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

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Abstract

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) require further study.

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

Methods: Landmark analyses (week 4) were performed.

Results: eGFR change was available in 3547 patients out of 3730 (95%). The tertiles of post initiation eGFR % change for empagliflozin were: tertile 1 (T1) ≤-11.4%; T2 ≥-11.4% to ≤-1.0% and T3 ≥0.0%. The placebo group tertiles were: T1 ≤-6.5%; T2 ≥-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^2 vs. placebo. In the 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 placebo group, patients in whom early post treatment initiation eGFR decreased (T1) 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 HR 1.37, 95%CI 1.01-1.85, respectively.

Conclusion: A mild eGFR decrease may be expected after the initiation of empagliflozin, and it is not associated with untoward HF, mortality or kidney safety

events. Clinicians should not be concerned with early eGFR changes post-initiation of empagliflozin.

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

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).[1] 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.[2-4] 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.[11] 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.[12]

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 (EMPEROR-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.[13] 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/1.73m^2 (if the baseline eGFR was ≥30 mL/min/1.73m^2) or <10 mL/min/1.73m^2 (if the baseline eGFR was <30 mL/min/1.73m^2) 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

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 the composite renal outcome and 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-by-visit 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).

Results

eGFR change post-initiation and baseline characteristics

Changes in eGFR from randomization to week 4 occurred both in the empagliflozin and in the placebo groups, with a shift in eGFR change distribution to the left (i.e., higher decrease) in the empagliflozin group of -2.5, 95%CI -3.1 to -1.9 ml/min/1.73m^2 on average compared to placebo (***Figure 1***).

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

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

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

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

eGFR progression at 4 weeks and after

At week 4, empagliflozin-treated patients experienced an eGFR change of -3.5 (95% CI -3.9 to -3.1) compared to -1.0 (95% CI -1.4 to -0.6) in placebo-treated patients (***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-treated patients but remained similar to the last "on-treatment" value in placebo-treated patients (***Figure 3a, right panel***).

In empagliflozin-treated patients, among those with the steepest decrease at week 4 (T1: ≤ -11.4% change), eGFR increased throughout the follow-up, while among 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 mean" phenomenon (***Figure 3b, left panel***). After treatment discontinuation, eGFR increased across all tertiles (***Figure 3b, right panel***).

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 the 2 other tertiles, eGFR decreased continuously throughout the follow-up (***Figure 3c, left panel***). After placebo discontinuation, eGFR remained stable across all tertiles (***Figure 3c, right panel***).

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

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

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 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 (***Figure 5d***). The effect of empagliflozin on cardiovascular death and all-cause mortality was consistent and neutral across the % eGFR change 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 in patients with an eGFR decrease >20% versus those without, and without significant differences

between the empagliflozin and placebo groups (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 patients with an eGFR decrease >30% versus those without, and without significant differences between the empagliflozin and placebo groups (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 ≥2.02% 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 ≥2.02% (***Supplemental Figure 3b***). The risk of composite renal outcome was increased in patients with an eGFR decrease >30% compared to patients with eGFR increase ≥2.02%, 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: ≥ 0.0% change), patients who experienced the steepest eGFR decrease (T1: ≤ -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: ≥ +3.6% change), patients who experienced the steepest eGFR decrease (T1: ≤ -6.5% change) had a higher risk of acute renal failure (adjusted HR 1.58, 95%CI 1.08-2.32). The risk of acute kidney injury was not statistically different across tertiles

(***Figure 7b***).

The risk of acute renal failure was increased in patients with an eGFR decrease >30% compared to patients with eGFR increase ≥2.02%, regardless of the treatment group, but not for acute kidney injury with empagliflozin (***Supplemental Figure 4b***).

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 in the lowest tertile was only associated with subsequent higher risk for the kidney composite outcome and all-cause mortality, if occurring in the placebo group, and not with empagliflozin. Any post-empagliflozin initiation decrease in eGFR did not deprive patients from benefiting from empagliflozin therapy.

These findings are in line with those from DAPA-HF where patients experiencing an early eGFR decrease with dapagliflozin had better outcomes but not 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.[15] 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).[5, 16] In addition, it is possible that inflammation, circulating proinflammatory cytokines and oxidative stress, which are overamplified in heart failure, also contribute to kidney dysfunction.[17] 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.[7] 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.[5, 6, 19]

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.[10]

An initial eGFR decrease can also occur after the initiation of inhibitors of the renin-angiotensin aldosterone system (RAAS), often leading clinicians to withhold or stop RAAS inhibitors, despite their proven benefit in HFrEF regardless of the initial eGFR decrease.[9] 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 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 not recommend to routinely monitor eGFR within the first month post SGLT2i initiation, and this decision should be left at the discretion of the treating physician.

