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Association of Empagliflozin Treatment With Albuminuria Levels in Patients With Heart Failure

A Secondary Analysis of EMPEROR-Pooled

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IMPORTANCE Albuminuria, routinely assessed as spot urine albumin-to-creatinine ratio (UACR), indicates structural damage of the glomerular filtration barrier and is associated with poor kidney and cardiovascular outcomes. Sodium-glucose cotransporter-2 (SGLT2) inhibitors have been found to reduce UACR in patients with type 2 diabetes, but its use in patients with heart failure (HF) is less well studied.

OBJECTIVE To analyze the association of empagliflozin with study outcomes across baseline levels of albuminuria and change in albuminuria in patients with HF across a wide range of ejection fraction levels.

DESIGN, SETTING, AND PARTICIPANTS This post hoc analysis included all patients with HF from the EMPEROR-Pooled analysis using combined individual patient data from the international multicenter randomized double-blind parallel-group, placebo-controlled EMPEROR-Reduced and EMPEROR-Preserved trials. Participants in the original trials were excluded from this analysis if they were missing baseline UACR data. EMPEROR-Preserved was conducted from March 27, 2017, to April 26, 2021, and EMPEROR-Reduced was conducted from April 6, 2017, to May 28, 2020. Data were analyzed from January to June 2022.

INTERVENTIONS Randomization to empagliflozin or placebo.

MAIN OUTCOMES AND MEASURES New-onset macroalbuminuria and regression to normoalbuminuria and microalbuminuria.

RESULTS A total of 9673 patients were included (mean [SD] age, 69.9 [10.4] years; 3551 [36.7%] female and 6122 [63.3%] male). Of these, 5552 patients had normoalbuminuria (UACR <30 mg/g) and 1025 had macroalbuminuria (UACR >300 mg/g). Compared with normoalbuminuria, macroalbuminuria was associated with younger age, races other than White, obesity, male sex, site region other than Europe, higher levels of N-terminal pro–hormone brain natriuretic peptide and high-sensitivity troponin T, higher blood pressure, higher New York Heart Association class, greater HF duration, more frequent previous HF hospitalizations, diabetes, hypertension, lower eGFR, and less frequent use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers and mineralocorticoid receptor antagonists. An increase in events was observed in individuals with higher UACR levels. The association of empagliflozin with cardiovascular mortality or HF hospitalization was consistent across UACR categories (hazard ratio [HR], 0.80; 95% CI, 0.69-0.92 for normoalbuminuria; HR, 0.74; 95% CI, 0.63-0.86 for microalbuminuria; HR, 0.78; 95% CI, 0.63-0.98 for macroalbuminuria; interaction *P* trend = .71). Treatment with empagliflozin was associated with lower incidence of new macroalbuminuria (HR, 0.81; 95% CI, 0.70-0.94; *P* = .005) and an increase in rate of remission to sustained normoalbuminuria or microalbuminuria (HR, 1.31; 95% CI, 1.07-1.59; *P* = .009) but not with a reduction in UACR in the overall population; however, UACR was reduced in patients with diabetes, who had higher UACR levels than patients without diabetes (geometric mean for diabetes at baseline, 0.91; 95% CI, 0.85-0.98 and for no diabetes at baseline, 1.08; 95% CI, 1.01-1.16; interaction *P* = .008).

CONCLUSIONS AND RELEVANCE In this post hoc analysis of a randomized clinical trial, compared with placebo, empagliflozin was associated with reduced HF hospitalizations or cardiovascular death irrespective of albuminuria levels at baseline, reduced progression to macroalbuminuria, and reversion of macroalbuminuria.

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Supplemental content

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Albuminuria, determined as spot urine albumin-to-creatinine ratio (UACR), indicates structural damage of the glomerular filtration barrier and, along with reduced estimated glomerular filtration rate (eGFR), is a key variable in defining chronic kidney disease (CKD).[1,2] Albuminuria is common in patients with CKD related to diabetes, hypertension, and other cardiovascular diseases that can lead to endothelial dysfunction or increase intraglomerular capillary pressure, and is associated with cardiovascular events, including heart failure (HF) and cardiovascular mortality as well as CKD progression.[3-8]

Angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARBs) have been shown to reduce albuminuria and the progression to macroalbuminuria.[9-11] In addition, mineralocorticoid receptor antagonists (MRAs) have been found to reduce albuminuria in patients with diabetic kidney disease and HF.[12-16] More recently, sodium glucose cotransporter-2 inhibitors were found to reduce the progression to macroalbuminuria in patients with diabetes and CKD with and without diabetes.[17-20]

In patients with HF who participated in the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) study,[21] microalbuminuria and macroalbuminuria were associated with an increased risk of HF hospitalization and mortality irrespective of ejection fraction, but treatment with candesartan did not reduce excessive albuminuria. In the Aldosterone Antagonist Therapy for Adults With Heart Failure and Preserved Systolic Function (TOPCAT) trial,[13] microalbuminuria and macroalbuminuria were associated with an increased risk of HF hospitalizations and mortality and spironolactone with a reduction in albuminuria. In the Study to Evaluate the Efficacy and Safety of LCZ696 Compared to Enalapril on Morbidity and Mortality of Patients With Chronic Heart Failure (PARADIGM-HF)[22] and the Study of Renal Effects of the Angiotensin Receptor Neprilysin Inhibitor LCZ696 in Patients With Heart Failure and Preserved Ejection Fraction (PARAMOUNT),[23] sacubitril-valsartan was associated with an increase in albuminuria throughout follow-up compared with enalapril or valsartan. The effect of sodium glucose cotransporter-2 inhibitors in reducing HF hospitalizations or cardiovascular mortality across baseline albuminuria levels and their impact on the progression of albuminuria in HF patients is yet to be reported.

In this post hoc analysis, we studied the association of empagliflozin with the study outcomes across baseline levels of albuminuria and change in albuminuria in patients with HF across a wide range of left ventricular ejection fraction (LVEF) levels using data from the EMPEROR-Pooled analysis[24] (ie, Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction [EMPEROR-Reduced][25] and Empagliflozin in Heart Failure with a Preserved Ejection Fraction [EMPEROR-Preserved] trials combined).

Key Points

Question Is empagliflozin associated with a reduction in albuminuria in patients with heart failure?

