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ORIGINAL RESEARCH

Short-Term Changes in Albuminuria and Risk of Cardiovascular and Renal Outcomes in Type 2 Diabetes Mellitus: A Post Hoc Analysis of the EMPA-REG OUTCOME Trial

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BACKGROUND: Early reduction in albuminuria with an SGLT2 (sodium-glucose cotransporter 2) inhibitor may be a positive indicator of long-term cardiovascular and renal benefits. We assessed changes in albuminuria during the first 12 weeks of treatment and subsequent long-term cardiovascular and renal risks associated with the SGLT2 inhibitor, empagliflozin, in the EMPA-REG OUTCOME (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 diabetes Mellitus Patients) trial.

METHODS AND RESULTS: We calculated the percentage urinary albumin creatinine ratio (UACR) change from baseline to week 12 in 6820 participants who did not experience a cardiovascular outcome (including 3-point major cardiovascular events and cardiovascular death or hospitalization for heart failure) or renal outcome (defined as 40% decline in estimated glomerular filtration rate from baseline, estimated glomerular filtration rate <15 mL/min per 1.73 m^2, need for continuous renal-replacement therapy, or renal death) during the first 12 weeks. Multivariable Cox regression models were used to estimate the hazard ratio (HR) for each 30% reduction in UACR with outcomes. Empagliflozin reduced UACR by 18% (95% CI, 14–22) at week 12 compared with placebo, and increased the likelihood of a >30% reduction in UACR (odds ratio, 1.42; 95% CI, 1.27–1.58; *P*<0.001). During 3.0 years of follow-up, 704 major cardiovascular events, 440 cardiovascular deaths/hospitalizations for heart failure, and 168 renal outcomes were observed. Each 30% decrease in UACR during the first 12 weeks was statistically significantly associated with a lower hazard for major cardiovascular events (HR, 0.96; 95% CI, 0.93–0.99; *P*=0.012), cardiovascular deaths/hospitalizations for heart failure (HR, 0.94; 95% CI, 0.91–0.98; *P*=0.003), and renal outcomes (HR, 0.83; 95% CI, 0.78–0.89; *P*<0.001).

CONCLUSIONS: Short-term reduction in UACR was more common with empagliflozin and was statistically significantly associated with a decreased risk of long-term cardiovascular and renal outcomes.

REGISTRATION: URL: https://www.clinicaltrials.gov. Unique identifier: NCT01131676.

Key Words: cardiovascular outcomes ■ empagliflozin ■ kidney (diabetes) ■ sodium-glucose cotransporter 2 inhibitors

Patients with type 2 diabetes mellitus face a high risk of cardiovascular disease and progressive renal function loss despite stringent glycemic, blood pressure (BP), and lipid control.[1,2] Albuminuria is a strong predictor of long-term adverse cardiovascular and renal outcomes in patients with type

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CLINICAL PERSPECTIVE

What Is New?

- Short-term reduction in urinary albumin creatinine ratio was more common with empagliflozin than with placebo and was statistically significantly associated with a decreased risk of long-term cardiovascular and renal outcomes during a median follow-up period of 3 years.

What Are the Clinical Implications?

- Short-term albuminuria change may be a useful prognostic marker for cardiovascular and renal outcomes.

Nonstandard Abbreviations and Acronyms

HbA1c	glycated hemoglobin
HHF	hospitalization for heart failure
MACE	major adverse cardiovascular event
UACR	urinary albumin creatinine ratio

2 diabetes mellitus.[3–6] Previous studies have shown that various interventions, including renin-angiotensin-aldosterone system inhibitors, decrease albuminuria and that the degree of albuminuria reduction during the first months of treatment is associated with a reduction in the risk of cardiovascular and renal outcomes.[5,7,8] This consistent finding, confirmed in various patient populations,[9–13] supports regular monitoring of albuminuria to assess cardiovascular and renal prognosis. However, most of the evidence on associations between treatment effect on changes in albuminuria and clinical outcomes is derived from clinical trials with drugs that modulate the renin-angiotensin-aldosterone system. Whether drugs that reduce albuminuria but do not directly modulate the renin-angiotensin-aldosterone system have a similar association is not clear.

Empagliflozin is a selective inhibitor of SGLT2 (sodium-glucose cotransporter 2), which reduces hyperglycemia in patients with type 2 diabetes mellitus by inhibiting the reabsorption of glucose in the proximal tubule, thereby increasing urinary glucose excretion.[14,15] Previous studies with empagliflozin demonstrated improvements in glycated hemoglobin (HbA1c), BP, body weight, and albuminuria and reductions in cardiovascular and renal risks.[16–18]

In this post hoc analysis of the EMPA-REG OUTCOME (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 diabetes Mellitus Patients) trial, we investigated whether an early change in albuminuria upon treatment with empagliflozin is associated with long-term cardiovascular and renal outcomes and whether this association is independent of the change in estimated glomerular filtration rate (eGFR) and other cardiovascular risk factors.

METHODS

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.

Patients and Study Design

A post hoc analysis of the EMPA-REG OUTCOME trial (NCT01131676) was performed. EMPA-REG OUTCOME was a randomized, double-blind, placebo-controlled trial conducted at 590 clinical sites in 42 countries. The study design and main results have been published elsewhere.[17–19] In short, 7020 patients with type 2 diabetes mellitus with an HbA1c ≥7% (53 mmol/mol) and established cardiovascular disease were treated with empagliflozin 10 mg, empagliflozin 25 mg, or placebo once daily in addition to standard care. Participants were also required to have a minimum eGFR of 30 mL/min per 1.73 m^2 on the basis of the 4 variables of the Modification of Diet in Renal Disease formula.[20] Randomized patients were followed for a median of 3.1 years for occurrence of cardiovascular and renal outcomes. All patients signed informed consent before entry into the study, and an independent local ethics committee or institutional review board approved the clinical protocol at each participating center.

Albuminuria Measurements

Urinary albumin creatinine ratio (UACR) was measured by a central laboratory at baseline (week 0) and at week 12 using spot urine samples collected at a random time of the day. The initial change in UACR was defined as the percentage change from baseline to week 12. The 12-week time window was chosen because it was the first time point at which follow-up UACR measurements were available and prior studies have shown that the albuminuria-lowering effect of empagliflozin is fully present at that time point.[16,21]

Outcomes

The primary cardiovascular outcome for this study was the composite of time to the first cardiovascular

death, nonfatal myocardial infarction, or nonfatal stroke (major adverse cardiovascular event [MACE]). The secondary cardiovascular outcomes were a composite of time to the first cardiovascular death and hospitalization for heart failure (HHF) and time to cardiovascular death alone. The renal outcomes were defined as a composite of time to the first event of >40% decrease in eGFR from baseline sustained at the next study visit, eGFR of <15 mL/min per 1.73 m^2 (calculated using the Chronic Kidney Disease Epidemiology Collaboration creatinine equation[22]), initiation of renal replacement therapy, or death from renal disease. A 40% eGFR decline has been accepted by regulatory agencies as a valid surrogate component of a composite renal outcome and is used in various confirmatory clinical trials to register new drugs to treat chronic kidney disease.[23,24] All components of the cardiovascular and renal outcomes were prespecified using rigorous definitions,[19] except for sustained 40% decrease in eGFR, which was a post hoc exploratory outcome.

Statistical Analysis

UACR was transformed into natural logarithm before analysis because of its skewed distributions. Change in UACR was expressed as percentage change and stratified into 3 groups: >30% reduction (<–30%), minor change (≥–30% to ≤+30%), >30% increase (>+30%). A 30% threshold was selected as previous work showed that ≈30% UACR reduction is required to infer clinical benefit.[9,10] Baseline characteristics in each stratum of UACR change are presented as mean and standard deviation or median (25th and 75th percentile [interquartile range]) for variables with a nonparametric distribution. Categorical variables are presented as percentages of observations. Missing value of baseline UACR, week 12 UACR, and other covariates were imputed using multiple imputation for analysis with the SAS PROC MI and MIANALYZE commands. Missing variables selected for the multiple imputation to create 20 imputed data sets were log-transformed UACR, HbA1c, eGFR, low-density lipoprotein cholesterol and high-density lipoprotein cholesterol (HDL-C), systolic BP, and body weight. Differences in baseline characteristics according to subgroups of change in UACR were tested with 1-way analysis of variance or chi-squared test where appropriate.

A multivariable Cox regression model was used to estimate the association between baseline UACR and cardiovascular and renal risks, with baseline UACR fitted both as a continuous variable and a categorical variable (stratified into 4 subgroups: <30, ≥30–300, >300–1000, and ≥1000 mg/g). The lowest baseline UACR category was used as a common reference to compute the hazard ratios (HRs) and 95% CIs for the other baseline UACR strata. The model was adjusted for baseline covariates of age, sex, current smoking status (yes/no), body mass index, systolic BP, diastolic BP, HbA1c, eGFR, low-density lipoprotein cholesterol, HDL-C, use of angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers (yes/no), use of diuretics (yes/no), region, and assignment to empagliflozin or placebo.

Biological or laboratory random variations in UACR measurements may lead to an underestimation of the relationship between UACR with cardiovascular and renal outcomes. To evaluate the impact of this so-called regression-dilution bias on the relationship between baseline UACR and cardiovascular and renal outcomes, we computed the regression-dilution coefficient using the MacMahon-Peto method[25] and repeated the analyses with adjustment for the regression-dilution coefficient.

For assessment of the association between change in UACR at week 12 and the cardiovascular and renal outcomes, we performed a multivariable Cox regression analysis. Change in UACR was analyzed as a continuous variable, and the obtained HRs were expressed per 30% reduction. Change in UACR was also analyzed as a categorical variable (>30% reduction, minor change, >30% increase, as previously defined). To further examine whether the change in UACR in the placebo and empagliflozin treatment arms had similar or different relationships with cardiovascular and renal outcomes, we stratified the population by quartiles of UACR change in each treatment separately. All models were adjusted for the baseline covariates as described previously as well as baseline UACR and change in HbA1c, body weight, systolic BP, and eGFR at 12 weeks.

