR at last value on treatment (LVOT) and follow-up according to 'eGFR dipping' category in empagliflozin-treated participants (c). (**a**) Percentage of participants who received at least 1 dose of study drug (empagliflozin vs. placebo) and had eGFR (Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI]) values at both baseline and week 4 categorized by percent eGFR change from baseline at week 4 to >10% decline ('eGFR dipper'), >0% to ≤10% decline ('eGFR intermediate'), or no decline ('eGFR non-dipper'). (**b**) Mixed-model repeated-measures results of eGFR (CKD-EPI) on treatment over time by category of percent change in all participants treated with at least 1 dose of study drug who had baseline and week 4 eGFR values available. The model includes baseline eGFR and baseline glycated hemoglobin (HbA1c) as linear covariates and geographical region, baseline body mass index category, treatment, visit, visit-by-treatment interaction, baseline HbA1c-by-visit interaction, and baseline eGFR-by-visit interaction as fixed effects applied for each 'eGFR dipping' category. (**c**) Participants treated with at least 1 dose of study drug who had baseline and (continued)

'eGFR dip' at week 4. The percent mediation was calculated as follows: mediation % = 100 * ([lnHR - $lnHR_C$]/lnHR), where HR (hazard ratio) denotes a comparison of treatment groups in the model with treatment group alone and HR_C denotes a comparison of treatment groups in the model adjusting for the 'eGFR dip'. To be considered a mediator, the 'eGFR dip' should have an effect on the studied outcome, and the effect of empagliflozin on outcome must be reduced in the analysis adjusted for 'eGFR dip'. Mediation was indicated if the HR for outcome between treatment groups adjusted for 'eGFR dip' was closer to unity than the HR from the model with treatment group alone (primary model). Complete mediation would be indicated by an HR of 1.0 in the model adjusted for 'eGFR dip'. A positive mediation value indicates that effect of empagliflozin on outcome was partially mediated by the 'eGFR dip,' and a negative value indicates that the effect of empagliflozin was partially diminished by the 'eGFR dip.'

All analyses were performed at the nominal α level of 0.05 without correction for multiple hypothesis testing.

Safety analyses of kidney and overall AEs were descriptive across predictive baseline factors for an 'eGFR dip'. Kidney AEs represent reporting of the narrow Standardised Medical Dictionary for Regulatory Activities (MedDRA) Query for acute renal failure (ARF) by study investigators, which included the preferred term AKI. Statistical analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

There was wide interindividual variability in the initial eGFR change among the participants. Whereas the median (IQR) eGFR change from baseline at week 4 was –0.05 (IQR, –4.04 to +4.27) ml/min per 1.73 m^2 in the placebo-treated participants (–21.4 and +21.4 for the 1st and 99th percentiles, respectively), it shifted toward a median reduction of –2.69 (IQR, –7.87, +1.30) ml/min per 1.73 m^2 with empagliflozin (–24.9 and +17.7 for the 1st and 99th percentiles, respectively).

Baseline characteristics of 'eGFR dipping' categories

Categorization resulted in 28.3% and 13.4% of 'eGFR dipper,' 41.1% and 39.5% of 'eGFR intermediate,' and 30.5% and 47.1% of 'eGFR non-dipper' participants in the empagliflozin and placebo groups, respectively (Figure 1a). Baseline characteristics of 'eGFR dip' categories are shown in Table 1. Among empagliflozin-treated participants, most baseline characteristics were comparable in the 'eGFR non-dipper' and 'eGFR intermediate' groups, except for SBP and eGFR, which were slightly higher in the latter group. In contrast, there were some relevant differences in baseline characteristics between empagliflozin-treated 'eGFR dippers' and 'eGFR non-dippers'; 'eGFR dippers' were older, had a longer-standing history of diabetes, and had higher rates of impaired kidney function and albuminuria and hence a higher KDIGO risk category. Hemoglobin, hematocrit, and albumin levels were slightly lower in 'eGFR dippers.' The 'eGFR dippers' were more likely to have suboptimal SBP control, even though they were taking more antihypertensive medications. In addition, more 'eGFR dippers' were treated with insulin and fewer were treated with metformin, while study participants using insulin had a lower baseline eGFR compared with nonusers, and metformin users had a higher baseline eGFR compared with nonusers.[24] Characteristics of the participant subset that experienced an initial eGFR decline of >30% on initiation of empagliflozin (1.4%; $n = 64$) are summarized in Supplementary Table S1. Overall, their baseline characteristics were comparable to those of the 'eGFR dippers,' but they tended to have more comorbidities and CV risk factors.

eGFR over time and after treatment discontinuation according to 'eGFR dipping' category

The baseline mean ± SD eGFR values in the empagliflozin-treated participants were 68.3 ± 18.1, 79.5 ± 22.9, and 72.9 ± 20.6 ml/min per 1.73 m^2 for the 'eGFR dipper,' 'eGFR intermediate,' and 'eGFR non-dipper' groups, respectively. The respective mean ± SD eGFR changes from baseline at week 4 in these 3 groups were –12.6 ± 5.7, –3.3 ± 2.4, and +5.4 ± 5.7 ml/min per 1.73 m^2. Few participants experienced an eGFR decline >30% at week 4 (1.4% [$n = 64$] on empagliflozin and 0.9% [$n = 20$] on placebo). Among these, 1 patient on empagliflozin and no patients on placebo discontinued the study following week 4.

In participants receiving empagliflozin treatment, the mean eGFR remained stable from week 12 onward in all 'eGFR dipping' categories (Figure 1b), as well as in the subset with an initial empagliflozin-induced eGFR decline >30% (Supplementary Figure S1). In contrast, mean eGFR levels in placebo recipients declined across all categories (Supplementary Figure S2A): the mean eGFR slope from week 12 to the LVOT was –1.598 (95% confidence interval [CI], –2.076 to –1.121) ml/min per 1.73 m^2/year in 'eGFR non-dippers,' –1.278 (95% CI, –1.752 to –0.804) ml/min per 1.73 m^2/year in the 'eGFR intermediate' group, and –0.718 (95% CI, –1.713 to 0.278) ml/min per 1.73 m^2/year in 'eGFR dippers.'