Findings In this secondary analysis from EMPEROR-Pooled, treatment with empagliflozin was associated with a reduction in incidence of new macroalbuminuria and an increase in rate of remission to sustained normoalbuminuria or microalbuminuria among patients with macroalbuminuria at baseline. The association of empagliflozin with cardiovascular and kidney outcomes was consistent across albumin-to-creatinine ratio categories.

Meaning Compared with placebo, empagliflozin was associated with a reduction in progression to macroalbuminuria and a reversion from macroalbuminuria as well as a decrease in heart failure hospitalizations or cardiovascular death, irrespective of baseline albuminuria.

Methods

Study Design and Patient Population

The design and primary results of the EMPEROR-Pooled analysis have been previously published.[24,26] In brief, EMPEROR-Pooled combined individual patient data from EMPEROR-Reduced and EMPEROR-Preserved, 2 phase 3 international multicenter randomized double-blind parallel-group, placebo-controlled trials that enrolled adult patients with chronic HF with New York Heart Association class II to IV symptoms for at least 3 months and elevated natriuretic peptide levels across a wide range of LVEF (≤40% in EMPEROR-Reduced[25] and >40% with no prior measurement ≤40% in EMPEROR-Preserved).[27]

The protocol of each trial complied with the Declaration of Helsinki and was approved by the ethical committees of the participating sites. All patients gave written informed consent to participate in the study.

Randomization, Study Visits, and Event Definition

Patients were randomized in a double-blind manner to receive placebo or empagliflozin, 10 mg daily (1:1 ratio), in addition to their usual therapy. Following entry into the trial, treatments for HF or other medical conditions could be managed at the clinical discretion of the investigator.

Albuminuria was assessed using UACR from a morning void spot urine sample and collected at randomization and each subsequent study visit (weeks 4, 12, 32, and 52 and every 24 weeks thereafter) and analyzed by the central laboratory. Normoalbuminuria was defined as UACR less than 30 mg/g, microalbuminuria as UACR ranging from 30 to 300 mg/g, and macroalbuminuria as UACR greater than 300 mg/g.[28]

End Points

To analyze the use of empagliflozin in patients with HF across albuminuria categories, the prespecified primary and some secondary end points were studied. The primary outcome in the EMPEROR trials was a composite of cardiovascular death or HF hospitalization. Additionally, the association of empagliflozin with first and recurrent HF hospitalizations, cardiovascular and all-cause death, 2 composite kidney end points (consisting of sustained decline in eGFR ≥40% or ≥50% from baseline and sustained eGFR <15 or <10 ml/min/1.73 m^2 for patients with baseline eGFR ≥ or <30 ml/min/1.73 m^2, respectively, long-term dialysis, or kidney transplant), and changes in annualized eGFR slope (chronic slope) were studied across baseline UACR levels.

In an additional post hoc analysis, the association of empagliflozin with change in albuminuria was studied using progression to macroalbuminuria in patients without macroalbuminuria at baseline and sustained remission to normoalbuminuria or microalbuminuria in patients with macroalbuminuria at baseline. Relative changes in UACR over time were also evaluated in the overall cohort and by UACR and diabetes subgroups at baseline. Lastly, we evaluated treatment safety by baseline UACR categories.

Statistical Analysis

Baseline characteristics were compared across categories of baseline UACR (normoalbuminuria, microalbuminuria, and macroalbuminuria) using ordinal regression likelihood ratio test. Associations between baseline UACR categories and subsequent outcomes were studied by comparing the placebo events rates across categories. The association of treatment (empagliflozin vs placebo) with the study outcomes was assessed using a Cox proportional hazards model including the prespecified baseline covariates of age, sex, geographical region, diabetes, study (EMPEROR-Reduced or EMPEROR-Preserved), LVEF, eGFR, UACR category, and a treatment-by-UACR category interaction term according to the intention-to-treat principle. Race data were reported in accordance with the requirements of the US Food and Drug Administration (FDA) and self-reported according to multiple-choice categories as per FDA guidance, with multiple answers possible. Total number of hospitalizations (first and recurrent) was analyzed using a joint frailty model that accounted for informative censoring because of cardiovascular death. Progression to and remission from macroalbuminuria to microalbuminuria or normoalbuminuria were studied with a Cox proportional hazards model including the prespecified baseline covariates described above (except UACR and the interaction term). The consistency of association of empagliflozin with macroalbuminuria was assessed across a range of clinically relevant participant characteristics, including age, eGFR, LVEF, body mass index, previous HF hospitalization, and diabetes, along with the respective interaction tests. The association of empagliflozin with UACR changes over time was studied using a linear mixed model for repeated measurements with adjustment for the covariates referenced above and treatment-by-visit interaction. *P* values and 95% CIs presented in this report have not been adjusted for multiplicity. All analyses were performed using SAS version 9.4 (SAS Institute). All tests were 2-sided, and $P < .05$ was considered statistically significant.

Results

Patient Characteristics by UACR Categories

A total of 9673 patients were included (mean [SD] age, 69.9 [10.4] years; 3551 [36.7%] female and 6122 [63.3%] male; 1496 [15.5%] Asian, 514 [5.3%] Black, 7130 [73.7%] White, and 476 [4.9%] of another race [including American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, and multiple races, consolidated owing to low numbers]), 3710 from EMPEROR-Reduced and 5963 from EMPEROR-Preserved; 45 (0.5%) patients from the total population were excluded due to missing baseline UACR. In the pooled population, 5552 patients had normoalbuminuria (UACR <30 mg/g), and 1025 patients had macroalbuminuria (UACR >300 mg/g). Compared with normoalbuminuria, macroalbuminuria was associated with younger age, races other than White, obesity, male sex, site region other than Europe, higher levels of N-terminal prohormone brain natriuretic peptide and high-sensitivity troponin T, higher blood pressure, higher New York Heart Association class, greater HF duration; more frequent previous HF hospitalizations, diabetes (including insulin use), hypertension, lower eGFR, and less frequent use of ACEi or ARBs and MRAs. LVEF was similar across UACR categories (**Table**).

Risks and Associations of Empagliflozin Across UACR Categories

An increase in events was observed for higher UACR categories. For example, patients receiving placebo with UACR greater than 300 mg/g had a 2.7-fold higher rate of primary outcome events (22.2 vs 8.2 events per 100 person-years) and 2.3-fold higher rate of cardiovascular death events (8.2 vs 3.6 events per 100 person-years) than patients with UACR less than 30 mg/g.