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 as well as outcomes between treatment groups across initial eGFR changes. 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. Importantly, also patients within certain categories of % eGFR changes are not comparable between empagliflozin and placebo in terms of their baseline characteristics. Therefore, none of the applied landmark analyses 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. Furthermore, as occurrence of eGFR decreases of >30% were uncommon in both treatments, also outcomes were very rare, therefore comparisons made with this group should be interpreted with caution.

Conclusions

A mild eGFR decrease may be expected after the initiation of empagliflozin, and it is not associated with untoward HF, mortality or kidney safety events. Clinicians should not be concerned with early eGFR changes post-initiation of empagliflozin.

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Data sharing

Data will be made available upon request in adherence with transparency conventions in medical research and through requests to the corresponding author. The executive committee of EMPEROR has developed a comprehensive analysis plan and numerous prespecified analyses, which will be presented in future scientific meetings and publications. At a later time-point, the full database will be made available in adherence with the transparency policy of the sponsor (available at https://trials.boehringer-ingelheim.com/transparency_policy.html).

Disclosures

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Author Contributions

All authors contributed to the conceptualization of this analysis. The sponsor representatives (BJK, SJH 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.

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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/1.73m².

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

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; NT-proBNP, 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-by-visit-by-treatment interaction as fixed effects.

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., with variable by treatment interaction P <0.05 at week 4.

Baseline variables with homogeneous treatment effect of empagliflozin vs placebo on eGFR change at week 4 were: age, sex, BMI, race, region, LVEF, NYHA functional class, NT-proBNP, cause of HF, time since diagnosis of HF, heart rate, history of AF, history of hypertension, diabetes status, smoking status, eGFR,

UACR, anemia, ACEi/ARB use, ARNi use, beta-blocker use, thiazide or low-ceiling 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, ICD or CRT-D use, CRT use, and HF physiology.

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 ≤ -11.4%; Tertile 2 ≥ -11.4% to ≤ -1.0% and Tertile 3 ≥ 0.0%

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

Corresponding mean eGFR changes per year (annualized slopes): empagliflozin: T1 +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 ≤ -11.4%; Tertile 2 ≥ -11.4% to ≤ -1.0% and Tertile 3 ≥ 0.0%
Placebo: Tertile 1 ≤ -6.5%; Tertile 2 ≥ -6.4% to ≤ +3.6%; and Tertile 3 ≥ +3.6%.

Figure 5. Effect of empagliflozin versus placebo following week 4 across the spectrum of % eGFR change at Week 4.

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. Primary outcome following week 4 by eGFR decrease >20% and >30% from randomization

Legend: The risk of primary outcome following week 4 was similar in patients with an eGFR decrease >20% or >30% versus those without, and consistent across empagliflozin and placebo (interaction P =0.64 and interaction P =0.50, respectively).