In participants who also had data available for the follow-up period, mean eGFR increased after empagliflozin treatment discontinuation compared with the LVOT (Figure 1c). After placebo discontinuation, eGFR did not change in any category compared with the LVOT (Supplementary Figure S2B).

Figure 1 | (continued) week 4 eGFR values available, as well as an eGFR value after treatment cessation (follow-up). Descriptive statistics for eGFR (CKD-EPI) at baseline, last value on treatment (LVOT), and follow-up. Median percent change at follow-up compared with LVOT: +2.12% (interquartile range [IQR], –2.98 to +8.94%) in the 'eGFR non-dipper' group, +2.67% (IQR, –2.27 to +10.64%) in the 'eGFR intermediate' group, and +6.63% (IQR, –0.08 to +16.07%) in the 'eGFR dipper' group.

Predictive baseline factors for an 'eGFR dip' with empagliflozin treatment

To focus on one harmonized 'eGFR dip' event, and because the baseline characteristics of the 'eGFR intermediate' and 'eGFR non-dipper' groups were generally comparable, further analyses were performed based on pooled data from these 2 categories. To define baseline characteristics associated with an initial empagliflozin-induced 'eGFR dip' >10%, and to identify participants particularly prone to experiencing such an 'eGFR dip' with empagliflozin, we performed logistic regression analyses on specified factors. Figure 2a presents the overall odds ratio (OR) for an initial 'eGFR dip' with empagliflozin treatment

Table 1 | Baseline characteristics for empagliflozin-treated participants according to 'eGFR dipping' categories

Characteristics	'eGFR dipper' (>10% eGFR decline)	'eGFR intermediate' (>0% to ≤10% eGFR decline)	'eGFR non-dipper' (no eGFR decline)
Number (%)	1259 (28.3)	1827 (41.1)	1357 (30.5)
Age, yr, mean ± SD	64.6 ± 8.3[c]	62.8 ± 8.4	62.2 ± 8.8
Male sex, n (%)	875 (69.5)	1316 (72.0)	980 (72.2)
BMI, kg/m^2, mean ± SD	30.9 ± 5.4[b]	30.6 ± 5.2[a]	30.2 ± 5.2
HbA1c, %, mean ± SD[d]	8.11 ± 0.8	8.04 ± 0.8	8.05 ± 0.9
FPG, mg/dl, mean ± SD[e]	150.4 ± 44.1[a,c]	152.7 ± 42.8[a]	153.8 ± 43.4
Time since diagnosis of T2D, n (%)			
≤1 yr	22 (1.7)	51 (2.8)	52 (3.8)
>1 to 5 yr	161 (12.8)	286 (15.7)	239 (17.6)
>5 to 10 yr	293 (23.3)	457 (25.0)	362 (26.7)
>10 yr	783 (62.2)	1033 (56.5)	704 (51.9)
eGFR, ml/min per 1.73 m^2, mean ± SD	68.3 ± 18.1[c]	79.5 ± 22.9[c]	72.9 ± 20.6
eGFR category, n (%)			
≥90 ml/min per 1.73 m^2	132 (10.5)	599 (32.8)	272 (20.0)
60 to <90 ml/min per 1.73 m^2	716 (56.9)	859 (47.0)	731 (53.9)
<60 ml/min per 1.73 m^2	411 (32.6)	369 (20.2)	354 (26.1)
UACR (median, IQR)[f]	27.4 (7.1–121.1)[c]	16.8 (7.1–59.2)	15.0 (6.2–55.7)
UACR category, n (%)			
<30	643 (51.1)	1137 (62.2)	870 (64.1)
≥30 to 300	409 (32.5)	513 (28.1)	339 (25.0)
>300	193 (15.3)[c]	163 (8.9)[a]	128 (9.4)
KDIGO risk category, n (%)			
Low risk of CKD	473 (37.6)	961 (52.6)	690 (50.8)
Moderate risk of CKD	391 (31.1)	510 (27.9)	371 (27.3)
High risk of CKD	246 (19.5)	251 (13.7)	165 (12.2)
Very high risk of CKD	135 (10.7)	91 (5.0)	111 (8.2)
Hemoglobin, g/dl, mean ± SD[g]	13.5 ± 1.5[c]	13.8 ± 1.4	13.9 ± 1.5
Hematocrit, %, mean ± SD[h]	40.6 ± 4.5[c]	41.6 ± 4.2[a]	41.9 ± 4.4
Albumin, g/dl, mean ± SD[i]	4.39 ± 0.32[c]	4.43 ± 0.29[a]	4.46 ± 0.31
Cholesterol, mg/dl, mean ± SD			
HDL[j]	44.3 ± 12.1	44.6 ± 11.4	44.9 ± 12.2
LDL[k]	85.0 ± 33.7[a]	85.0 ± 35.2[a]	88.2 ± 38.5
TG[j]	176.8 ± 147	167.8 ± 129	167.4 ± 116
SBP, mmHg, mean ± SD	137.3 ± 17.4[c]	135.3 ± 16.4[b]	133.3 ± 16.8
DBP, mmHg, mean ± SD	76.6 ± 9.9[c]	76.8 ± 9.4[a]	76.6 ± 9.8
BP control, categorical, n (%)			
SBP <140 and DBP <90 mmHg	728 (57.8)	1130 (61.9)	898 (66.2)
SBP ≥140 or DBP ≥90 mmHg	531 (42.2)	697 (38.1)	459 (33.8)
Concomitant medication, n (%)			
ACEi/ARB	1094 (86.9)[c]	1462 (80.0)	1054 (77.7)
Beta-blocker	853 (67.8)[a]	1186 (64.9)	856 (63.1)
Diuretic	685 (54.4)[c]	695 (38.0)	539 (39.7)
Loop diuretic	252 (20.0)[c]	234 (12.8)	178 (13.1)
CCB	441 (35.0)[a]	581 (31.8)	426 (31.4)
Statin	973 (77.3)	1431 (78.3)	1033 (76.1)
ASA	1068 (84.8)[a]	1500 (82.1)	1112 (81.9)
Metformin	864 (68.6)[c]	1389 (76.0)	1031 (76.0)
Sulfonylurea	513 (40.7)[a]	787 (43.1)	615 (45.3)
Insulin	666 (52.9)[c]	858 (47.0)	592 (43.6)
CV high risk factor, n (%)			
CHD history	965 (76.6)	1379 (75.5)	1008 (74.3)
Stroke history	294 (23.4)	427 (23.4)	307 (22.6)
PAD history	301 (23.9)[a]	366 (20.0)	270 (19.9)
HF history	138 (11.0)	149 (8.2)	135 (9.9)