The association of empagliflozin with all analyzed trial outcomes was consistent across UACR categories. For example, the primary outcome was reduced by 20% in patients with UACR less than 30 mg/g (hazard ratio [HR] in patients with UACR <30 mg/g, 0.80; 95% CI, 0.69-0.92; HR in patients with UACR 30-300 mg/g, 0.74; 95% CI, 0.63-0.86; HR in patients with UACR >300 mg/g, 0.78; 95% CI, 0.63-0.98; interaction *P* trend = .71) (**Figure 1**).

Empagliflozin was associated with a slower decline in annualized eGFR slope. This association was also consistent across UACR categories: UACR <30 mg/g-placebo slope, −2.4 (95% CI, −2.6 to −2.1) mL/min/1.73 m^2/y; empagliflozin slope, −0.8 (95% CI, −1.0 to −0.5) mL/min/1.73 m^2/y; empagliflozin vs placebo slope difference 1.6 (95% CI, 1.2 to 1.9) mL/min/1.73 m^2/y; UACR 30-300 mg/g-placebo slope, −2.5 (95% CI, −2.9 to −2.2) mL/min/1.73 m^2/y; empagliflozin slope, −1.4 (95% CI, −1.7 to −1.0) mL/min/1.73 m^2/y empagliflozin vs placebo slope difference, 1.2 (95% CI, 0.7 to 1.6) mL/min/1.73 m^2/y; UACR >300 mg/g-placebo slope, −4.0 (95% CI, −4.6 to −3.3) mL/min/1.73 m^2/y; empagliflozin slope, −2.3 (95% CI, −2.9 to −1.6); empagliflozin vs placebo slope difference, 1.7 (95% CI, 0.8 to 2.6) mL/min/1.73 m^2/y (interaction *P* trend = .57).

Regarding safety, we detected higher frequencies of adverse events, adverse events leading to discontinuation, serious adverse events, and acute kidney failure events for patients in higher UACR categories. However, no relevant differences were detected between patients in the placebo vs empagliflozin groups (eTable 1 in the Supplement).

Association of Empagliflozin With Onset of Macroalbuminuria and Remission to Normoalbuminuria or Microalbuminuria

Among the 8648 patients without macroalbuminuria at baseline (4312 empagliflozin and 4336 placebo), treatment with empagliflozin was associated with a reduction in incidence of new macroalbuminuria (5.7 events per 100 person-years with empagliflozin vs 7.1 events per 100 person-years with placebo, cor-

Table. Characteristics of the EMPEROR-Pooled Population by Categories of Urinary Albumin-to-Creatinine Ratio (UACR) at Baseline

Characteristic	UACR categories, No. (%)			*P* value[a]
	<30 mg/g	30-300 mg/g	>300 mg/g	
No. of patients (total = 9673)	5552	3096	1025	NA
Empagliflozin rand	2765 (49.8)	1547 (50.0)	525 (51.2)	.54
Demographic characteristics				
Age, mean (SD), y	70 (10)	71 (10)	67 (11)	.003
Female	2151 (38.7)	1099 (35.5)	301 (29.4)	<.001
Male	3401 (61.3)	1997 (64.5)	724 (70.6)	
BMI, mean (SD)[b]	29 (6)	29 (6)	30 (6)	.001
BMI categories				
<30	3440 (62.0)	1836 (59.3)	554 (54.0)	<.001
≥30	2112 (38.0)	1260 (40.7)	471 (46.0)	
Race[c]				
Asian	762 (13.7)	535 (17.3)	199 (19.4)	<.001
Black	263 (4.7)	174 (5.6)	77 (7.5)	
White	4240 (76.4)	2214 (71.5)	676 (66.0)	
Other[d]	256 (4.6)	153 (4.9)	67 (6.5)	
Site region				
Asia	586 (10.6)	443 (14.3)	150 (14.6)	<.001
Europe	2607 (47.0)	1120 (36.2)	280 (27.3)	
Latin America	1488 (26.8)	929 (30.0)	381 (37.2)	
North America	550 (9.9)	444 (14.3)	144 (14.0)	
Other[e]	321 (5.8)	160 (5.2)	70 (6.8)	
Laboratory values				
Troponin T, median (IQR), ng/mL[f]	17 (11-26)	22 (14-33)	28 (18-44)	<.001
NT-proBNP, median (IQR), pg/mL[f]	1085 (577-1916)	1568 (824-2890)	1740 (897-3739)	<.001
UACR, median (IQR), mg/g	9 (5-16)	68 (43-125)	793 (450-1637)	NA
eGFR, mean (SD), mL/min/1.73 m^2	63 (20)	60 (21)	54 (22)	<.001
eGFR categories				
≥60	3091 (55.7)	143 (46.3)	389 (38.0)	<.001
45 to <60	1375 (24.8)	832 (26.9)	244 (23.8)	
30 to <45	899 (16.2)	663 (21.4)	235(22.9)	
<30	187 (3.4)	167 (5.4)	157 (15.3)	
Potassium, mean (SD), mmol/L	4.6 (0.5)	4.6 (0.5)	4.6 (0.6)	.74
Albumin, mean (SD), g/dL	4.4 (0.3)	4.4 (0.3)	4.2 (0.4)	<.001
Hemoglobin, mean (SD), g/dL	13.5 (1.5)	13.4 (1.7)	13.3 (1.9)	<.001
Vital signs, mean (SD)				
Heart rate, bpm	70 (11)	72 (12)	72 (12)	<.001
Blood pressure, mm Hg				
Systolic	126 (16)	128 (17)	137 (17)	<.001
Diastolic	74 (10)	75 (11)	78 (11)	<.001
HF characteristics				
NYHA class III/IV	1012 (18.2)	745 (24.1)	257 (25.1)	<.001
HF diagnosis, mean (SD), y	4.9 (5.6)	5.3 (5.7)	5.2 (5.8)	.02
HHF<12 mo	1360 (24.5)	842 (27.2)	308 (30.0)	<.001
Ischemic HF	2281 (41.1)	1296 (41.9)	443 (43.2)	.21
AFib/flutter	2552 (46.0)	1595 (51.5)	410 (40.0)	.27
LVEF, mean (SD), %	44 (15)	44 (15)	45 (16)	.81
LVEF categories				
≤40%[g]	2078 (37.4)	1236 (39.9)	396 (38.6)	.053
>40%[h]	3474 (62.6)	1860 (60.1)	629 (61.4)	