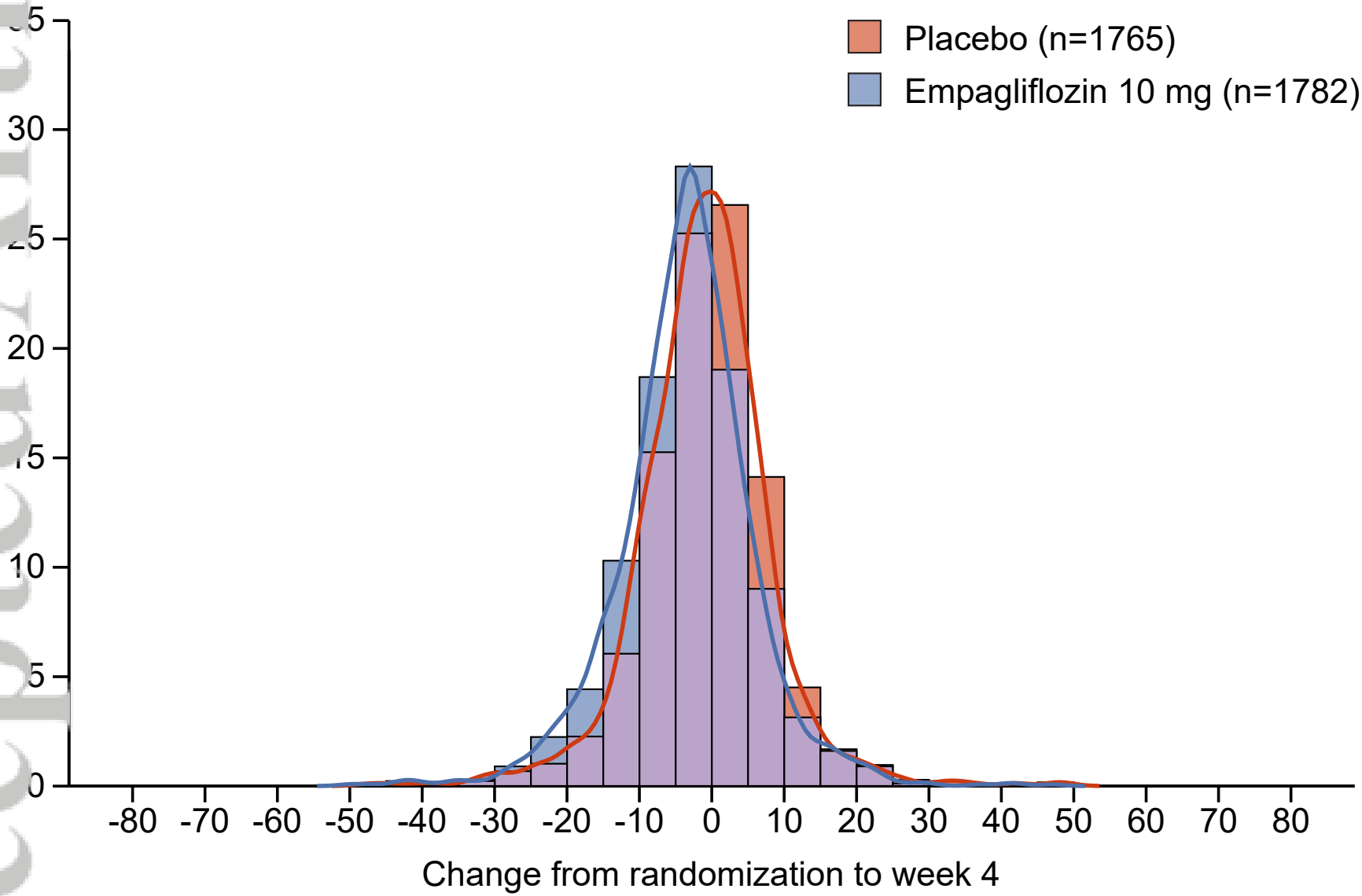
Figure 7. Kidney safety outcomes following week 4 by tertiles of %eGFR change at Week 4 by treatment group.

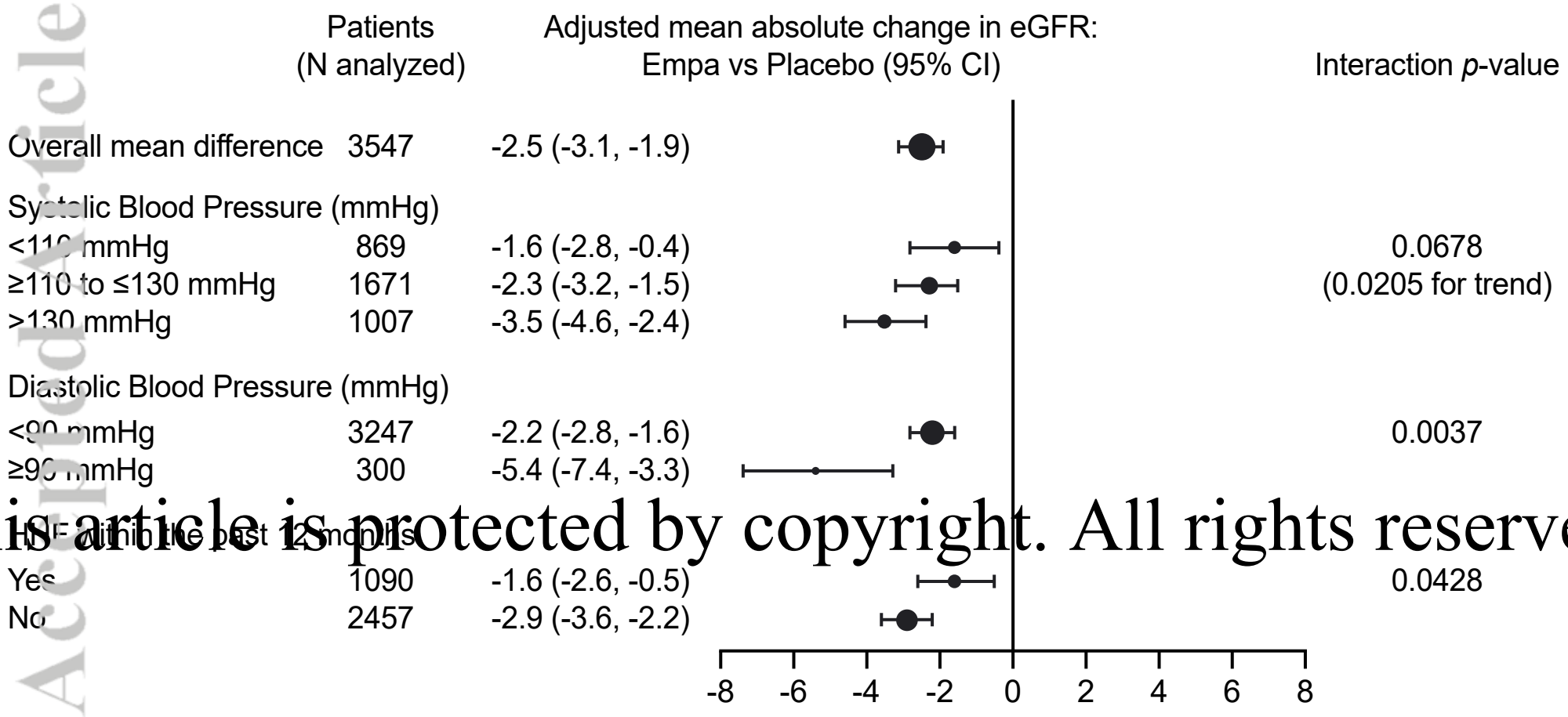
Legend: a, empagliflozin; b, placebo.