(*Continued on following page*)

Table 1 | (Continued) **Baseline characteristics for empagliflozin-treated participants according to 'eGFR dipping' categories**

Characteristics	'eGFR dipper' (>10% eGFR decline)	'eGFR intermediate' (>0% to ≤10% eGFR decline)	'eGFR non-dipper' (no eGFR decline)
Race, n (%)	[a]		
White	920 (73.1)	1328 (72.7)	970 (71.5)
Asian	242 (19.2)	412 (22.6)	308 (22.7)
Black/African-American	90 (7.1)	71 (3.9)	64 (4.7)

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ASA, acetylsalicylic acid; BMI, body mass index; CCB, calcium channel blocker; CHD, coronary heart disease; CKD, chronic kidney disease; CV, cardiovascular; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; HF, heart failure; KDIGO, Kidney Disease: Improving Global Outcomes; LDL, low-density lipoprotein; PAD, peripheral artery disease; SBP, systolic blood pressure; T2D, type 2 diabetes; TG, triglycerides; UACR, urine albumin-to-creatinine ratio.
[a]$P < 0.05$ compared with the non-dipping group.
[b]$P < 0.001$ compared with the non-dipping group.
[c]$P < 0.0001$ compared with the non-dipping group.
[d]N value: 1258 for the >10% decline group.
[e]N values: 1352, 1818, and 1257 for the no, >0 to ≤10%, and >10% decline groups, respectively.
[f]N values: 1337, 1813, and 1245 for the no, >0 to ≤10%, and >10% decline groups, respectively.
[g]N values: 1356, 1826, and 1259 for the no, >0 to ≤10%, and >10% decline groups, respectively.
[h]N values: 1353, 1821, and 1257 for the no, >0 to ≤10%, and >10% decline groups, respectively.
[i]N value: 1259 for the >10% decline group.
[j]N values: 1339, 1807, and 1243 for the no, >0 to ≤10%, and >10% decline groups, respectively.
[k]N values: 1339, 1805, and 1242 for the no, >0 to ≤10%, and >10% decline groups, respectively.

compared with placebo (2.7; 95% CI, 2.3–3.0) and for each baseline factor included in further multivariate models individually. Diuretic use, higher KDIGO risk category, and impaired kidney function at baseline were associated with a further increased odds of an initial 'eGFR dip' with empagliflozin versus placebo at week 4 (P value for interaction <0.05) (Figure 2a). Among subcategories of diuretic treatment, the OR for an 'eGFR dip' of empagliflozin versus placebo was consistent across participants with versus participants without baseline use of potassium-sparing agents and across participants with versus those without the baseline use of low-ceiling diuretics, excluding thiazides (Supplementary Figure S3A). However, treatment with loop diuretics or thiazides at baseline for an 'eGFR dip' with empagliflozin versus placebo (interaction $P = 0.0094$ and $P = 0.0072$, respectively) (Supplementary Figure S3A).

Based on a cutoff of $P < 0.1$ for treatment interaction, UACR categories and angiotensin-converting enzyme inhibitor (ACEi)/angiotensin receptor blocker (ARB) use at baseline were included in the subsequent multivariate analyses (Figure 2a). Other baseline factors, such as age, HbA1c, hematocrit, and blood pressure (BP), were not associated with higher or lower odds for an initial 'eGFR dip' with empagliflozin versus placebo (interaction $P > 0.1$) (Supplementary Figure S3).

In multivariate logistic regression with backward selection (using $P < 0.05$ for retention of the interaction in the model), only diuretic treatment and KDIGO risk category at baseline were identified as independent predictors of an initial 'eGFR dip' with empagliflozin. Figure 2b presents ORs for initial 'eGFR dip' with empagliflozin overall (left) and across the 8 subgroups for combinations of diuretic use and KDIGO risk at baseline (right). In participants with low KDIGO risk and not receiving diuretic treatment ($n = 1993$), empagliflozin was associated with a relatively low OR of 1.6 (95% CI, 1.2–2.1) for an initial 'eGFR dip'; however, OR increased to 2.7 (95% CI, 1.9–3.7) in low KDIGO risk category participants receiving diuretic therapy at baseline ($n = 1182$). Increasingly severe KDIGO risk category was further associated with an increased risk of an initial 'eGFR dip' (Figure 2b, right).