To assess the consistency of the association between change in UACR and cardiovascular and renal outcomes, we repeated the analyses in subgroups defined by age, sex, baseline UACR (<30, 30–300, >300 mg/g), baseline eGFR (<60, 60–90, >90 mL/min per 1.73 m^2), use of angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers and diuretic treatment, and randomized treatment assignment (empagliflozin or placebo).

Finally, mediation analysis was performed to analyze whether UACR is a mediator for effects of empagliflozin on cardiovascular and renal outcomes. HRs derived from the Cox proportional hazard regression models for the association between randomized treatment and the risk of MACE, cardiovascular death/HHF, and renal outcomes were compared before and after adjustment for the 12-week change in UACR. Log-transformed baseline albuminuria was added as a covariate to the model to minimize the effect of regression to the mean. For each

outcome, the percentage mediation was estimated as [(ln HR–ln $HR_{adjusted}$)/ln HR]×100%.

A sensitivity analysis was conducted in which we repeated all analyses of the association between baseline UACR or change in UACR with cardiovascular and renal outcomes in the nonimputed data set including 5257 patients without missing data.

Statistical analyses were performed using SAS 9.4 for Windows (SAS Institute, Cary, NC) and STATA 15SE (StataCorp LLC, College Station, TX). A 2-sided $P<0.05$ was considered as statistically significant.

RESULTS

Patient Flow and Characteristics

Of the 7020 patients included in the EMPA-REG OUTCOME trial, 6877 had available data at the 12-week visit and were eligible for the current analysis. A total of 57 patients experienced a cardiovascular or renal event in the initial 12 weeks and were excluded, leaving 6820 patients for analysis in this report (Figure S1). Missing value of baseline UACR (n=64), follow-up UACR (n=142), and other covariates (n=1357) were imputed using multiple imputation for analysis. Baseline characteristics of the study population are shown in Table 1.

Association Between Baseline UACR and Cardiovascular and Renal Outcomes

At baseline, the mean UACR was 17.7 mg/g with the 25th to 75th percentile ranging from 6.2 to 71.6 mg/g. During a median of 3.0 years of follow-up, 704 (10.3%) MACE, 440 (6.5%) cardiovascular death/HHF, and 168 (2.5%) composite renal outcomes were observed, with the renal outcome driven by the 40% eGFR decline component. After adjustment for baseline risk markers, a strong log-linear association was observed between baseline UACR and both cardiovascular and renal outcomes (Figure 1). Compared with the low UACR group (<30 mg/g), the intermediate high (>300–1000 mg/g), and high (>1000 mg/g) UACR groups experienced significantly more MACE, cardiovascular death/HHF, and renal outcomes. The relative risk gradient for the renal outcome was steeper than for the cardiovascular outcome (Figure 1A through 1C). When the absolute incidence rates were compared, the incidence rate for the low UACR group

Table 1. Baseline Characteristics by Change in Albuminuria at Week 12

Variable	Total (N=6820)	Change in Albuminuria From Baseline to Week 12			
		>30% Reduction (N=2428)	–30% to +30% (N=2279)	>30% Increase (N=2113)	*P* Value*
UACR reduction at 12 wks, %, median (IQR)	–7.3 (–44.7 to 50.0)	–57.1 (–70.9 to –42.6)	0 (–16.7 to 8.7)	100.0 (55.9 to 200.0)	<0.001
Baseline UACR, mg/g, median (IQR)	17.7 (6.2 to 71.6)	36.2 (14.1 to 141.4)	15.0 (6.2 to 64.5)	8.8 (4.4 to 30.1)	<0.001
Age, y	63.1±8.6	63.2±8.6	63.2±8.5	63.0±8.7	0.792
Female, n (%)	1946 (28.5)	722 (29.7)	590 (25.9)	634 (30.0)	0.003
BMI, kg/m^2	30.6±5.3	30.6±5.3	30.6±5.3	30.7±5.3	0.579
Systolic BP, mm Hg	135.4±16.9	137.1±17.1	135.4±17.2	133.4±16.2	<0.001
Diastolic BP, mm Hg	76.7±9.8	77.2±10.0	76.8±9.8	76.0±9.7	<0.001
Current smoker, n (%)	900 (13.2)	300 (12.4)	319 (14.0)	281 (13.3)	0.247
Current drinker, n (%)	2538 (37.2)	903 (37.2)	866 (38.0)	769 (36.4)	0.546
HbA1c, %	8.07±0.84	8.14±0.87	8.05±0.83	8.01±0.83	<0.001
eGFR, mL/min per 1.73 m^2	74.1±21.3	73.9±21.3	74.4±21.4	74.0±21.2	0.704
eGFR, n (%)					0.654
>90 mL/min per 1.73 m^2	1490 (21.8)	523 (21.5)	500 (21.9)	467 (22.1)	
60–90 mL/min per 1.73 m^2	3573 (52.4)	1253 (51.6)	1201 (52.7)	1119 (53.0)	
<60 mL/min per 1.73 m^2	1757 (25.8)	652 (26.9)	578 (25.4)	527 (24.9)	
LDL cholesterol, mmol/L	2.21±0.92	2.23±0.92	2.19±0.93	2.21±0.91	0.229
HDL cholesterol, mmol/L	1.15±0.30	1.15±0.30	1.14±0.30	1.15±0.30	0.466
Randomized to empagliflozin treatment, n (%)	4558 (66.8)	1743 (71.8)	1512 (66.3)	1303 (61.7)	<0.001
ACEi/ARB use, n (%)	5507 (80.7)	2000 (82.4)	1795 (78.8)	1712 (81.0)	0.007
Diuretics, n (%)	2941 (43.1)	1062 (43.7)	965 (42.3)	914 (43.3)	0.620

Continuous variables are shown as mean±SD or median (25th–75th percentile) and categorical variables are shown as number (percentage). ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; and UACR, urinary albumin creatinine ratio.

*P value for statistical significant difference for the 3 strata of change in albuminuria.

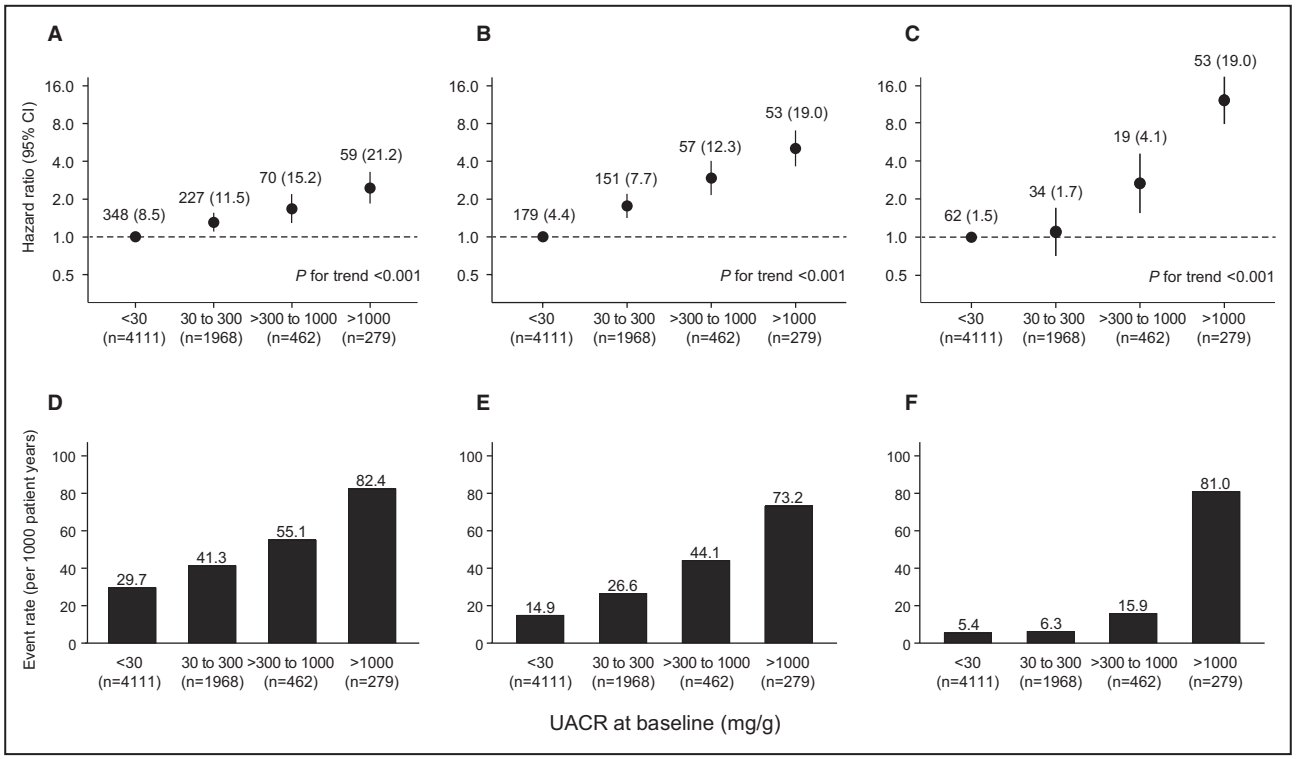

Figure 1. Relationship between baseline UACR and (A) major adverse cardiovascular event, (B) cardiovascular death/hospitalization for heart failure, and (C) renal outcome and the event rate of (D) major adverse cardiovascular event, (E) cardiovascular death/hospitalization for heart failure, and (F) renal outcome across the entire patient cohort.
The numbers above each circle (**A** through **C**) represent the number (percentage) of outcomes for each UACR category. The numbers above each bar represent the event rate (1000 patient×years). Cox regression models were adjusted for age, sex, smoking status, body mass index, systolic blood pressure, diastolic blood pressure, use of angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker, use of diuretics, treatment assignment (empagliflozin/placebo), region of residence, baseline glycated hemoglobin, estimated glomerular filtration rate, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol. UACR indicates urinary albumin creatinine ratio.

was lower for the renal than for the MACE outcome, but they were similar for the highest UACR group (Figure 1D through 1F). Similar results were found for cardiovascular death (Figure S2).