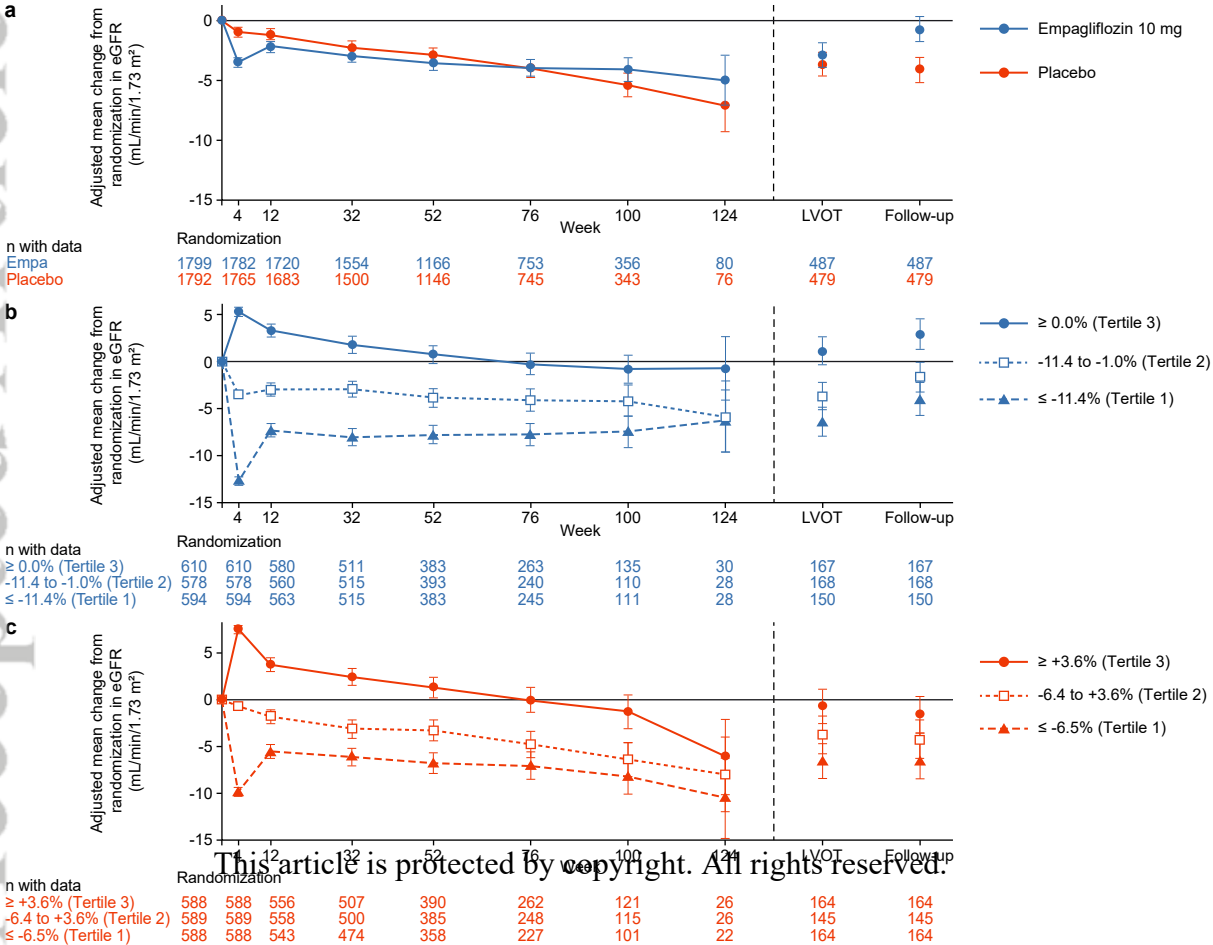
Hazard ratios based on a Cox regression with adjustment for the EMPEROR-Reduced all-cause mortality risk score. Based on data obtained up until 7 days following discontinuation of the study medication. The terms used for this analysis were defined following the Medical Dictionary for Regulatory Activities (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 ≤ -11.4%; Tertile 2 ≥ -11.4% to ≤ -1.0% and Tertile 3 ≥ 0.0%