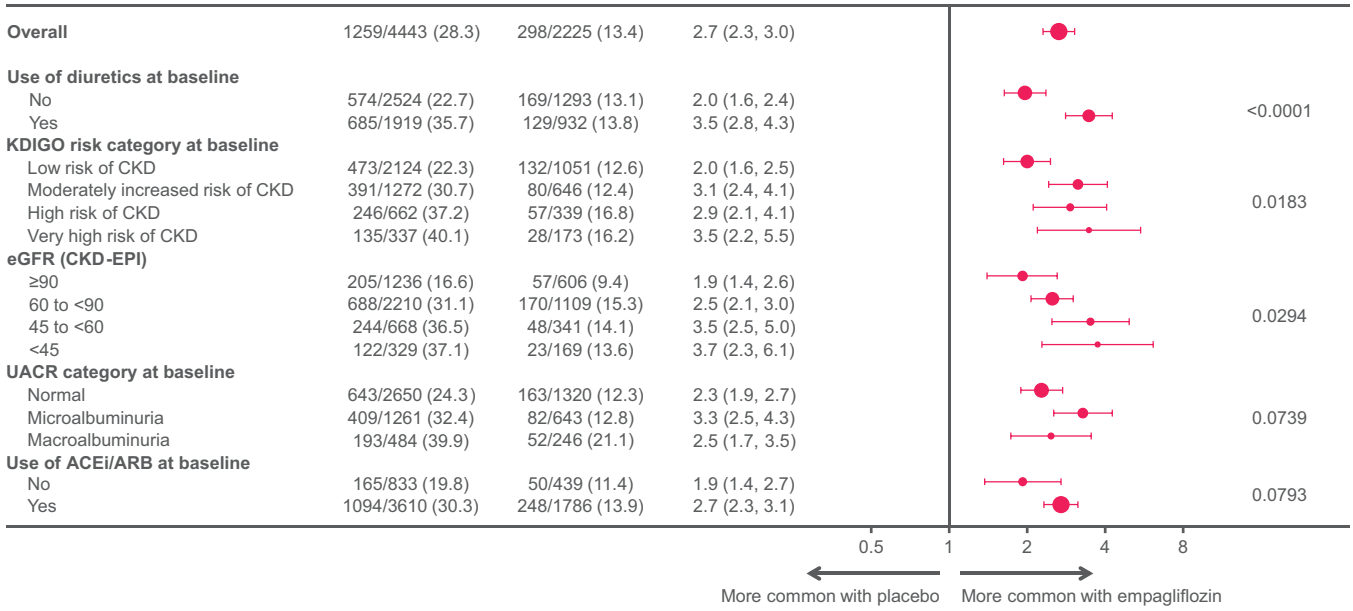
AE profile across subgroups by predictive baseline factors for an empagliflozin-induced 'eGFR dip'

To assess whether increasing risk of an empagliflozin-induced 'eGFR dip' was associated with increased risk of AEs, we investigated overall AEs and kidney AEs in participant subgroups based on predictive baseline factors. These AE analyses were based on reporting by study investigators. Kidney AEs refer to reporting of the narrow Standardised MedDRA Query ARF, which includes AKI. As shown in Figure 3, within both treatments, participants on diuretics at baseline had higher rates of serious (Figure 3a) and kidney (Figure 3b) AEs compared with participants not treated with diuretics. These rates were further increased in higher KDIGO risk categories, especially in high and very high KDIGO risk. Regardless of diuretic treatment and KDIGO risk category, AEs were generally lower or similar with empagliflozin versus placebo (Figure 3 and Supplementary Table S2).

From baseline to week 4, overall and serious AE rates were not increased with empagliflozin in any subgroup (Supplementary Table S3). Kidney AEs were slightly elevated in empagliflozin-treated participants (48 of 4635 [0.1%–4.9%] with empagliflozin vs. 16 of 2317 [0.5%–3.5%] with placebo across KDIGO risk and diuretic use groups) (Supplementary Table S3). In addition, kidney AEs leading to treatment discontinuation were reported more frequently with empagliflozin, especially in the participants not treated with diuretics at baseline (Supplementary Table S3). However, this affected only 9 patients with kidney events out of a total of 84 AEs leading to discontinuation of empagliflozin treatment, all of which reported the preferred term 'renal impairment.'

a

	Pooled empagliflozin n/N (%)	Placebo n/N (%)	Odds ratio (95% CI)	Interaction *P* value
Overall	1259/4443 (28.3)	298/2225 (13.4)	2.7 (2.3, 3.0)	
Use of diuretics at baseline				
No	574/2524 (22.7)	169/1293 (13.1)	2.0 (1.6, 2.4)	<0.0001
Yes	685/1919 (35.7)	129/932 (13.8)	3.5 (2.8, 4.3)	
KDIGO risk category at baseline				
Low risk of CKD	473/2124 (22.3)	132/1051 (12.6)	2.0 (1.6, 2.5)	
Moderately increased risk of CKD	391/1272 (30.7)	80/646 (12.4)	3.1 (2.4, 4.1)	0.0183
High risk of CKD	246/662 (37.2)	57/339 (16.8)	2.9 (2.1, 4.1)	
Very high risk of CKD	135/337 (40.1)	28/173 (16.2)	3.5 (2.2, 5.5)	
eGFR (CKD-EPI)				
≥90	205/1236 (16.6)	57/606 (9.4)	1.9 (1.4, 2.6)	
60 to <90	688/2210 (31.1)	170/1109 (15.3)	2.5 (2.1, 3.0)	0.0294
45 to <60	244/668 (36.5)	48/341 (14.1)	3.5 (2.5, 5.0)	
<45	122/329 (37.1)	23/169 (13.6)	3.7 (2.3, 6.1)	
UACR category at baseline				
Normal	643/2650 (24.3)	163/1320 (12.3)	2.3 (1.9, 2.7)	
Microalbuminuria	409/1261 (32.4)	82/643 (12.8)	3.3 (2.5, 4.3)	0.0739
Macroalbuminuria	193/484 (39.9)	52/246 (21.1)	2.5 (1.7, 3.5)	
Use of ACEi/ARB at baseline				
No	165/833 (19.8)	50/439 (11.4)	1.9 (1.4, 2.7)	0.0793
Yes	1094/3610 (30.3)	248/1786 (13.9)	2.7 (2.3, 3.1)	