When analyzed on a continuous scale, each 10-fold increment in UACR, which corresponds approximately to a change from one clinical stage of albuminuria to the next (ie, normo- to microalbuminuria or micro- to macroalbuminuria), was associated with an HR of 1.4 (95% CI, 1.3–1.5) for the MACE outcome, 1.9 (95% CI, 1.7–2.1) for the cardiovascular death/HHF outcome, and 2.9 (95% CI, 2.4–3.5) for the renal outcome. Because UACR shows substantial intraindividual day-to-day variation, we repeated our analyses correcting for the intraindividual variation. After correction for regression dilution, the strength of the association between baseline UACR and cardiovascular and renal outcomes increased (Figure S3) with HRs for each 10-fold increment in UACR of 1.5 (95% CI, 1.3–1.7) for the MACE outcome, 2.2 (95% CI, 1.9–2.5) for the cardiovascular death/HHF outcome, and 3.7 (95% CI, 2.9–4.7) for the renal outcome.

Association Between Change in UACR and Cardiovascular and Renal Outcomes

The geometric mean percentage reduction from baseline at week 12 in UACR with empagliflozin compared with placebo was 18% (95% CI, 14–22). Empagliflozin increased the likelihood of a >30% reduction in UACR compared with placebo (odds ratio, 1.42; 95% CI, 1.27–1.58). Among patients with baseline UACR ≥30 mg/g, we observed a geometric mean reduction from baseline in UACR of 34% (95% CI, 26–41) in the empagliflozin-treated group compared with placebo. The odds ratio associated with empagliflozin treatment for a >30% reduction in UACR within that subgroup was 2.05 (95% CI, 1.74–2.42); however, there was a wide variation in UACR changes that overlapped between the empagliflozin and placebo treatment groups (Figure S4).

We subsequently divided the overall population into 3 subgroups based on their change in UACR at 12 weeks. A reduction in UACR of >30% was observed in 2428 patients, minor change in UACR was observed

in 2279 patients, and an increase in UACR of >30% was observed in 2113 patients. Table 1 shows the baseline characteristics stratified by week 12 changes in UACR. Significant differences in baseline characteristics were observed among the 3 UACR subgroups. Patients with a >30% UACR reduction had higher baseline albuminuria, BP, and HbA1c and were more likely to be allocated to empagliflozin treatment (Table 1).

Figure 2 shows the relationship between change in UACR and MACE, cardiovascular death/HHF, and renal outcomes by change in UACR at week 12 (<–30%, –30% to +30%, and >+30%) after adjustment for multiple covariates. Across subgroups of UACR change, the risk of MACE, cardiovascular death/HHF, and renal outcomes increased in patients with UACR increase compared with those with a reduction in UACR at week 12 (Figure 2). Similar results were found for cardiovascular death (Figure S5C). Assessment of the relationship between change in UACR as a continuous variable with cardiovascular risk showed that each 30% decrease in UACR during the first 12 weeks was statistically significantly associated with an average 4% lower hazard for the MACE outcome (HR, 0.96; 95% CI, 0.93–0.99; P=0.012) and 6% lower hazard for the cardiovascular death/HHF outcome (HR, 0.94; 95% CI, 0.91–0.98; P=0.003). A stronger association was observed between change in UACR and the risk of renal outcome. Each 30% decrease in UACR during the first 12 weeks associated with an average 17% lower hazard for renal outcome (HR, 0.83; 95% CI, 0.78–0.89; P<0.001).

Figure 3 shows the results of the empagliflozin and placebo arms separately. After dividing the population in quartiles of change in UACR, the distribution of quartiles shifted in the empagliflozin toward the left, consistent with the reduction in UACR observed in the empagliflozin arm. The association between UACR changes and cardiovascular or renal outcomes was similar in both treatment groups.

The association between change in UACR and cardiovascular and renal outcomes was consistent in various subgroups, including subgroups defined by age, sex, baseline UACR, eGFR, use of angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, and use of diuretics (Figure 4, Figure S6 for cardiovascular death). Moreover, associations were consistent regardless of whether patients were assigned to placebo or empagliflozin treatment. There appeared to be a numerically stronger association between 12-week change in UACR and renal outcome in subgroups defined by baseline UACR, although the wide CIs preclude definitive conclusions.

The residual UACR level at week 12 showed an almost identical relationship with the effects on MACE, cardiovascular death/HHF, and renal outcomes as baseline UACR (Figure 5). The association between week 12 UACR and outcomes in the empagliflozin and placebo groups completely overlapped, suggesting that the residual UACR level after reduction with empagliflozin confers similar cardiovascular and renal risks as the (unchanged) UACR level in placebo-treated patients.

Table 2 shows the percentage mediation by change in UACR. In the overall population, UACR mediated the effect on MACE, cardiovascular death/HHF, and renal outcomes by 30.4%, 15.2%, and 22.1%, respectively. Mediating effects of UACR were highly dependent on the baseline level; UACR mediated 58.2%, 17.0%, and

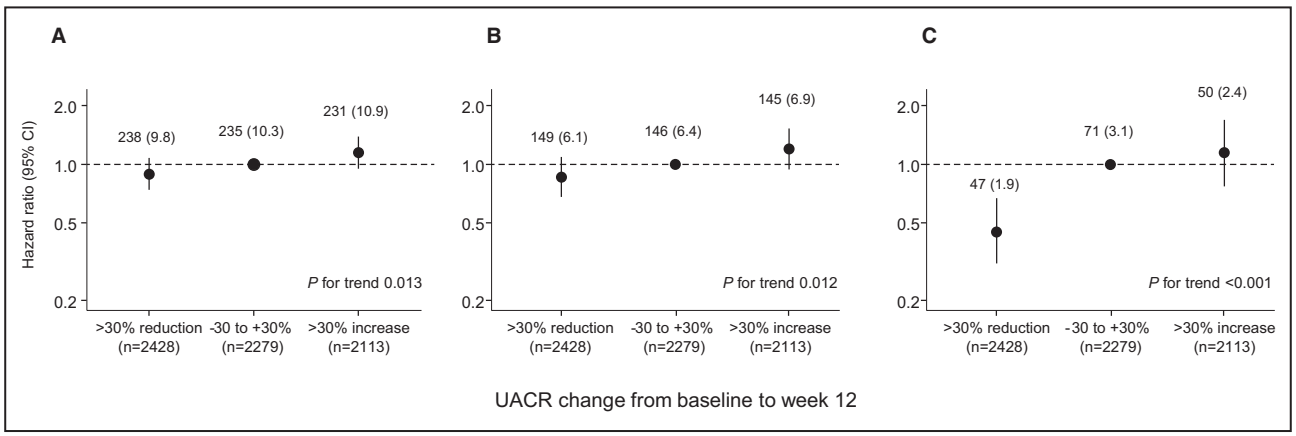

Figure 2. Relationship between change in UACR at week 12 and (A) major adverse cardiovascular event, (B) cardiovascular death/hospitalization for heart failure, and (C) renal outcome compared with the referent group (–30% to +30%).
The numbers above each circle represent the number (percentage) of outcomes for each change in UACR category. Cox regression models were adjusted for age, sex, smoking status, body mass index, baseline systolic and diastolic blood pressure, treatment assignment (empagliflozin/placebo), use of angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker, use of diuretics, region of residence, baseline UACR, glycated hemoglobin, estimated glomerular filtration rate, low-density lipoprotein cholesterol and high-density lipoprotein cholesterol, and percentage changes in estimated glomerular filtration rate, systolic blood pressure, glycated hemoglobin, and body weight at week 12. UACR indicates urinary albumin creatinine ratio.

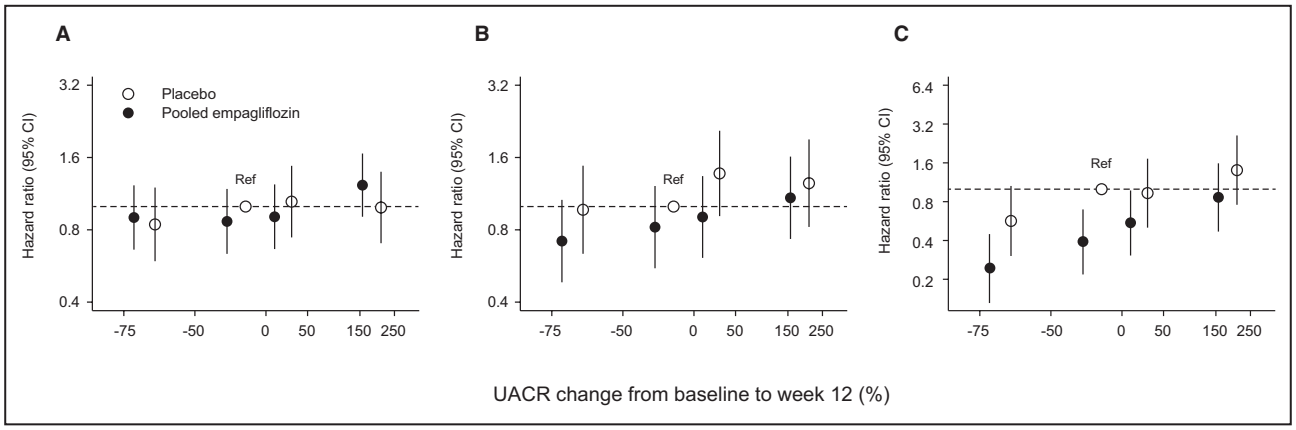

Figure 3. Relationship between change in UACR at week 12 and (A) major adverse cardiovascular event, (B) cardiovascular death/hospitalization for heart failure, and (C) renal outcome in the placebo and empagliflozin groups.
Each point represents the median of each quartile change in albuminuria within the treatment group. Cox regression models were adjusted for age, sex, smoking status, body mass index, systolic blood pressure, diastolic blood pressure, use of angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker, use of diuretics, region of residence, baseline UACR, glycated hemoglobin, estimated glomerular filtration rate, low-density lipoprotein cholesterol and high-density lipoprotein cholesterol, percentage changes in estimated glomerular filtration rate, systolic blood pressure, glycated hemoglobin, and body weight at 12 weeks. UACR indicates urinary albumin creatinine ratio.