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







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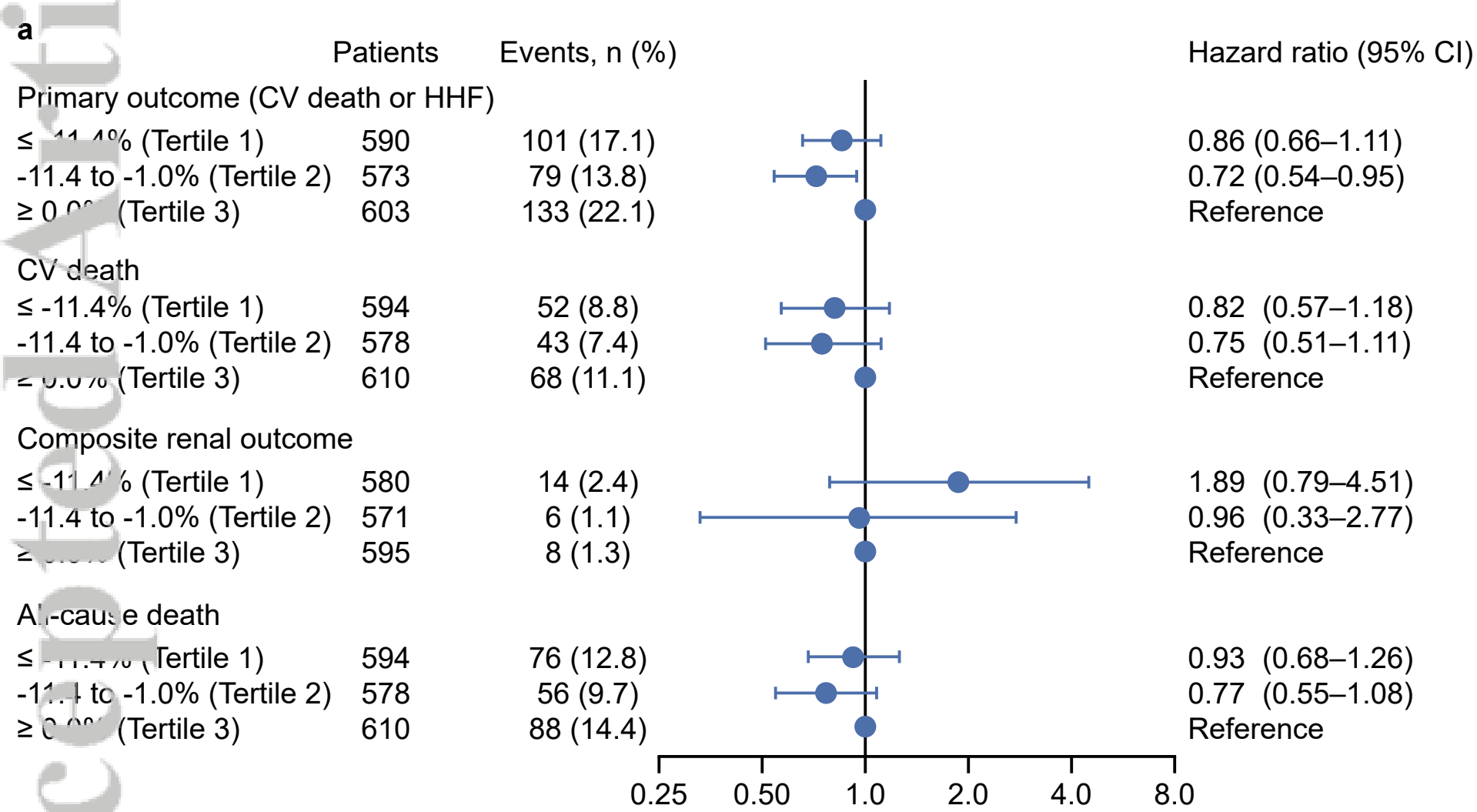