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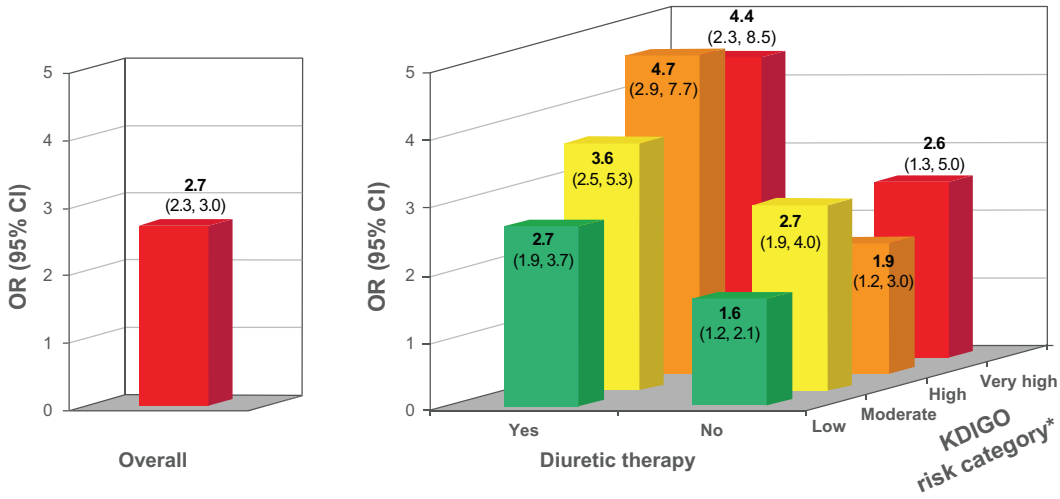

Figure 2 | Odds ratios (ORs) for an 'estimated glomerular filtration rate (eGFR) dip' with empagliflozin versus placebo: factors included in the multivariate prediction analysis (a) and multivariate analysis yielding 8 subgroups of combinations of diuretic use and Kidney Disease: Improving Global Outcomes (KDIGO) risk (b). (**a**) Participants treated with at least 1 dose of study drug who had eGFR (Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI]) values available for baseline and week 4. OR (95% confidence interval [CI]) for an 'eGFR dip' for empagliflozin versus placebo. Logistic regression with baseline factor, treatment, and interaction of baseline factor with treatment showing baseline factors with $P < 0.1$ for interaction. (**b**) Participants treated with at least 1 dose of study drug who had eGFR values available for baseline and week 4. OR (95% CI) for an 'eGFR dip' for empagliflozin versus placebo. (Left) Logistic regression including treatment, sex, baseline body mass index category, baseline glycated hemoglobin category, baseline eGFR category, geographical region, and age. (Right) Number of patients per subgroup (diuretic/KDIGO risk category): no/low, 1993; no/moderate, 1063; no/high, 511; no/very high, 215; yes/low, 1182; yes/moderate, 855; yes/high, 490; yes/very high, 295. Following a backward selection procedure, the multivariate logistic regression model included factors for use of diuretics and KDIGO risk category at baseline ($P = 0.1542$), treatment ($P = 0.0006$), use of angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers at baseline ($P < 0.0001$), and treatment-by-use of diuretics and KDIGO risk category at baseline interaction ($P = 0.0006$) as categorical variables. *Prognosis of chronic kidney disease (CKD) according to 2012 KDIGO guidelines. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; UACR, urine albumin-to-creatinine ratio.

Risk for CV and kidney outcomes with empagliflozin across subgroups by predictive baseline factors

For further analyses of CV and kidney outcomes, the 8 subgroups of predictive baseline factors were pooled into 2 groups based on their OR above versus below or equal to the overall OR for an empagliflozin-induced 'eGFR dip.' Thereby, participants with no diuretic use and any KDIGO risk and those with diuretic use and low KDIGO

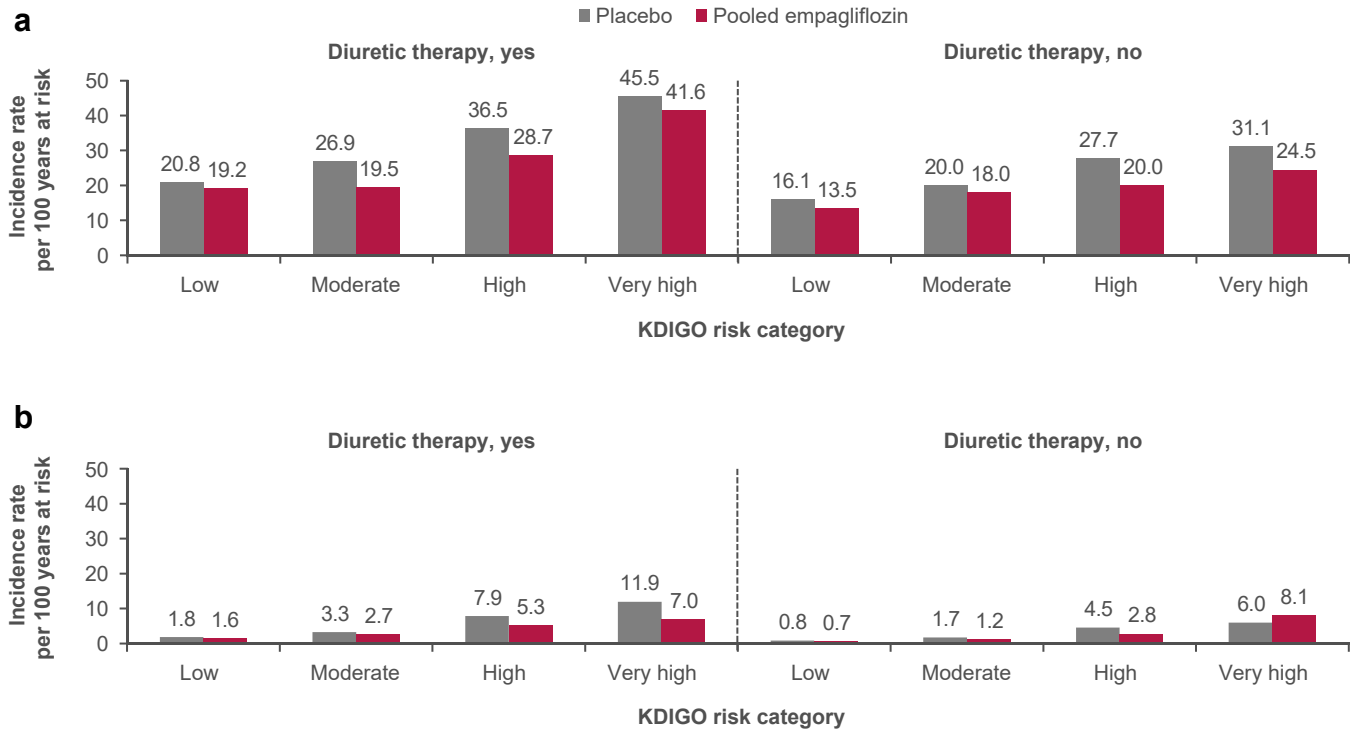

Figure 3 | Adverse events (AEs) by subgroup of baseline predictive factors for an initial 'estimated glomerular filtration rate dip': serious (a) and kidney (b) AEs. Analysis based on participants treated with at least 1 dose of study drug using events obtained on treatment + 7 days. Kidney AE: narrow Standardised Medical Dictionary for Regulatory Activities Query acute renal failure reported by study investigators, which included the preferred term acute kidney injury. KDIGO, Kidney Disease: Improving Global Outcomes.