(continued)

Table. Characteristics of the EMPEROR-Pooled Population by Categories of Urinary Albumin-to-Creatinine Ratio (UACR) at Baseline (continued)

Characteristic	UACR categories, No. (%)			*P* value[a]
	<30 mg/g	30-300 mg/g	>300 mg/g	
Comorbidities				
Hypertension	4508 (81.2)	2659 (85.9)	920 (89.8)	<.001
Diabetes	2306 (41.5)	1714 (55.4)	750 (73.2)	<.001
Comedication				
Insulin use	465 (8.4)	508 (16.4)	352 (34.3)	<.001
ACEi/ARB	4255 (76.6)	2278 (73.6)	744 (72.6)	<.001
ARNI	457 (8.2)	309 (10.0)	90 (8.8)	.04
β-Blockers	4954 (89.2)	2790 (90.1)	920 (89.8)	.25
Thiazides	912 (16.4)	454 (14.7)	152 (14.8)	.03
Loop diuretics	4010 (72.2)	2349 (75.9)	813 (79.3)	<.001
MRA	2962 (53.4)	1486 (48.0)	435 (42.4)	<.001
CCB	1007 (18.1)	724 (23.4)	369 (36.0)	<.001
Assist devices				
ICD	631 (11.4)	356 (11.5)	80 (7.8)	.052
CRT (CRT-D or -P)	264 (4.8)	161 (5.2)	37 (3.6)	.71

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; AFib, atrial fibrillation; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; BMI, body mass index; CCB, calcium channel blocker; CRT, cardiac resynchronization therapy with or without a defibrillator; eGFR, estimated glomerular filtration rate; FDA, US Food and Drug Administration; HF, heart failure; HHF, hospitalization for heart failure; ICD, implantable cardiac defibrillator with or without cardiac resynchronization therapy; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NA, not applicable; NT-proBNP, N-terminal pro-hormone brain natriuretic peptide; NYHA, New York Heart Association.

[a] *P* values from ordinal regression likelihood ratio test based on log-transformed data.

[b] Calculated as weight in kilograms divided by height in meters squared.

[c] Race was recorded for this study in accordance with the requirements of the FDA. Race was self-reported according to multiple-choice categories as per FDA guidance, with multiple answers possible.

[d] Included American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, and multiple races, consolidated owing to small numbers.

[e] Included Australia, India, and South Africa, consolidated owing to small numbers.

[f] To convert to µg/L, multiply by 1.

[g] EMPEROR-Reduced.[25]

[h] EMPEROR-Preserved.[27]

responding to a hazard ratio [HR] of 0.81; 95% CI, 0.70-0.94; *P* = .005) (**Figure 2**). The association was consistent across subgroups (**Figure 3**).

Among the 1025 patients (525 empagliflozin and 500 placebo) with macroalbuminuria at baseline, treatment with empagliflozin was associated with an increase in the rate of remission to sustained normoalbuminuria or microalbuminuria (HR, 1.31; 95% CI, 1.07-1.59; *P* = .009) (Figure 2). The association was generally consistent across subgroups, except across age subgroups where a trend toward a larger association of empagliflozin with reversion to macroalbuminuria to sustained normoalbuminuria or microalbuminuria was observed for older patients (HR for patients aged <65 years, 1.04; 95% CI, 0.75-1.44; HR for patients aged 56-75 years, 1.30; 95% CI, 0.91-1.86; HR for patients aged >75 years, 1.77; 95% CI, 1.23-2.56; interaction *P* trend = .03) (Figure 3).

Association of Empagliflozin With Albuminuria Over Time

Empagliflozin was not significantly associated with relative changes in UACR over time in the overall population (baseline to week 52 geometric mean relative change vs placebo, 0.99; 95% CI, 0.95-1.05) (eTable 2 in the Supplement; **Figure 4**A). However, albuminuria reduction was more pronounced in higher UACR categories (baseline to week 52 geometric mean relative change in UACR with empagliflozin vs placebo in baseline UACR <30 mg/g, 1.04 [95% CI, 0.97-1.11]; in UACR 30-300 mg/g, 0.95 [95% CI, 0.87-1.04]; and in UACR >300 mg/g, 0.88 [95% CI, 0.75-1.03]; interaction *P* trend, .04) (eTable 2 in the Supplement; Figure 4B-D). Regarding diabetes status at baseline, the geometric mean relative change of UACR from baseline to week 52 was significant in patients with diabetes (0.91; 95% CI, 0.85-0.98) but not in patients without diabetes (1.08; 95% CI, 1.01-1.16); interaction *P* = .008 (eTable 2 in the Supplement).

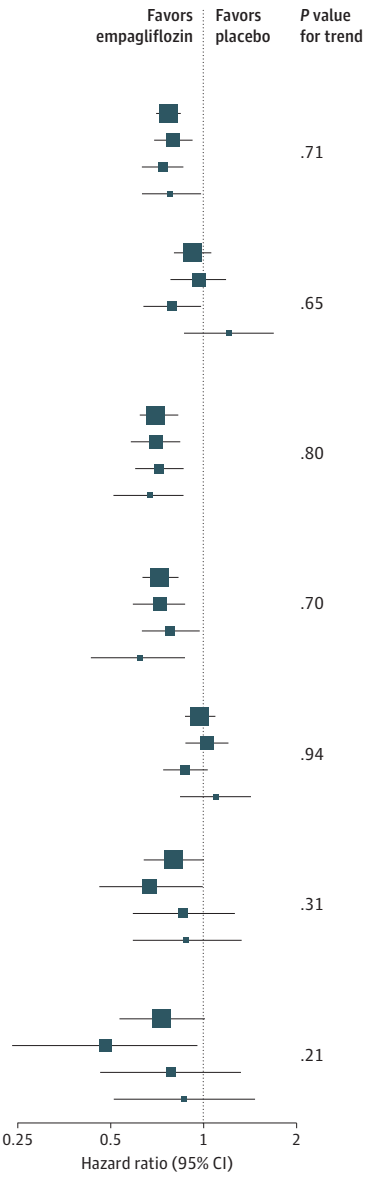
Discussion

This study confirms that albuminuria above the normal range was frequent (microalbuminuria 32% and macroalbuminuria 11%) and associated with poor prognosis in patients with HF, and showed that empagliflozin was associated with a reduction in new-onset macroalbuminuria and an increase in sustained remission from macroalbuminuria to normoalbuminuria or microalbuminuria in patients with HF, regardless of ejection fraction or diabetes status. Furthermore, empagliflozin was associated with improved cardiovascular and kidney outcomes irrespective of baseline UACR.