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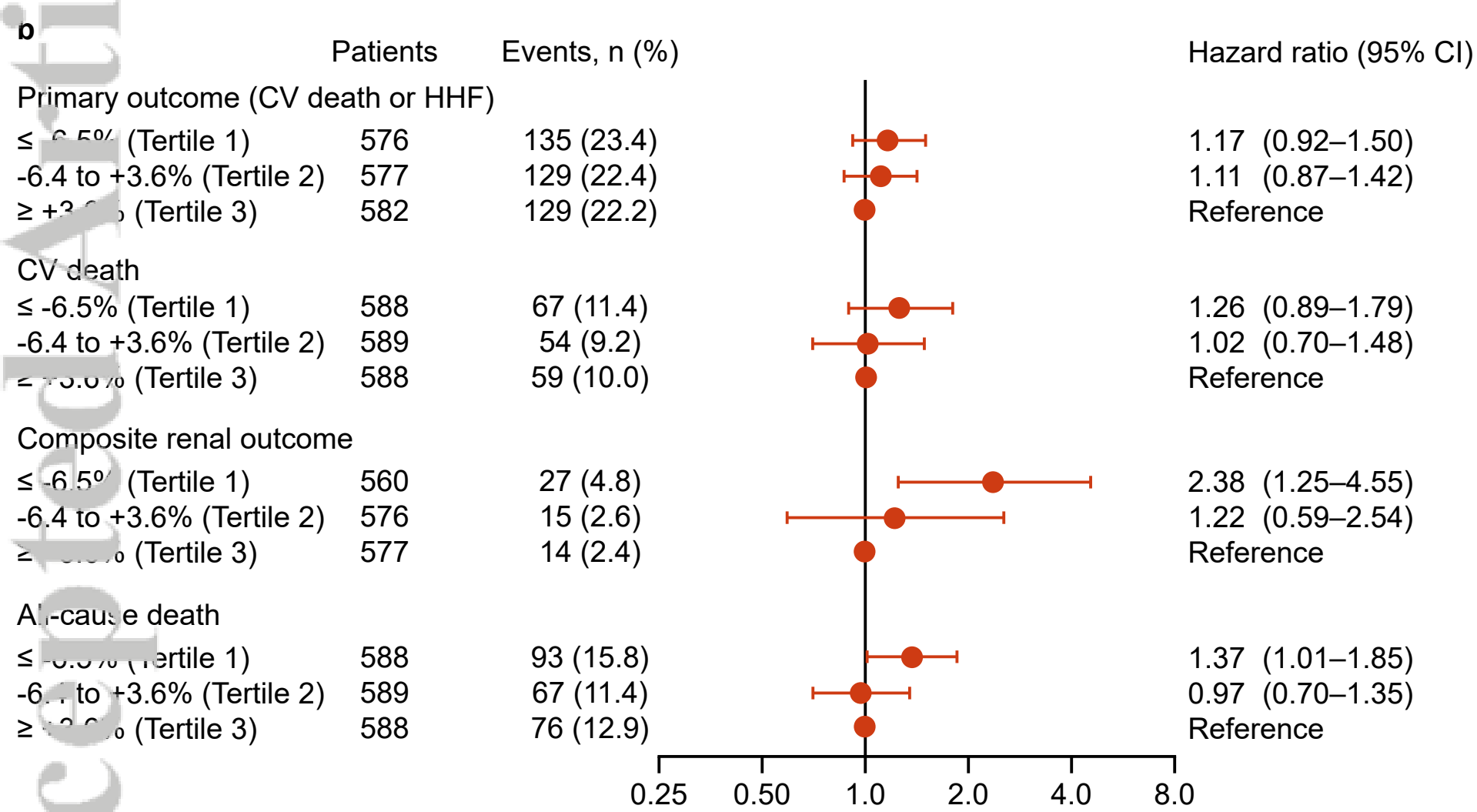