risk at baseline were pooled into category 'OR ≤ 2.7,' while participants with baseline diuretic use and moderate-to-high KDIGO risk were pooled into category 'OR > 2.7.'

CV death, HHF, and incident or worsening nephropathy (Figure 4a), as well as additional CV and kidney outcomes (Supplementary Figure S4) were consistently reduced by empagliflozin versus placebo in these 2 pooled subgroups (all *P* values for interaction >0.1) (Figure 4a and Supplementary Figure S4). Consistent results were retrieved when all 8 subgroups were investigated individually (data not shown).

Event rates for all outcomes after week 4 were higher in participants with an increased OR for an 'eGFR dip' compared with an OR below or equal to the overall OR (Figure 4a and Supplementary Figure S4) in both treatment groups. Therefore, we analyzed the association of an 'eGFR dip' with outcomes and found a tendency toward a slightly increased risk of CV-related death (HR, 1.24; 95% CI, 0.95–1.62) and HHF (HR, 1.18; 95% CI, 0.86–1.63) and a significantly increased risk for incident or worsening nephropathy (HR, 1.22; 95% CI, 1.05–1.44) in participants with an 'eGFR dip,' consistently with empagliflozin and placebo treatment (all *P* values for treatment-by-'eGFR dip' interaction around 0.5–0.8).

Impact of the 'eGFR dip' on the treatment effect of empagliflozin on CV and kidney outcomes: mediation analysis

We then assessed whether the treatment effect of empagliflozin on these outcomes was affected by the 'eGFR dip.' Figure 4b presents the HRs for CV death, HHF, and incident or worsening nephropathy following week 4 from the primary analysis, along with HRs after additional adjustment for the 'eGFR dip,' along with the resulting percent mediation of the treatment effect attributable to the 'eGFR dip.' The 95% CIs of the treatment effect from the primary analysis and the adjusted analysis overlapped, and the 'eGFR dip' resulted in –14.7%, –11.7%, and –10.2% of the empagliflozin treatment effect being mediated for CV death, HHF, and incident or worsening nephropathy, respectively.

DISCUSSION

An initial eGFR decline of approximately –3 to –5 ml/min per 1.73 m^2 on treatment has been reported across SGLT2i outcomes trials,[2,4,6,8] but its categorization and potential implications for safety and efficacy have not yet been explored. In EMPA-REG OUTCOME, the proportion of participants with an initial 'eGFR dip' >10% was doubled with empagliflozin versus placebo, but a more pronounced eGFR decline >30% was rare in both arms. Nevertheless, the wide variability of the initial eGFR changes after treatment initiation was present in both arms, reflecting the biological variability of eGFR previously reported in healthy and diseased cohorts, including diabetic patients.[25-27] In the participants randomized to empagliflozin, the mean eGFR over time remained stable after week 12 in all dipping categories, even in participants with more pronounced initial eGFR decline (>30%). Stabilization of eGFR regardless of the degree of acute changes after