The association between macroalbuminuria and age, race, obesity, diabetes, higher N-terminal pro-hormone brain natriuretic peptide and troponin T levels, and poorer kidney function suggests that albuminuria could serve as a marker of dis-

Figure 1. Association of Empagliflozin With Baseline Urinary Albumin-to-Creatinine Ratio (UACR) Categories

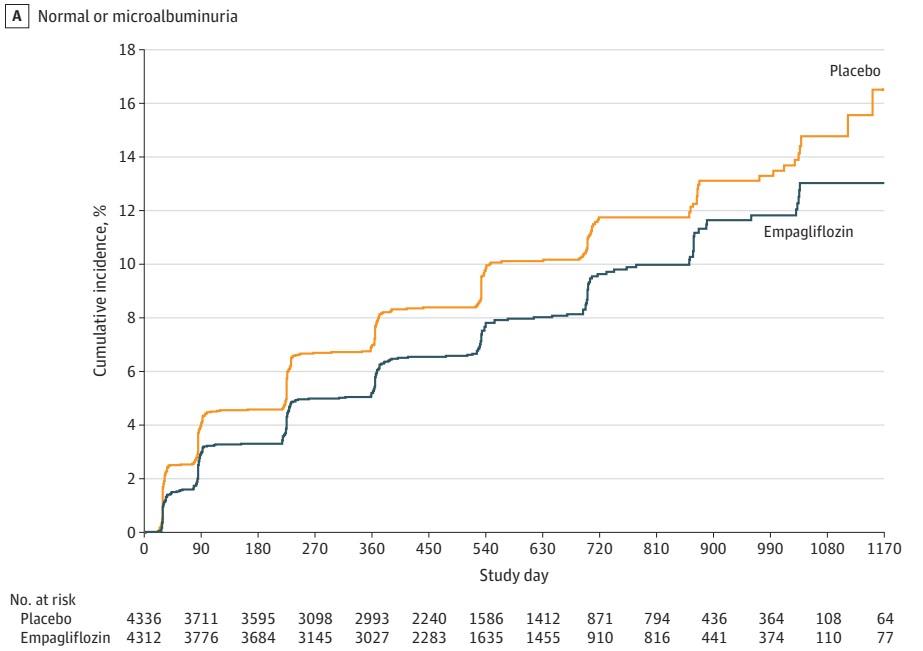
End point	Empagliflozin, 10 mg No./total No.	Empagliflozin, 10 mg Events/100 py	Placebo No./total No.	Placebo Events/100 py	NNT	Hazard ratio (95% CI)	P value for trend
Cardiovascular death or first heart failure hospitalization							
All patients	776/4860 (16.0)	9.3	973/4858 (20.0)	12.0	41	0.77 (0.70-0.84)	
UACR <30 mg/g	324/2765 (11.7)	6.6	398/2787 (14.3)	8.2	66	0.80 (0.69-0.92)	.71
UACR 30-300 mg/g	303/1547 (19.6)	11.8	399/1549 (25.8)	16.2	27	0.74 (0.63-0.86)	
UACR >300 mg/g	148/525 (28.2)	18.3	167/500 (33.4)	22.2	33	0.78 (0.63-0.98)	
Cardiovascular death							
All patients	406/4860 (8.4)	4.6	446/4858 (9.2)	5.0	236	0.91 (0.80-1.05)	
UACR <30 mg/g	178/2765 (6.4)	3.5	186/2787 (6.7)	3.6	800	0.96 (0.78-1.18)	
UACR 30-300 mg/g	152/1547 (9.8)	5.4	194/1549 (12.5)	7.0	68	0.79 (0.64-0.98)	.65
UACR >300 mg/g	75/525 (14.3)	6.7	61/500 (12.2)	8.2	71 (NNH)	1.20 (0.86-1.68)	
First heart failure hospitalization							
All patients	505/4860 (10.4)	6.1	694/4858 (14.3)	8.6	43	0.70 (0.62-0.78)	
UACR <30 mg/g	195/2765 (7.1)	4.0	274/2787 (9.8)	5.7	62	0.70 (0.58-0.84)	
UACR 30-300 mg/g	209/1547 (13.5)	8.1	282/1549 (18.2)	11.4	34	0.72 (0.60-0.86)	.80
UACR >300 mg/g	101/525 (19.2)	12.5	132/500 (26.4)	17.5	24	0.67 (0.51-0.86)	
Total (first and recurrent) hospitalizations							
All patients	795/4860	NA	1094/4858	NA	24	0.72 (0.63-0.82)	
UACR <30 mg/g	301/2765	NA	423/2787	NA	37	0.72 (0.59-0.87)	
UACR 30-300 mg/g	347/1547	NA	434/1549	NA	24	0.78 (0.63-0.97)	.70
UACR >300 mg/g	147/525	NA	229/500	NA	9	0.62 (0.43-0.87)	
All-cause death							
All patients	671/4860 (13.8)	7.6	693/4858 (14.3)	7.8	451	0.97 (0.87-1.08)	
UACR <30 mg/g	300/2765 (10.8)	5.9	294/2787 (10.5)	5.7	668 (NNH)	1.02 (0.87-1.20)	
UACR 30-300 mg/g	250/1547 (16.2)	9.0	286/1549 (18.5)	10.3	79	0.87 (0.74-1.03)	.94
UACR >300 mg/g	119/525 (22.7)	13.0	107/500 (21.4)	11.8	88 (NNH)	1.10 (0.84-1.42)	
Composite kidney end point							
All patients	138/4860 (2.8)	2.0	170/4858 (3.5)	2.5	210	0.80 (0.64-1.00)	
UACR <30 mg/g	43/2765 (1.6)	1.0	64/2787 (2.3)	1.6	191	0.67 (0.46-0.99)	
UACR 30-300 mg/g	50/1547 (3.2)	2.3	58/1549 (3.7)	2.7	273	0.86 (0.59-1.26)	.31
UACR >300 mg/g	45/525 (8.6)	6.5	47/500 (9.4)	7.0	190	0.88 (0.59-1.33)	
Alternative composite kidney end point							
All patients	64/4860 (1.3)	0.9	85/4858 (1.7)	1.2	325	0.73 (0.53-1.01)	
UACR <30 mg/g	12/2765 (0.4)	0.3	25/2787 (0.9)	0.6	314	0.48 (0.24-0.95)	
UACR 30-300 mg/g	25/1547 (1.6)	1.2	32/1549 (2.1)	1.5	313	0.78 (0.46-1.32)	.21
UACR >300 mg/g	27/525 (5.1)	3.8	28/500 (5.6)	4.1	317	0.86 (0.51-1.46)	