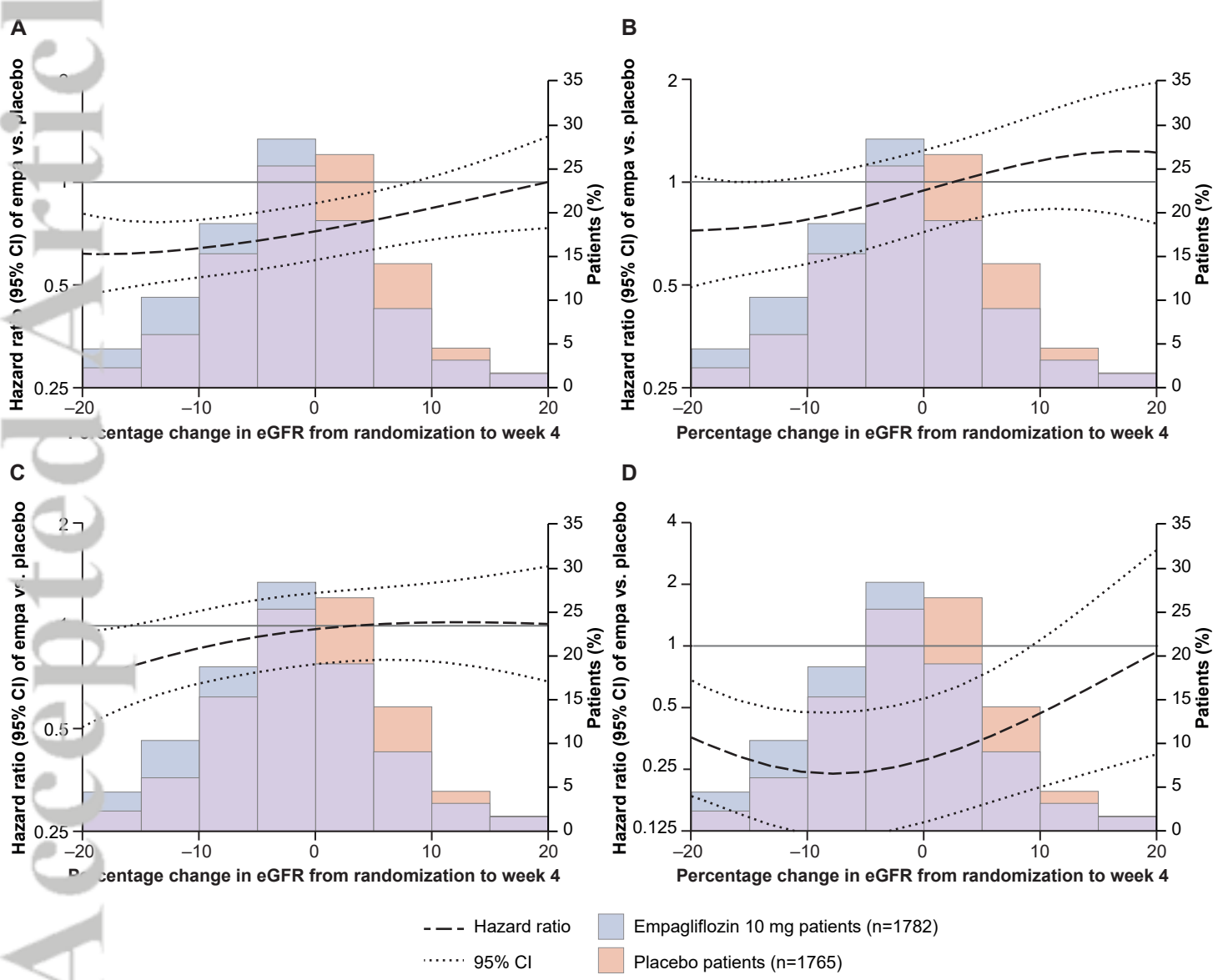

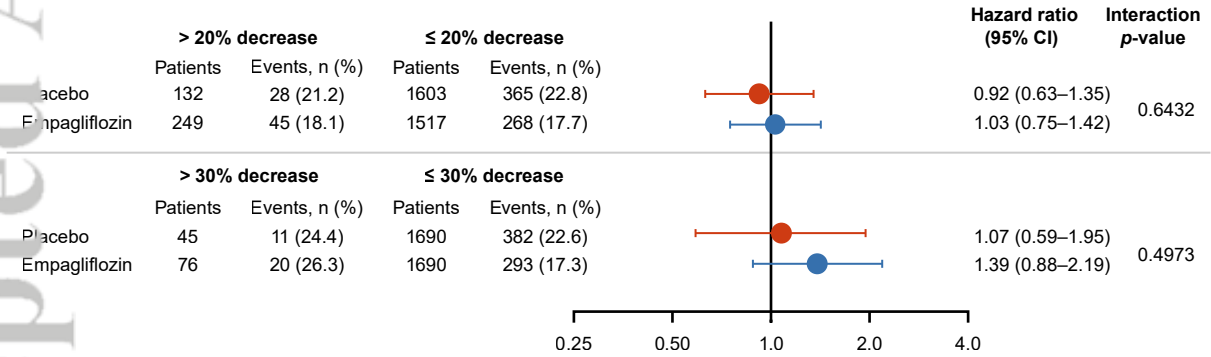

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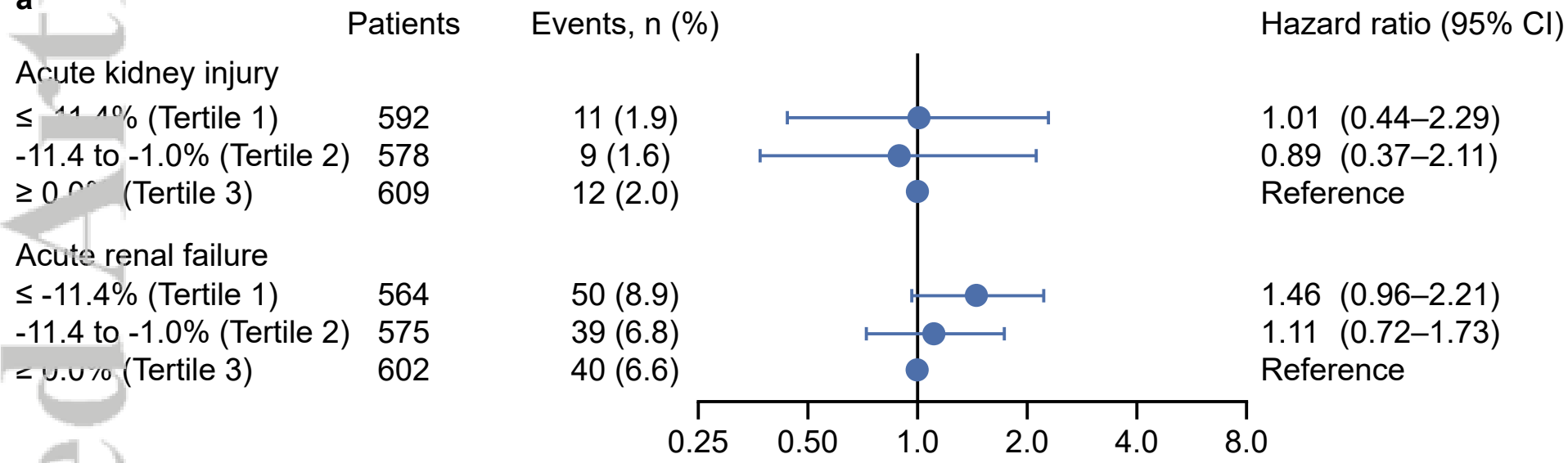