32.3% of the effect on MACE, cardiovascular death/HHF, and renal outcomes in those with baseline UACR ≥30 mg/g but only 7.9%, 9.8%, and 4.5%, respectively, in those with baseline UACR <30 mg/g (Table 2).

Results remained unchanged when the analysis of the association between baseline UACR and change in UACR and cardiovascular and renal outcomes was repeated in the nonimputed data set, which consisted of 5257 patients without missing UACR value and covariates (Figures S5 through S9). Associations of the individual components of the composite renal and cardiovascular outcomes are presented in Table S1. Results of the mediation analyses in the complete case analysis were also similar to the main analyses (Table S2).

DISCUSSION

In this post hoc analysis of the EMPA-REG OUTCOME trial, we confirmed the positive association between

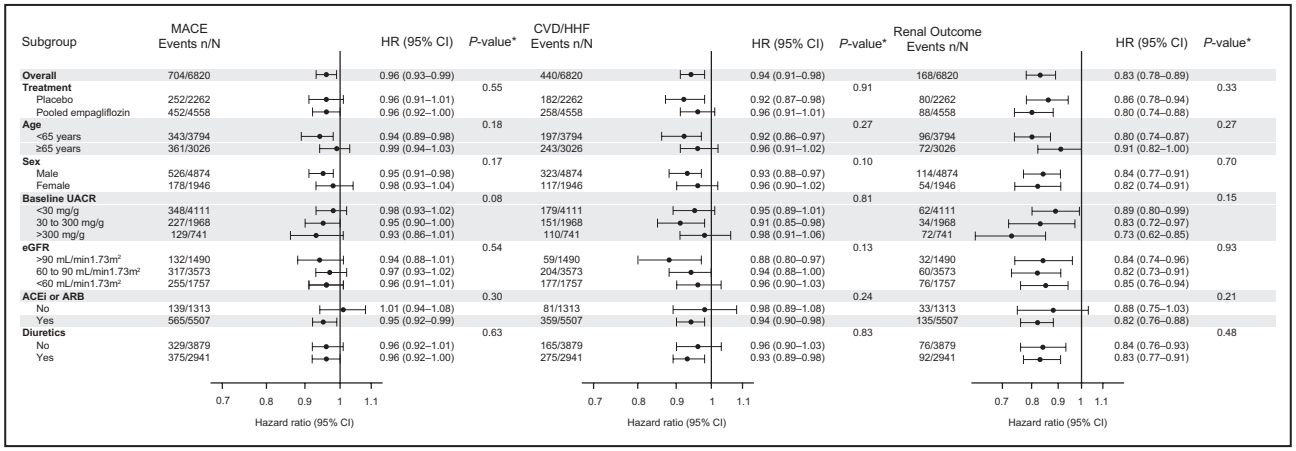

Figure 4. Adjusted HR for the association between >30% reduction in UACR from baseline to week 12 and cardiovascular and renal outcomes in all patients and within different subgroups.
Cox regression models were adjusted for age, sex, smoking status, body mass index, baseline systolic and diastolic blood pressure, treatment assignment (empagliflozin/placebo), use of ACEi/ARB, use of diuretics, region of residence, baseline UACR, glycated hemoglobin, eGFR, low-density lipoprotein cholesterol and high-density lipoprotein cholesterol, and percentage changes in eGFR, systolic blood pressure, glycated hemoglobin, and body weight at week 12. ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CVD, cardiovascular death; eGFR, estimated glomerular filtration rate; HHF, hospitalization for heart failure; HR, hazard ratio; MACE, major adverse cardiovascular event; and UACR, urinary albumin creatinine ratio. **P* value is the test of interaction between each subgroup.

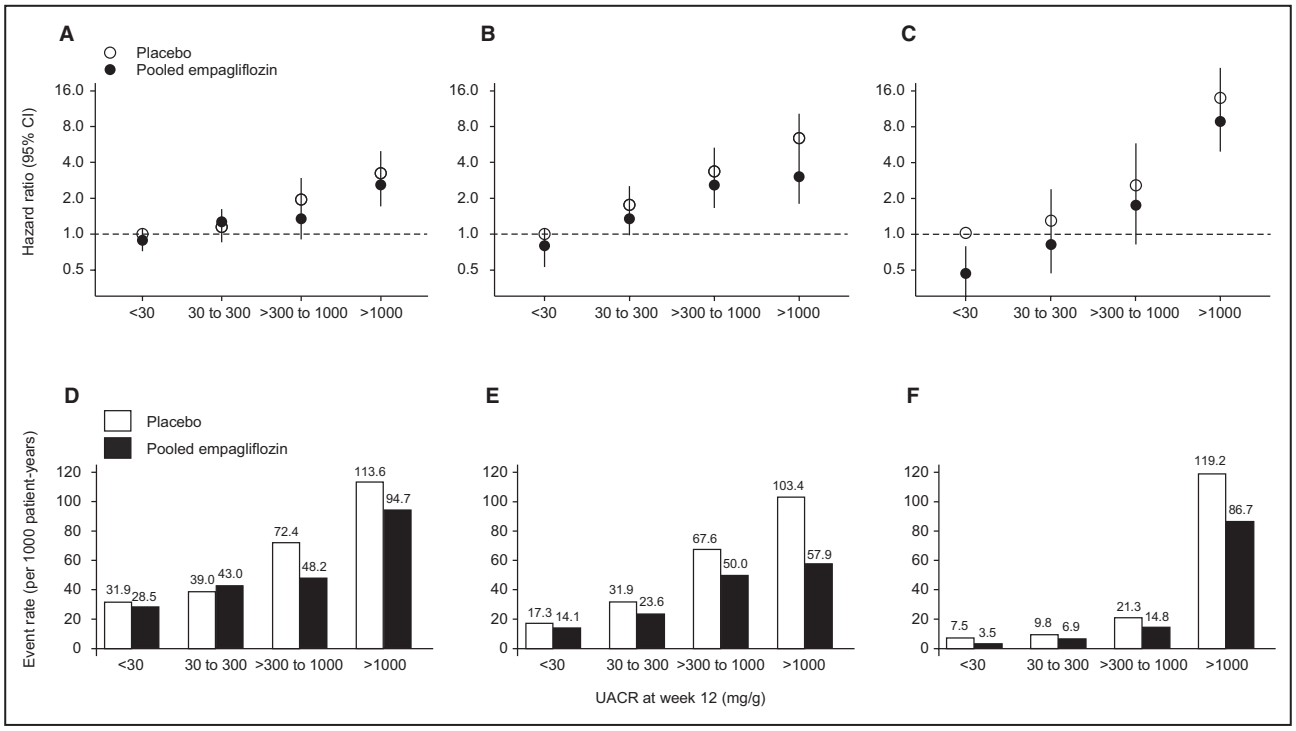

Figure 5. Relationship between UACR at week 12 and (A) major adverse cardiovascular event, (B) cardiovascular death/hospitalization for heart failure, and (C) renal outcome, and the event rate of (D) major adverse cardiovascular event, (E) cardiovascular death/hospitalization for heart failure, and (F) renal outcome in both the empagliflozin and placebo groups. The numbers above each circle (**A** through **C**) represent the number (percentage) of outcomes for each UACR category. The numbers above each bar represent the event rate (1000 patient×years). The <30 mg/g category in the placebo group was used as a reference for both the empagliflozin and placebo groups. Cox regression models were adjusted for age, sex, smoking status, body mass index, systolic blood pressure, diastolic blood pressure, use of angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker, use of diuretics, region of residence, baseline glycated hemoglobin, estimated glomerular filtration rate, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol. UACR indicates urinary albumin creatinine ratio.

albuminuria and cardiovascular, heart failure (HF), and renal outcomes in patients with type 2 diabetes mellitus and established cardiovascular disease. In addition, we demonstrated that empagliflozin treatment increased the likelihood of achieving a 30% reduction in UACR after 12 weeks of treatment and showed that reductions in albuminuria over 12 weeks were associated with a reduction in the long-term risk of cardiovascular and renal outcomes. These associations were consistent in various subgroups and independent of treatment assignment to empagliflozin or placebo. Mediation analyses revealed that the early reduction

Table 2. Assessment of Albuminuria as a Mediator of the Effect of Empagliflozin on Cardiovascular and Renal Outcomes

	Overall Population			Baseline UACR <30 mg/g			Baseline UACR ≥30 mg/g		
	$HR_{control}$* (95% CI)	$HR_{adjusted}$† (95% CI)	Proportion Mediated	$HR_{control}$* (95% CI)	$HR_{adjusted}$† (95% CI)	Proportion Mediated	$HR_{control}$* (95% CI)	$HR_{adjusted}$† (95% CI)	Proportion Mediated
MACE	0.88 (0.75–1.03)	0.91 (0.78–1.07)	30.4%	0.90 (0.73–1.13)	0.91 (0.73–1.14)	7.9%	0.86 (0.69–1.06)	0.94 (0.75–1.17)	58.2%
Cardiovascular death/HHF	0.69 (0.57–0.83)	0.73 (0.60–0.88)	15.2%	0.84 (0.62–1.13)	0.85 (0.63–1.16)	9.8%	0.60 (0.47–0.77)	0.66 (0.51–0.84)	17.0%
Renal outcome	0.51 (0.38–0.69)	0.59 (0.43–0.80)	22.1%	0.50 (0.31–0.83)	0.52 (0.32–0.86)	4.5%	0.51 (0.35–0.74)	0.63 (0.43–0.93)	32.3%
Cardiovascular death	0.66 (0.52–0.83)	0.70 (0.55–0.89)	14.6%	0.83 (0.58–1.20)	0.84 (0.59–1.22)	8.6%	0.55 (0.40–0.75)	0.60 (0.44–0.84)	16.4%

Mediation% = $100 \times [(\ln HR_{control} - \ln HR_{adjusted}) / \ln HR_{control}]$. HHF indicates hospitalization for heart failure; HR, hazard ratio; MACE, major adverse cardiovascular event; and UACR, urinary albumin creatinine ratio.