Cox proportional hazard model adjusted for age (continuous), baseline estimated glomerular filtration rate (eGFR; continuous), baseline left ventricular ejection fraction (continuous), study, region, baseline diabetes status, sex, UACR category, treatment, and treatment-by-UACR category. Composite kidney end point defined by sustained decline in eGFR ≥40% from baseline and sustained eGFR <15 or <10 mL/min/1.73 m^2 for patients with baseline eGFR ≥ or <30 mL/min/1.73 m^2, respectively; long-term dialysis; or kidney transplant. Alternative kidney end point defined by sustained decline in eGFR ≥50% from baseline and sustained eGFR <15 or <10 mL/min/1.73 m^2 for patients with baseline eGFR ≥ or <30 mL/min/1.73 m^2, respectively; long-term dialysis; or kidney transplant. Total hospitalizations for heart failure were analyzed using a joint frailty model accounting for cardiovascular death and adjusting for the same covariates as the Cox model. Hazard ratios (HRs) for the composite kidney end point should be interpreted with caution due to significant heterogeneity across the 2 trials. The subgroup analysis by trial estimated an HR of 0.51 (95% CI, 0.33 to 0.79) in the EMPEROR-Reduced trial[25] and 0.95 (95% CI, 0.73 to 1.24) in the EMPEROR-Preserved trial;[27] *P* value for interaction between trials = .02. NA indicates not applicable; NNH, number needed to harm; NNT, number needed to treat; py, person-year.

ease severity in younger patients with obesity, diabetes, and HF. In our study, patients with macroalbuminuria had a 2- to 3-fold higher risk of HF hospitalizations and cardiovascular mortality compared with patients with normoalbuminuria. The rate of eGFR decline throughout follow-up was also greater in patients with macroalbuminuria. These findings support albuminuria measurement as a cardiovascular risk predictor, associated with HF hospitalizations, mortality from cardiovascular causes, and kidney function decline.[29,30] Still, treatment with empagliflozin was associated with reduced rate of HF hospitalizations or cardiovascular death irrespective of albuminuria at baseline; the event reduction ranged from 20%

Figure 2. Cumulative Incidence Curves Considering All-Cause Mortality as Competing Risk for Time to Incidence of Macroalbuminuria



A, Time to incidence of macroalbuminuria in patients with normoalbuminuria or microalbuminuria (urinary albumin-to-creatinine ratio [UACR] ≤300 mg/dL) at baseline. B, Time to remission to normoalbuminuria or microalbuminuria in patients with macroalbuminuria (UACR >300 mg/dL) at baseline.

to 26% relative reduction, so that patients with macroalbuminuria treated with empagliflozin had event rates similar to patients with microalbuminuria treated with placebo. The rate of eGFR slope decline was also consistently slower in association with empagliflozin irrespective of baseline albuminuria.

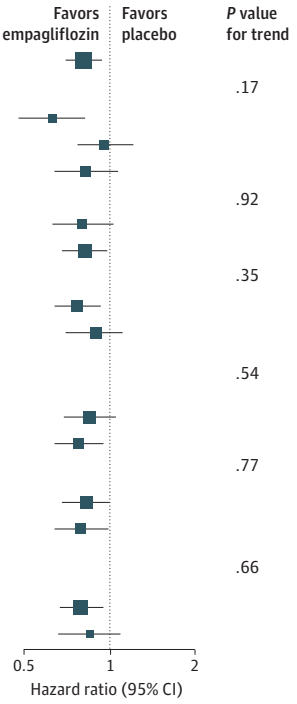
Empagliflozin was associated with reduced incidence of new macroalbuminuria in patients with normoalbuminuria or microalbuminuria at baseline, an association that was consistent across all studied subgroups, including patients with and without diabetes and with LVEF above or below 40%. Furthermore, empagliflozin was associated with reversion to normoalbuminuria or microalbuminuria among more patients who had macroalbuminuria at baseline.

In some cases, the association of HF therapies with albuminuria has been discordant to the effect of the same drug class reported in patients with diabetes or hypertension and not necessarily in agreement with the association of these therapies with HF hospitalizations and cardiovascular mortality. For example, in the CHARM study,[21] the proportion of patients with microalbuminuria and macroalbuminuria was similar to that

Figure 3. Association of Empagliflozin With Incidence of Macroalbuminuria in Subgroups of Interest