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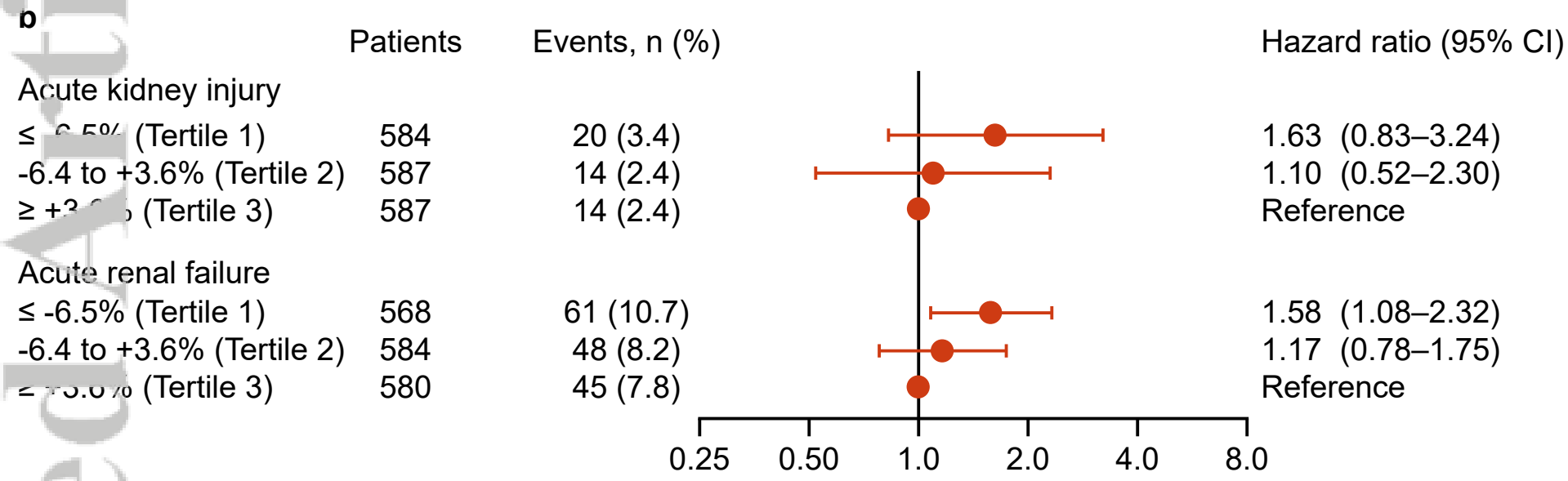

PERMISSION STATEMENT

All material is original to this submission; therefore, no permissions are required.