*$HR_{control}$ reflects the HR for the comparison empagliflozin vs placebo.

†$HR_{adjusted}$ reflects the HR for the comparison of the treatment comparison empagliflozin vs placebo with further adjustment of the model for change in UACR at week 12 and baseline UACR (to correct for potential regression to the mean).

in UACR mediated a proportion of the effect of empagliflozin on long-term clinical outcomes, in particular, in patients with increased albuminuria.

Our study extends the evidence of the association between baseline albuminuria and cardiovascular and renal outcomes to a contemporary population treated according to current clinical guidelines. HF may be one of the first cardiovascular manifestations of type 2 diabetes mellitus. Our findings that albuminuria in EMPA-REG OUTCOME participants is associated with the risks of HHF and cardiovascular death is in keeping with prior studies.[5,26] In this context, it is of interest to note that albuminuria is associated with both HF with preserved ejection fraction and HF with reduced ejection fraction, with a suggestion for a stronger association for HF with preserved ejection fraction.[27,28] Unfortunately, information about ejection fraction was not recorded in the EMPA-REG OUTCOME trial, precluding our ability to compare the strength of the association for both HF phenotypes.

Renal outcomes occurred less frequently compared with cardiovascular outcomes in the lower albuminuria subgroup, but the frequency was similar in the highest albuminuria subgroup. Accordingly, the relative risk relationship was stronger for renal compared with cardiovascular outcomes, suggesting that albuminuria is a dominant risk marker for renal outcomes and may also contribute to cardiovascular risk in addition to classical risk markers, such as BP and cholesterol. Collectively, these data support implementation strategies to screen for elevated albuminuria in patients with type 2 diabetes mellitus, which remains suboptimal in many parts of the world.[29–32]

Albuminuria measurements show substantial day-to-day variability,[33,34] in particular when assessed from random daytime urine samples as was done in the EMPA-REG OUTCOME trial. The random measurement error that occurs may attenuate the observed strength of the association between albuminuria and outcomes. Indeed, after correction for regression-dilution bias, the associations between albuminuria and adverse outcomes strengthened. Only a few other studies have considered regression-dilution bias and unequivocally show stronger associations after its correction.[4,35,36] These results reinforce clinical practice guideline recommendations to use albuminuria measurements across multiple study visits to more precisely determine albuminuria change.[37]

Empagliflozin reduces albuminuria and increases the likelihood of achieving a >30% reduction in albuminuria after 12 weeks of treatment. The effect of empagliflozin on albuminuria was stronger in patients with micro- or macroalbuminuria at baseline, a finding observed with other SGLT2 inhibitors as well.[38,39] Because albuminuria was affected by empagliflozin and because both baseline and short-term changes in albuminuria were associated with cardiovascular and renal outcomes, albuminuria qualifies as a potential mediator of the effect of empagliflozin. The mediation analyses demonstrated that albuminuria mediated 15% to 30% of the treatment effect of empagliflozin. The mediating effect of albuminuria may be attributed to reductions in intraglomerular pressure secondary to restoration of tubuloglomerular feedback. Favorable effects on endothelial function and glycocalyx barrier function may also be involved and might potentially explain either or both the cardiovascular and renal benefits with empagliflozin.[40–42] Interestingly, mediating effects were larger in patients with micro- or macroalbuminuria compared with normoalbuminuria. This disparity suggests that the mechanisms of cardiovascular or renal protection may vary in importance between these subgroups. We recognize, however, that mediation analyses do not necessarily explain a drug's efficacy because they are observational analyses and are prone to confounding.

The strengths of this study include the large available database and the rigorous methods of data collection, reporting, and analysis, including correction for regression-dilution bias and multiple imputation. However, this study also has certain limitations. First, our study cohort was derived from a randomized trial of patients with type 2 diabetes mellitus with a history of cardiovascular disease, and therefore, the results have limited generalizability to a broader population with type 2 diabetes mellitus. Second, renal failure and HF were not primary outcomes of the EMPA-REG OUTCOME trial. Third, despite our best efforts to adjust for clinically relevant characteristics, because of the nature of post hoc study, the possibility of residual confounding remains. A wide variation in albuminuria changes between patients was observed both in the empagliflozin and placebo arms, suggesting that changes in the empagliflozin arm may not always indicate treatment effects but could also reflect, in part, random variation. Finally, albuminuria was measured in a single first morning void. It is known that the day-to-day variability in albuminuria derived from single first morning void urine samples is larger compared with the average of 3 consecutive first morning void samples as recommended by clinical practice guidelines.[33] This may have introduced random noise and may have attenuated the strength of the reported associations. However, robust and highly significant associations were observed despite the use of single first morning void samples.

In conclusion, an early change in albuminuria after initiation of empagliflozin is associated with long-term cardiovascular and renal risks. This implies that changes in albuminuria could be used to monitor the risk of outcomes for an individual patient on empagliflozin therapy. The suggestion that the early reduction

in albuminuria may have contributed to the long-term treatment effect of empagliflozin requires confirmation in a dedicated prospective clinical trial.

ARTICLE INFORMATION

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Supplementary Materials

Tables S1–S2
Figures S1–S9

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SUPPLEMENTAL MATERIAL

Table S1. Associations Between Baseline Albuminuria, Change in Albuminuria, and Residual Week-12 Albuminuria with the Individual Components of the Composite Renal and Cardiovascular Outcomes.

	eGFR 40% decline		HHF		Myocardial Infarction		Stroke	
	Events (n [%])	HR (95%CI)	Events (n [%])	HR (95%CI)	Events (n [%])	HR (95%CI)	Events (n [%])	HR (95%CI)
Baseline UACR (mg/g)								
<30 (n=4111)	54 (1.3)	Ref	73 (1.8)	Ref	162 (3.9)	Ref	102 (2.5)	Ref
30 to 300 (n=1968)	29 (1.5)	1.29 (0.67–2.45)	78 (4.0)	2.28 (1.37–3.81)	113 (5.7)	1.16 (0.76–1.78)	68 (3.5)	1.25 (0.70–2.25)
>300 to 1000 (n=462)	17 (3.7)	3.31 (1.47–7.45)	25 (5.4)	3.54 (1.67–7.51)	28 (6.1)	1.18 (0.55–2.53)	21 (4.5)	2.66 (1.25–5.68)
>1000 (n=279)	50 (17.9)	12.21 (6.11–24.41)	22 (7.9)	8.61 (3.91–19.00)	18 (6.5)	2.48 (1.17–5.25)	18 (6.5)	2.80 (1.09–7.21)
Continuous (per log unit change)	150 (2.2)	3.04 (2.48–3.73)	198 (2.9)	2.10 (1.76–2.51)	321 (4.7)	1.22 (1.05–1.41)	209 (3.1)	1.38 (1.16–1.65)
Change UACR								
<–30% (n=2428)	40 (1.6)	0.40 (0.27–0.61)	71 (2.9)	0.81 (0.58–1.15)	108 (4.4)	0.85 (0.65–1.12)	72 (3.0)	0.97 (0.68–1.37)
≥–30 to ≤+30% (n=2279)	65 (2.9)	Ref	69 (3.0)	Ref	116 (5.1)	Ref	63 (2.8)	Ref
>+30% (n=2113)	45 (2.1)	1.16 (0.77–1.75)	58 (2.7)	1.01 (0.70–1.45)	97 (4.6)	0.94 (0.71–1.24)	74 (3.5)	1.42 (1.00–2.02)
Continuous (per 30% decline)	150 (2.2)	0.82 (0.77–0.88)	198 (2.9)	0.94 (0.88–0.99)	321 (4.7)	0.97 (0.93–1.02)	209 (3.1)	0.96 (0.91–1.02)
Residual UACR (mg/g)								
<30 (n=4284)	50 (1.2)	Ref	79 (1.8)	Ref	173 (4.0)	Ref	105 (2.5)	Ref
30 to 300 (n=1914)	34 (1.8)	1.46 (0.93–2.29)	72 (3.8)	2.13 (1.54-2.95)	108 (5.6)	1.32 (1.02-1.69)	65 (3.4)	1.27 (0.93-1.75)
>300 to 1000 (n=384)	14 (3.6)	2.95 (1.59–5.48)	28 (7.3)	3.72 (2.35–5.90)	17 (4.4)	0.97 (0.58–1.62)	22 (5.7)	2.12 (1.32–3.40)
>1000 (n=238)	52 (21.8)	19.26 (12.19–30.42)	19 (8.0)	5.32 (3.10–9.13)	23 (9.7)	2.33 (1.47–3.70)	17 (7.1)	2.71 (1.55–4.74)
Continuous (per log unit change)	150 (2.2)	3.41 (2.78–4.19)	198 (2.9)	2.15 (1.80–2.57)	321 (4.7)	1.27 (1.10–1.48)	209 (3.1)	1.45 (1.21–1.74)

CI, confidence interval; eGFR: estimated glomerular filtration rate; HHF, hospitalization for heart failure; HR: hazard ratio; Ref, reference; UACR, urinary albumin creatinine ratio.

Table S2. Assessment of Albuminuria as Mediator of the Effect of Empagliflozin on CV and Renal Outcomes in the Complete Cases Analysis (N=5257).