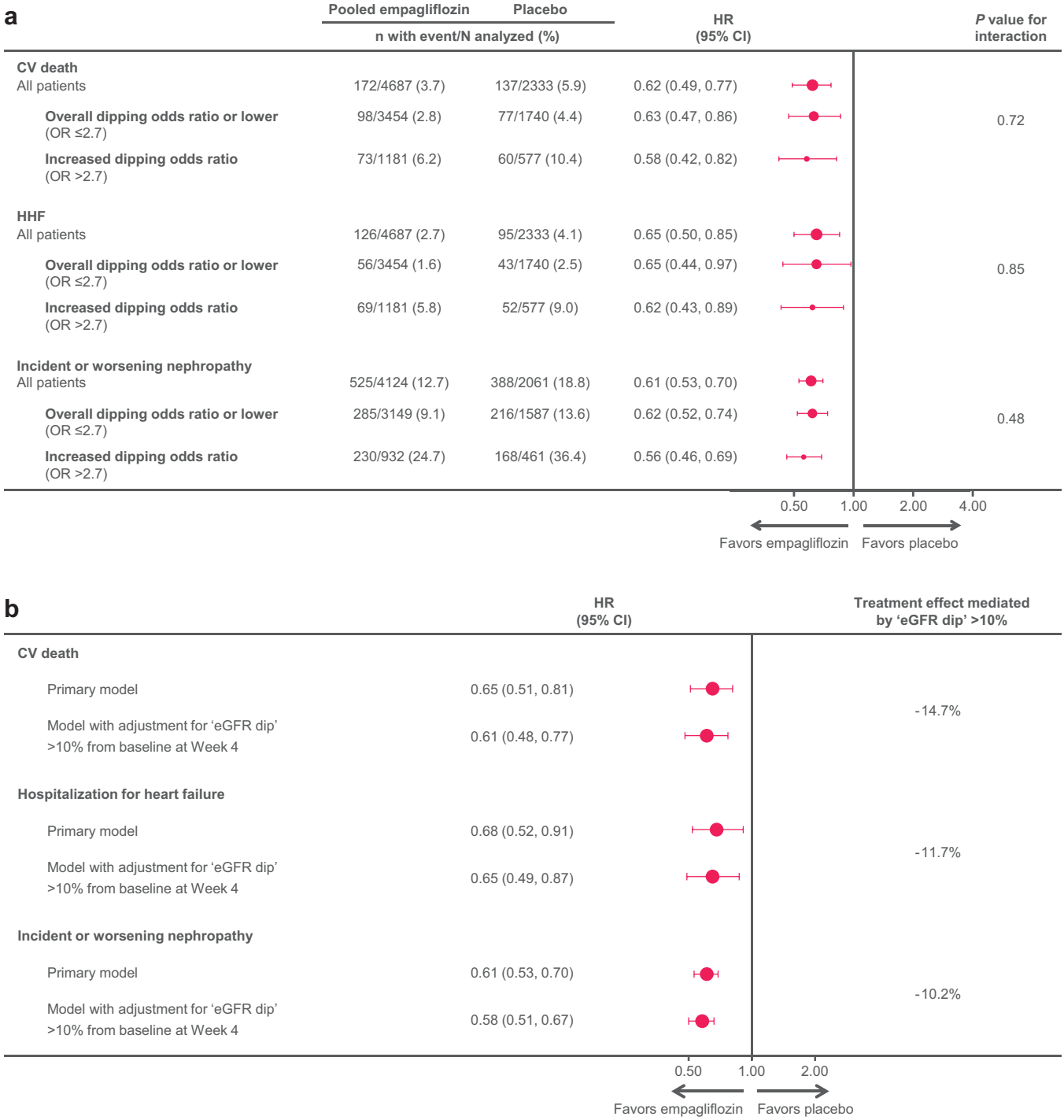

Figure 4 | Cardiovascular (CV) and kidney outcomes by baseline predictive factors for an initial 'estimated glomerular filtration rate (eGFR) dip' and proportion of the risk reduction in outcomes following week 4 mediated by an 'eGFR dip.' (**a**) Participants treated with ≥1 dose of study drug who had eGFR (Chronic Kidney Disease Epidemiology Collaboration) values available at baseline and at week 4. Risk reduction overall (all patients) and by baseline diuretic use/Kidney Disease: Improving Global Outcomes (KDIGO) category subgroups categorized according to their risk below or equal to and above the overall effect for an initial 'eGFR dip' with empagliflozin versus placebo: odds ratio (OR) ≤2.7 versus >2.7. OR for an 'eGFR dip' in empagliflozin versus placebo in the overall population: 2.7 (95% confidence interval, 2.3–3.0). Overall dipping OR lower (≤2.7): participants with no diuretic use at baseline and any KDIGO risk or diuretic use at baseline and low KDIGO risk. Increased dipping OR (>2.7): participants with baseline diuretic use and KDIGO risk moderate to high. Results are based on Cox regression with factors for treatment, age, sex, baseline body mass index (BMI), baseline glycated hemoglobin (HbA1c), region, subgroup, and subgroup-by-treatment interaction. (**b**) Percentage of empagliflozin treatment effect mediated by an 'eGFR dip' resulting from a comparison of the treatment effect from the primary model with the treatment effect from the model also adjusted for 'eGFR dip' based on landmark analyses after week 4. A Cox proportional hazards model was used, with adjustment for treatment group, age, sex, baseline BMI, baseline HbA1c, baseline eGFR, and region in participants treated with ≥1 dose of study drug who had eGFR values available at both baseline and week 4. HHF, hospitalization for heart failure; HR, hazard ratio.

initiation of another SGLT2i, luseogliflozin, was recently reported in Japanese patients with T2D.[28]

An initial decline in eGFR after treatment initiation followed by stabilization of kidney function during the chronic maintenance therapy is highly reminiscent of the eGFR responses observed with RAAS inhibitors in several trials.[14,16,29-33] In such trials, initial 'eGFR dipping' versus 'eGFR non-dipping,' mostly within the first 3–6 months, was inversely related to the course of eGFR over the subsequent 3–4 years. Patients with an initial eGFR increase were generally reported to have steeper eGFR slopes during chronic maintenance therapy compared with those with an initial eGFR decrease irrespective of the use of an ARB,[16,32] ACEi, or other BP-lowering agents, such as direct renin inhibitors or beta-blockers.[29,33] A meta-analysis of trials in patients with preexisting kidney impairment suggested that a beneficial relationship holds especially for serum creatinine increases of ≤30% and for patients with a starting creatinine value >1.4 mg/dl,[14] but this was not confirmed in all trials.[32]

In EMPA-REG OUTCOME, the majority of participants received randomized treatment in addition to preexisting RAAS inhibition. With empagliflozin, stabilization of long-term mean eGFR occurred in all dipping categories with differing baseline kidney function, including the subset with a >30% eGFR decline. With RAAS inhibitors, the extent of an initial eGFR decline is thought to indicate treatment response,[14,29] but in our analysis, we found a comparable stabilization of long-term mean eGFR in all 'eGFR dipping' categories on empagliflozin treatment. Recently reported data on treatment with canagliflozin or dapagliflozin show that stabilization of eGFR can be obtained with SGLT2i even in diabetic patients with chronic kidney disease stage 3b–4.[34,35] Future studies of empagliflozin in patients with impaired kidney function, such as EMPEROR (NCT03057977, NCT03057951)[36,37] and EMPA-KIDNEY (NCT03594110),[38] may reveal whether this can also be confirmed with empagliflozin.