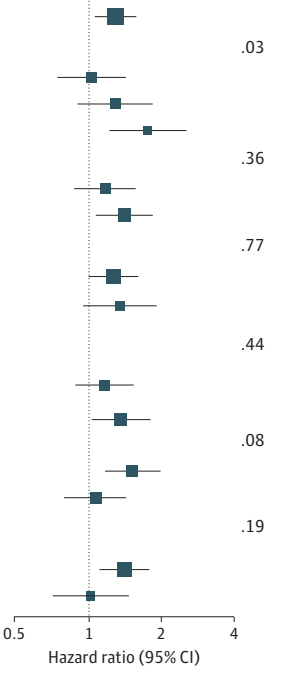
A Incidence of macroalbuminuria

Subgroup	Empagliflozin, 10 mg No./total No.	Empagliflozin, 10 mg Events/100 py	Placebo No./total No.	Placebo Events/100 py	Hazard ratio (95% CI)	P value for trend
All patients	336/4312 (7.8)	5.67	410/4336 (9.5)	7.05	0.81 (0.70-0.94)	
Age, y						.17
<65	84/1082 (7.8)	6.10	138/1132 (12.2)	9.97	0.63 (0.48-0.82)	
65 to <75	146/1597 (9.1)	6.56	147/1553 (9.5)	6.83	0.96 (0.77-1.21)	
≥75	106/1633 (6.5)	4.56	125/1651 (7.6)	5.49	0.82 (0.64-1.07)	
LVEF, %						.92
≤40	116/1646 (7.0)	7.24	144/1669 (8.6)	9.14	0.80 (0.63-1.03)	
>40	220/2666 (8.3)	5.08	266/2667 (10.0)	6.28	0.82 (0.68-0.98)	
Diabetes status						.35
With diabetes	195/1985 (9.8)	7.32	255/2035 (12.5)	9.58	0.77 (0.64-0.93)	
Without diabetes	141/2327 (6.1)	4.32	155/2301 (6.7)	4.92	0.89 (0.70-1.11)	
Baseline eGFR, mL/min/1.73 m^2						.54
≥60	161/2257 (7.1)	5.09	188/2267 (8.3)	6.03	0.85 (0.69-1.05)	
<60	175/2055 (8.5)	6.33	221/2068 (10.7)	8.21	0.78 (0.64-0.95)	
BMI						.77
<30	192/2626 (7.3)	5.46	232/2650 (8.8)	6.73	0.83 (0.68-1.00)	
≥30	144/1686 (8.5)	5.97	178/1686 (10.6)	7.53	0.79 (0.64-0.99)	
History of HHF at baseline						.66
No	222/3199 (6.9)	4.89	278/3247 (8.6)	6.21	0.79 (0.67-0.95)	
Yes	114/1113 (10.2)	8.18	132/1089 (12.1)	9.87	0.85 (0.66-1.09)	



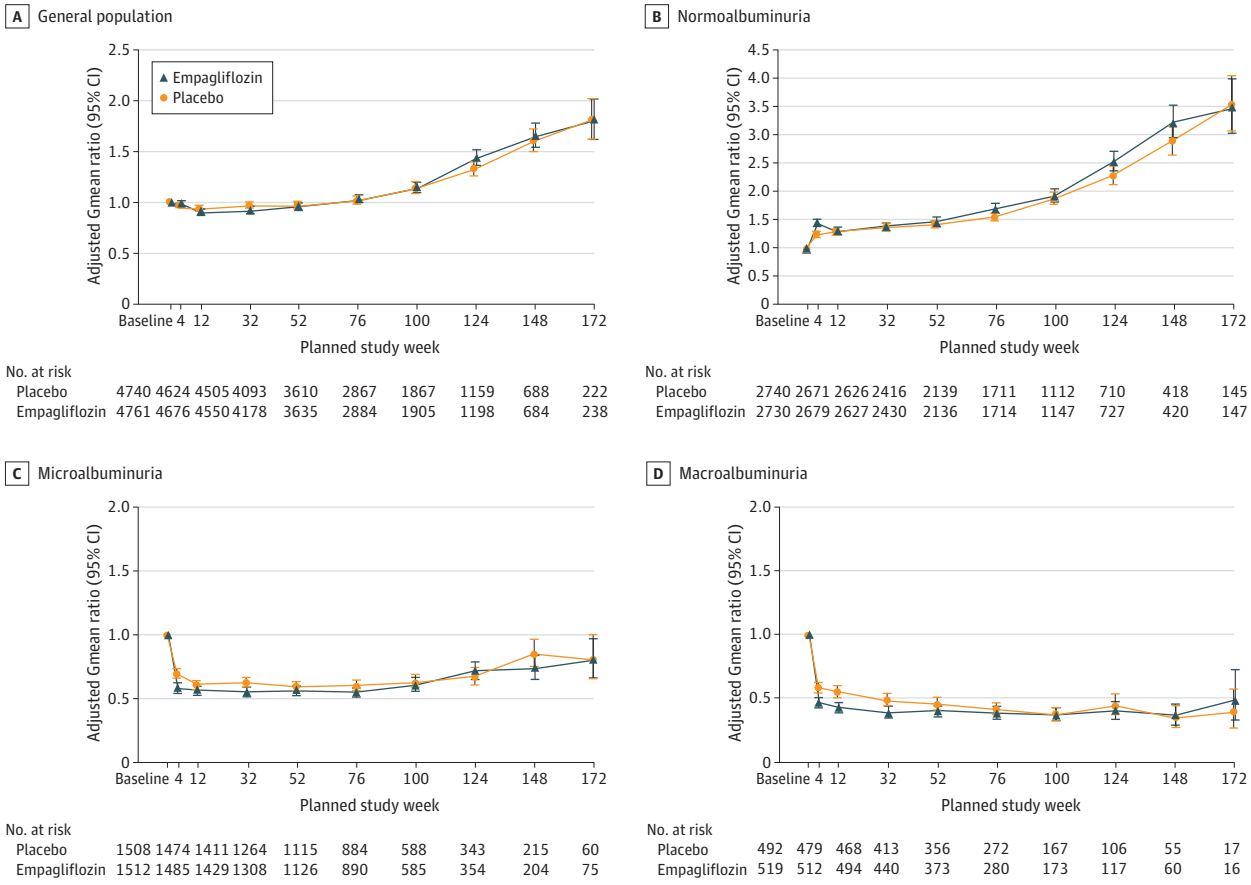
B Incidence of remission to normal or microalbuminuria

Subgroup	Empagliflozin, 10 mg No./total No.	Empagliflozin, 10 mg Events/100 py	Placebo No./total No.	Placebo Events/100 py	Hazard ratio (95% CI)	P value for trend
All patients	222/525 (42.3)	48.61	181/500 (36.2)	37.46	1.31 (1.07-1.59)	
Age, y						.03
<65	70/184 (38.0)	41.94	82/208 (39.4)	43.46	1.04 (0.75-1.44)	
65 to <75	78/202 (38.6)	42.74	51/164 (31.1)	30.85	1.30 (0.91-1.86)	
≥75	74/139 (53.2)	68.96	48/128 (37.5)	37.14	1.77 (1.23-2.56)	
LVEF, %						.36
≤40	99/207 (47.8)	77.25	85/189 (45.0)	67.04	1.18 (0.88-1.58)	
>40	123/318 (38.7)	37.44	96/311 (30.9)	26.93	1.42 (1.08-1.86)	
Diabetes status						.77
With diabetes	155/396 (39.1)	42.26	121/354 (34.2)	34.49	1.28 (1.01-1.62)	
Without diabetes	67/129 (51.9)	74.51	60/146 (41.1)	45.30	1.36 (0.96-1.93)	
Baseline eGFR, mL/min/1.73 m^2						.44
≥60	108/199 (54.3)	72.75	93/190 (48.9)	61.32	1.17 (0.89-1.55)	
<60	114/326 (35.0)	36.98	88/310 (28.4)	26.54	1.37 (1.04-1.82)	
BMI						.08
<30	127/276 (46.0)	58.67	101/278 (36.3)	39.05	1.53 (1.18-2.00)	
≥30	95/249 (38.2)	39.54	80/222 (36.0)	35.63	1.08 (0.80-1.45)	
History of HHF at baseline						.19
No	160/366 (43.7)	48.60	124/351 (35.3)	35.75	1.42 (1.12-1.80)	
Yes	62/159 (39.0)	48.64	57/149 (38.3)	41.79	1.06 (0.74-1.53)	