	Overall population			Baseline UACR <30 mg/g			Baseline UACR ≥30 mg/g		
	$HR_{control}$* (95% CI)	$HR_{adjusted}$† HR (95% CI)	Proportion mediated	$HR_{control}$* (95% CI)	$HR_{adjusted}$† HR (95% CI)	Proportion mediated	$HR_{control}$* (95% CI)	$HR_{adjusted}$† HR (95% CI)	Proportion mediated
MACE	0.85 (0.73–1.00)	0.89 (0.76–0.04)	24.6%	0.88 (0.71–1.10)	0.89 (0.71–1.11)	6.0%	0.83 (0.67–1.03)	0.91 (0.72–1.13)	47.4%
CV death/HHF	0.68 (0.56–0.83)	0.72 (0.59–0.87)	14.2%	0.84 (0.62–1.15)	0.86 (0.63–1.17)	9.6%	0.59 (0.46–0.76)	0.64 (0.50–0.83)	15.1%
Renal outcome	0.52 (0.38–0.70)	0.60 (0.44–0.82)	21.7%	0.49 (0.30–0.81)	0.51 (0.31–0.84)	3.9%	0.52 (0.36–0.78)	0.65 (0.44–0.97)	33.3%
CV death	0.65 (0.51–0.83)	0.69 (0.54–0.88)	12.8%	0.86 (0.59–1.24)	0.87 (0.60–1.26)	7.5%	0.53 (0.38–0.73)	0.58 (0.41–0.80)	14.0%

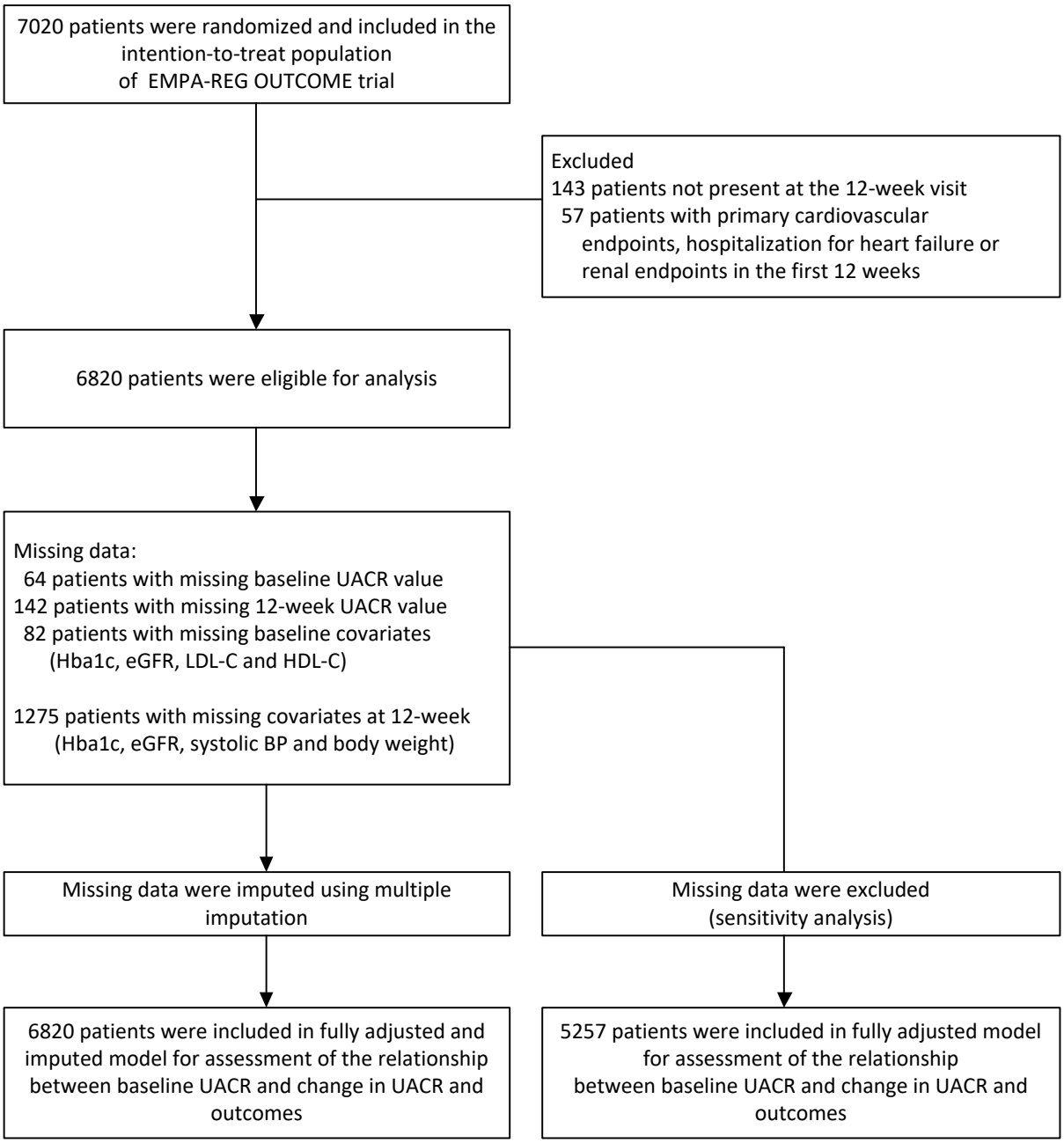
*Model 1 reflects the HR for the comparison empagliflozin versus placebo.

†$HR_{adjusted}$ reflects the HR for the comparison of the treatment comparison empagliflozin versus placebo with further adjustment of the model for change in UACR at Week 12 and baseline UACR (to correct for potential regression to the mean).

Mediation%=100*[(ln $HR_{control}$–ln $HR_{adjusted}$)/ln $HR_{control}$].

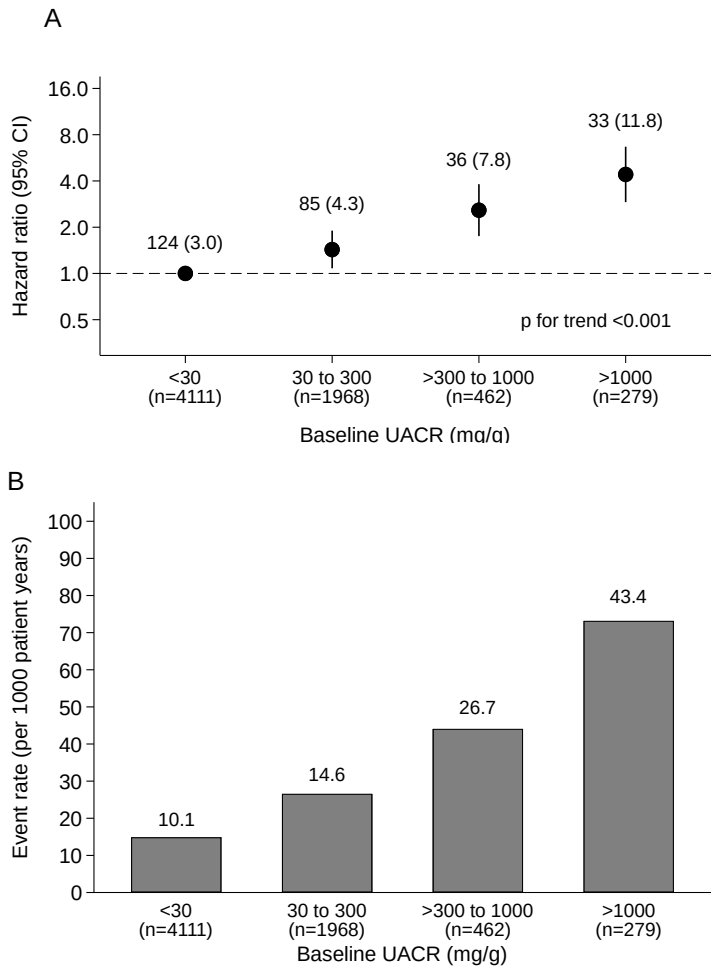
CI, confidence interval; CV death/HHF, cardiovascular death or hospitalization for heart failure; HR, hazard ratio, MACE, major adverse CV event; UACR, urinary albumin creatinine ratio.

Figure S1. Study design and identification of the study cohort.



BP, blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; UACR, urinary albumin creatinine ratio.

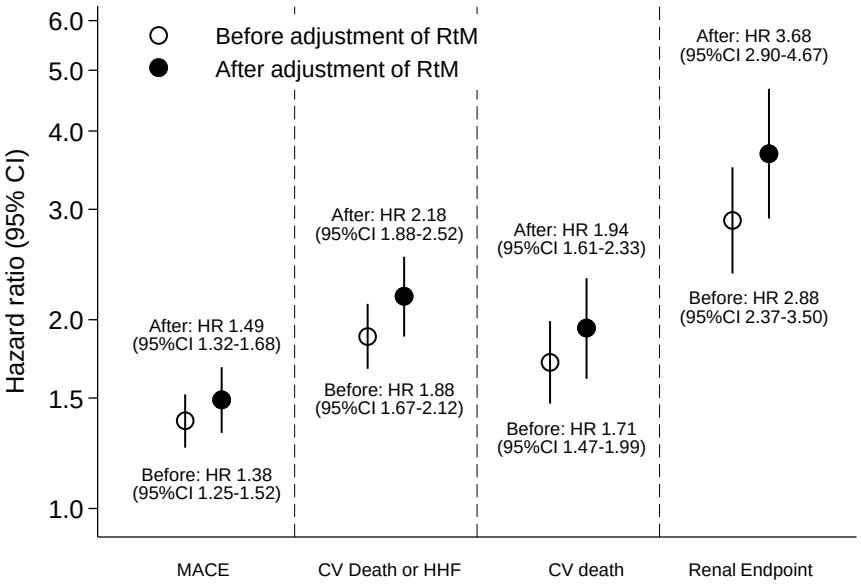
Figure S2. Relationship between baseline UACR and A) CV death outcome and B) the event rate of CV death across the entire patient cohort.