In the current analysis, eGFR increased following empagliflozin treatment cessation in all 'eGFR dipping' categories. This effect has also been described for RAAS inhibitors even after long-term treatment.[39] Interestingly, in our study, median eGFR values at 1 month after empagliflozin cessation increased even in the 'eGFR non-dipper' group to a similar extent as in the 'eGFR intermediate' group. Such an improvement in eGFR in participants who did not exhibit an initial 'eGFR dip' may raise questions regarding the pathophysiology of the initial 'eGFR dip' with empagliflozin. Although the restoration of tubuloglomerular feedback is likely an important kidney contributor to the mechanism of action of SGLT2i,[40,41] additional kidney mechanisms, such as tubular protection, reduced hypoxia and inflammation, or long-term effects of natriuresis, also may contribute to the renoprotective effects observed with SGLT2i.[42-45] Loss of randomization and apparent differences in baseline characteristics between 'eGFR dippers' on empagliflozin versus those on placebo did not allow for a direct comparison of AEs and outcomes within and across 'eGFR dipping' categories. Therefore, we focused on identifying baseline factors that could be predictive of an initial 'eGFR dip' after initiation of empagliflozin versus placebo. Participants on diuretic therapy, particularly those on loop diuretics and thiazides, were more likely to experience such an initial 'eGFR dip,' which was additionally and independently increased by higher KDIGO risk category. ACEi/ARB treatment at baseline also increased the OR for an 'eGFR dip' with empagliflozin versus placebo, but the interaction with empagliflozin treatment was statistically nonsignificant, especially in the multivariate analysis. Thus, ACEi/ARB use at baseline was higher in participants with an initial 'eGFR dip' compared with 'eGFR non-dippers' on empagliflozin but was not predictive of an 'eGFR dip' with empagliflozin treatment. Also, hemodynamic or volume markers, such as baseline BP, hematocrit, and hemoglobin, were not associated with an empagliflozin-induced 'eGFR dip.'

Empagliflozin did not increase the rate of AEs regardless of kidney risk or diuretic therapy at baseline. Most importantly, reporting of kidney AEs, including AKI, did not raise safety concerns in any of the subgroups. We found numerically elevated proportions of kidney AEs only for the initial treatment phase up to week 4, and few events leading to discontinuation of empagliflozin treatment, especially in participants not on diuretics at baseline. However, all referred to the preferred term 'renal impairment,' suggesting that these AEs may have reflected the initial empagliflozin-induced 'eGFR dip.' These safety data add to the reassuring findings on RAAS inhibition, with an eGFR decline of up to 20% after treatment initiation considered acceptably safe.[46]

CV and kidney outcomes were consistently reduced with empagliflozin across the subgroups based on predictive factors for an initial 'eGFR dip.' Furthermore, empagliflozin treatment was associated with improved CV mortality, HHF, and kidney outcomes after week 4 in the mediation analysis, which was not substantially weakened by adjustment for an initial 'eGFR dip,' as shown by the similar HRs with largely overlapping CIs. These data seem to contrast with previously reported data for RAAS inhibition, in which an initial 'eGFR dip' was suggested to be a positive prognostic marker associated with beneficial kidney outcomes and reduced declines in kidney function in patients with and without diabetes and in patients with and without impaired kidney function.[14,16,29,31,47-50] However, more recent analyses showed that an 'eGFR dip'/creatinine increase with RAAS inhibition might not be predictive of CV and kidney outcomes or associated with an increased risk.[17-19,27,51,52]

Our data are in line with findings from previous analyses on EMPA-REG OUTCOME, showing that outcome event rates were consistently reduced with empagliflozin in subgroups across various conditions,[2,53-59] such as participants using diuretic background medication at baseline,[53] or across KDIGO risk categories.[60] Our findings are also in line with results from the CV mediation analysis showing that eGFR over time had no or only negligible effects on the empagliflozin treatment effect on CV mortality, which was mainly mediated by changes in markers of plasma volume.[23]

Limitations

Our study has several limitations. First, this was a *post hoc* analysis of a CV outcomes trial that was not prespecified and of an exploratory nature. In addition, correction for multiple testing was not applied. Only single measurements of eGFR were available, and owing to their high biological variability, we might not have been able to correctly classify each patient. Also, this analysis did not include a randomized placebo-corrected comparison of 'eGFR dippers' versus 'eGFR non-dippers,' because dipping categories were defined post-randomization and had significant differences in baseline characteristics, and the 'eGFR dip' itself was already influenced by empagliflozin treatment. For a direct comparison, a dedicated trial that randomized participants after stratification for individual 'eGFR dipping' responses would be required. However, by comparing the subgroups based on predictive baseline factors, we did not break treatment randomization and were able to assess an empagliflozin treatment effect, and we shed some light on the impact of an 'eGFR dip' on outcomes occurring after week 4 in the mediation analysis.

Conclusions

An initial 'eGFR dip' >10% affected approximately 1 in 4 of the study participants treated with empagliflozin in EMPA-REG OUTCOME; a more pronounced initial eGFR decline >30% was rare. Participants with more advanced kidney disease and/or on diuretic therapy at baseline were more likely to experience an initial 'eGFR dip' >10%. However, empagliflozin treatment appears to be safe and associated with improved CV and kidney outcomes, irrespective of identified baseline predictive factors. In addition, the initial 'eGFR dip' did not have a major impact on the long-term CV and kidney benefits observed with empagliflozin in patients with T2D and CV disease.

DISCLOSURE

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DATA STATEMENT

The sponsor of the EMPA-REG OUTCOME trial (Boehringer Ingelheim) is committed to responsible sharing of clinical study reports, related clinical documents, and patient-level clinical study data. Researchers are invited to submit inquiries via the following website: https://trials.boehringer-ingelheim.com.

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Figure S1. eGFR over time for the subcategory of an initial eGFR decline >30% from baseline in empagliflozin-treated participants.
Figure S2. (**A**) eGFR over time by 'eGFR dipping' category in placebo-treated participants. (**B**) Mean eGFR at last value on treatment and follow-up per 'eGFR dipping' categories in placebo-treated participants.
Figure S3. (**A**) ORs for an 'eGFR dip' with empagliflozin versus placebo: analysis of diuretic subgroups. (**B**) Baseline factors not associated with an 'eGFR dip' with empagliflozin versus placebo.
Figure S4. Additional cardiovascular and kidney outcomes by baseline predictive factors for an initial 'eGFR dip.'
Table S1. Baseline characteristics for empagliflozin-treated participants including subcategory of an initial eGFR decline >30%.
Table S2. Adverse events of special interest by subgroup of predictive baseline factors for an 'eGFR dip.'
Table S3. Adverse events of special interest by subgroup of predictive baseline factors for an 'eGFR dip,' baseline to week 4.

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