A, Association of empagliflozin with macroalbuminuria in patients with normoalbuminuria or microalbuminuria (urinary albumin-to-creatinine ratio [UACR] ≤300 mg/dl) at baseline. B, Remission to microalbuminuria or normoalbuminuria in patients with macroalbuminuria (UACR >300 mg/dL) at baseline. Cox proportional hazard model adjusted for age (continuous), baseline estimated glomerular filtration rate (eGFR; continuous), baseline left ventricular ejection fraction (LVEF; continuous), study, region, baseline diabetes status, sex, subgroup of interest, treatment, and treatment-by-subgroup category.

Figure 4. Association of Empagliflozin With Urinary Albumin-to-Creatinine Ratio (UACR) Over Time



A, Overall population. B, Patients with normoalbuminuria (UACR <30 mg/g) at baseline. C, Patients with microalbuminuria (UACR 30-300 mg/g) at baseline. D, Patients with macroalbuminuria (UACR >300 mg/g) at baseline. Models analyzed using a mixed model for repeated measures, including age, baseline estimated glomerular filtration rate, and baseline left ventricular ejection fraction as linear covariates and study, region, baseline diabetes status, sex, log (baseline UACR) by visit, visit by treatment, and week reachable as fixed effects (overall population). For the subgroup analysis, visit by treatment-by-UACR subgroup was used. Gmean indicates geometric mean.

reported in the present study, and the risk of events increased with excessive albuminuria but candesartan was not associated with a reduction in development or excessive excretion of albumin in urine. However, the CHARM analysis was limited by a high proportion of missing values throughout follow-up. The association of candesartan with albuminuria levels in patients with diabetes was small,[31] and some studies have suggested that the doses of candesartan required to impact albuminuria are much higher than the doses recommended for clinical use.[32] A substudy from the Studies of Left Ventricular Dysfunction (SOLVD)[33] showed an antiproteinuric association with enalapril in patients with HF with reduced ejection fraction and diabetes, but not in those without diabetes.[33] These findings from CHARM and SOLVD suggest that the association of ACEi and ARBs with the proteinuria of patients with HF may be limited and only prevalent in specific subpopulations. Notwithstanding, ACEi and ARBs were associated with a reduction in HF hospitalizations and mortality in patients with HF with reduced ejection fraction and modestly associated with HF hospitalizations in patients with HF with preserved ejection fraction.[34-36] In patients with HF treated with ACEi or ARBs, MRAs were associated with reduced excessive albuminuria regardless of diabetes status or ejection fraction.[13,16] MRAs were also associated with improved outcomes in patients with HF with reduced ejection fraction[37,38] and many patients with HF with preserved ejection fraction.[39] Sacubitril-valsartan was associated with an increase in albuminuria in patients with HF with reduced ejection fraction and HF with preserved ejection fraction, but its association with a reduction in HF hospitalizations or cardiovascular death and a slower decline in eGFR were not influenced by albuminuria at baseline or changes during follow-up.[22,23] It is possible that an increase in natriuretic peptides and other vasoactive substances as result of neprilysin inhibition by sacubitril leads to an increase in glomerular endothelial permeability.[40,41]

Empagliflozin showed was associated with a reduction in macroalbuminuria, HF hospitalizations or cardiovascular death, and eGFR decline over time in patients with HF. If a reduction in intraglomerular pressure is key for albuminuria control in patients with diabetes,[42] albuminuria may be influ-

enced by many other factors, such as aldosterone activation, renal venous congestion, low-grade systemic inflammation, and microvascular and endothelial dysfunction, in patients with HF (with and without diabetes), all of which are processes that play a role in the progression of HF and can be mitigated by sodium glucose cotransporter-2 inhibitors.[43-49]

In our study, empagliflozin was not associated with a reduction in UACR in the overall population; however, UACR was reduced in patients with diabetes who had higher UACR levels than patients without diabetes. In addition, a trend toward UACR reduction was observed in patients with higher UACR levels at baseline. These findings support the need for an elevated albuminuria level for a reduction in albuminuria to be observed with empagliflozin and are aligned with the existing data from patients with diabetes and CKD.[19,20,50,51] In the EMPEROR trials, most patients had a UACR less than 30 mg/g, thus helping to explain why no association was seen in the overall population in this post hoc analysis.

Limitations

This study has limitations. Management of albuminuria was left to the discretion of the treating physician, but between-group variation in treatment approaches is expected to be small due to the randomized and double-blind nature of the study. We could not determine the exact mechanisms by which empagliflozin was associated with a reduction in macroalbuminuria and dedicated studies should address this question.

Conclusions

In this post hoc analysis of EMPEROR-Pooled, empagliflozin was more frequently associated with a reduction in HF hospitalizations and cardiovascular death irrespective of albuminuria levels at baseline, a reduction in progression to macroalbuminuria, and reversion of macroalbuminuria compared with placebo. Empagliflozin was not associated with a reduction in UACR in the overall population; however, UACR was reduced in patients with diabetes, who had higher UACR levels than patients without diabetes. In addition, a trend toward UACR reduction was observed in patients with higher UACR levels at baseline. These findings support the potential need for an elevated albuminuria level for reduction of albuminuria to be observed with empagliflozin.

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Acquisition, analysis, or interpretation of data: Ferreira, Zannad, Butler, Filippatos, Pocock, Brueckmann, Steubl, Schueler.
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