The numbers above each circle in **A** represent the number (percentage) of CV death outcomes for each baseline UACR category. Cox regression models were adjusted for age, sex, smoking status, body mass index, systolic BP, diastolic BP, treatment assignment (empagliflozin/placebo), use of ACEi/ARB, use of diuretics, region of residence, baseline HbA1c, eGFR, LDL-C, and HDL-C.

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BP, blood pressure; CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; UACR, urinary albumin creatinine ratio.

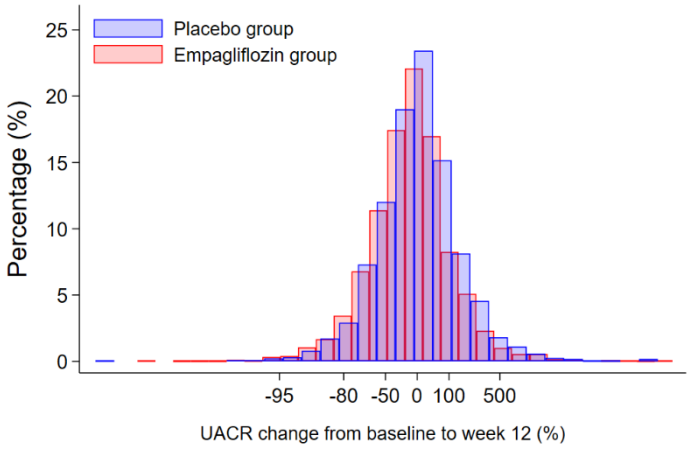
Figure S3. The relationship between baseline UACR (on the natural log scale) and CV and renal outcomes before and after adjustment by RtM coefficient at Week 12.



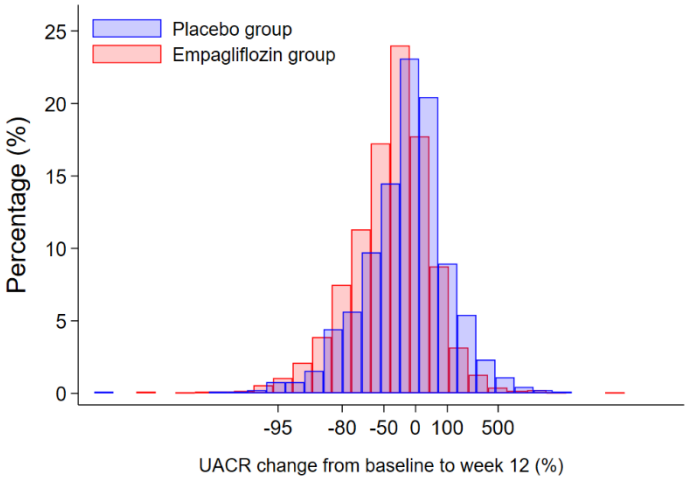
CI, confidence interval; CV, cardiovascular; HHF, hospitalization for heart failure; HR, hazard ratio; MACE, major adverse cardiovascular event; RtM, regression to mean coefficient; UACR, urinary albumin creatinine ratio.

Figure S4. Distribution of UACR changes in placebo and empagliflozin groups after 12 weeks of follow-up in A) all patients and B) patients with baseline UACR >30 mg/g.

A

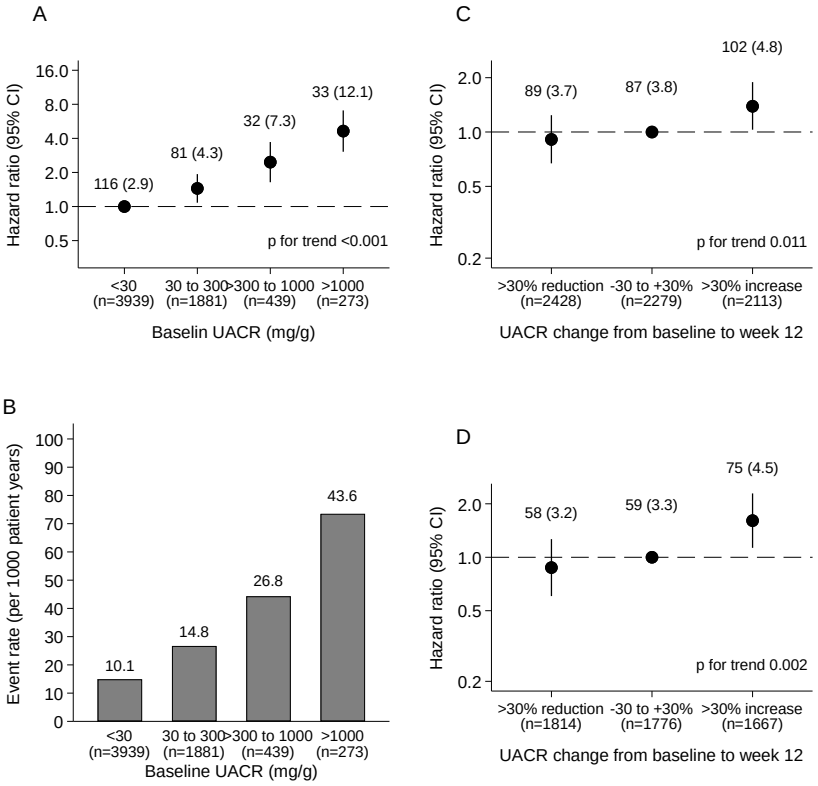


B



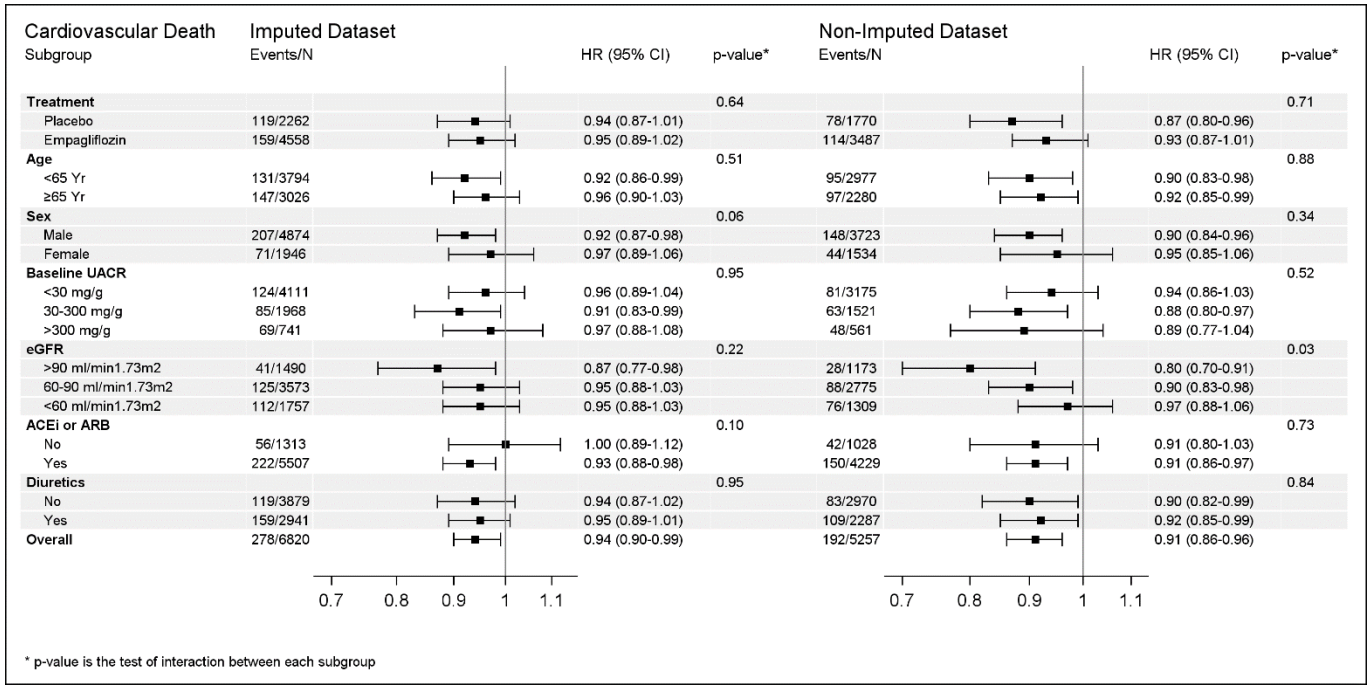
UACR, urinary albumin creatinine ratio.

Figure S5. A Relationship between baseline UACR and risk of CV death in each baseline UACR subgroup without imputation of missing data, **B** CV death event rate in patients without imputation of missing data (events per 1000 patient*years), and risk of CV death stratified by change in UACR at Week 12 in patients with **C** and without **D** imputation of missing data. The numbers above each square represent the number (percentage) of CV death outcomes. Cox regression models were adjusted for age, sex, smoking status, body mass index, systolic BP, diastolic BP, treatment assignment (empagliflozin/placebo), use of ACEi/ARB, use of diuretics, region of residence, baseline HbA1c, eGFR, LDL-C, and HDL-C. Cox models were further adjusted by baseline UACR as well as percentage changes in eGFR, systolic BP, HbA1c, and body weight at Week 12.



ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BP, blood pressure; CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; UACR, urinary albumin creatinine ratio.

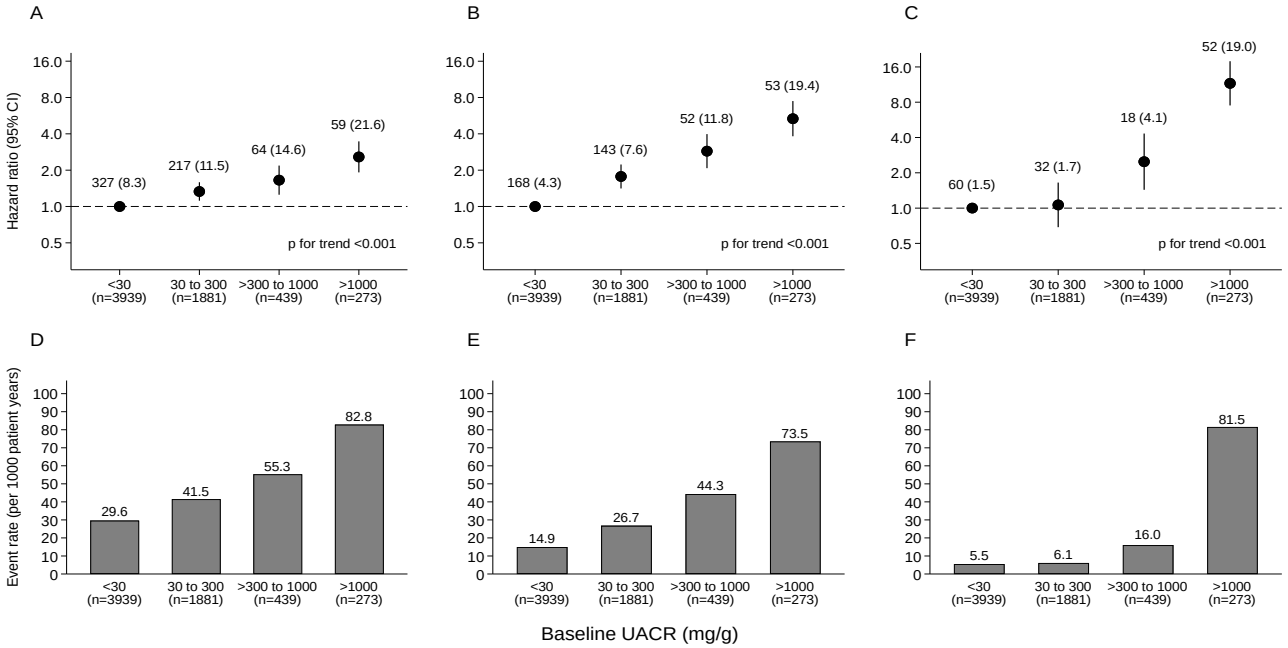
Figure S6. Adjusted HR for the association between >30% reduction in UACR from baseline to Week 12 and CV death in all patients and within different subgroups.



Cox regression models were adjusted for age, sex, smoking status, body mass index, baseline systolic and diastolic BP, treatment assignment (empagliflozin/placebo), use of ACEi/ARB, use of diuretics, region of residence, baseline UACR, HbA1c, eGFR, LDL-C and HDL-C, and percentage changes in eGFR, systolic BP, HbA1c, and body weight at Week 12.

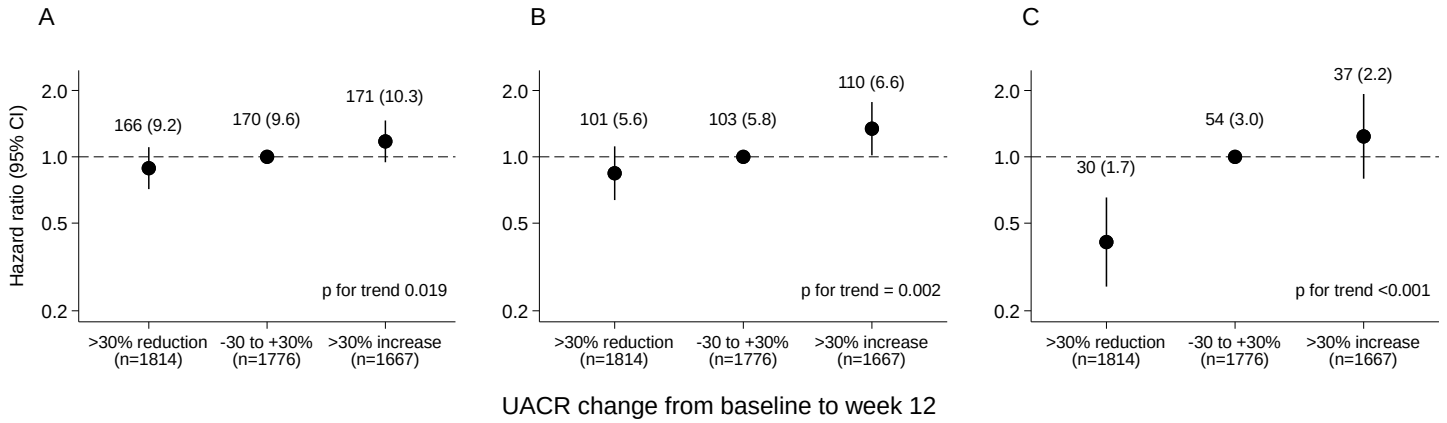
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BP, blood pressure; CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; UACR, urinary albumin creatinine ratio.

Figure S7. Relationship between baseline UACR and **A** MACE, **B** CV death/HHF, and **C** renal outcome, and the event rate of **D** MACE, **E** CV death/HHF, and **F** renal outcome using nonimputed dataset. The numbers above each circle in **A**, **B**, and **C** are the number (percentage) of outcomes for each UACR category. Cox regression models were adjusted for age, sex, smoking status, body mass index, systolic BP, diastolic BP, use of ACEi/ARB, use of diuretics, treatment assignment (empagliflozin/placebo), region of residence, baseline HbA1c, eGFR, LDL-C, and HDL-C.



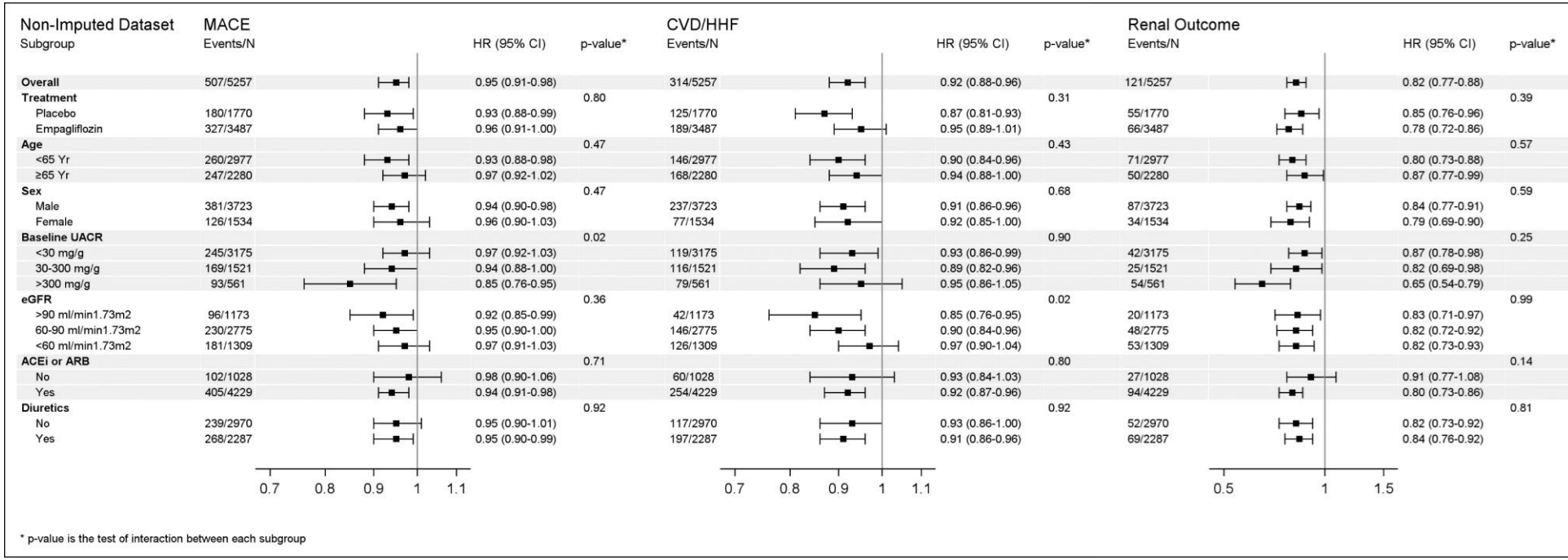
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BP, blood pressure; CI, confidence interval; CV death/HHF, cardiovascular death or hospitalization for heart failure; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse CV event; UACR, urinary albumin creatinine ratio.

Figure S8. Relationship between change in UACR at Week 12 and **A** MACE, **B** CV death/HHF, and **C** renal outcome compared with the referent group (–30% to +30%) using nonimputed dataset. The event rate (percentage) of the endpoint at each UACR change subgroup was also shown. Cox regression models were adjusted for age, sex, smoking status, body mass index, baseline systolic and diastolic BP, treatment assignment (empagliflozin/placebo), use of ACEi/ARB, use of diuretics, region of residence, baseline UACR, HbA1c, eGFR, LDL-C and HDL-C, and percentage changes in eGFR, systolic BP, HbA1c, and body weight at Week 12.



ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BP, blood pressure; CI, confidence interval; CV death/HHF, cardiovascular death or hospitalization for heart failure; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse CV event; UACR, urinary albumin creatinine ratio.

Figure S9. Adjusted HR for the association between >30% reduction in UACR from baseline to Week 12 and CV and renal outcomes in all patients and within different subgroups using the nonimputed dataset.



Cox regression models were adjusted for age, sex, smoking status, body mass index, baseline systolic and diastolic BP, treatment assignment (empagliflozin/placebo), use of ACEi/ARB, use of diuretics, region of residence, baseline UACR, HbA1c, eGFR, LDL-C, and HDL-C, and percentage changes in eGFR, systolic BP, HbA1c, and body weight at Week 12.

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BP, blood pressure; CI, confidence interval; CVD/HHF, cardiovascular death or hospitalization for heart failure; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; LDL-C: low-density lipoprotein cholesterol; MACE: major adverse cardiovascular event; UACR, urinary albumin creatinine ratio.