JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 81, NO. 19, 2023

Efficacy of Empagliflozin in Patients With Heart Failure Across Kidney Risk Categories

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ABSTRACT

BACKGROUND Empagliflozin reduces the risk of major heart failure outcomes in heart failure with reduced or preserved ejection fraction.

OBJECTIVES The goal of this study was to evaluate the effect of empagliflozin across the spectrum of chronic kidney disease in a pooled analysis of EMPEROR-Reduced and EMPEROR-Preserved (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Reduced or Preserved Ejection Fraction, respectively).

METHODS A total of 9,718 patients were grouped into Kidney Disease Improving Global Outcomes (KDIGO) categories based on estimated glomerular filtration rate (eGFR) and urine albumin-to-creatinine ratio into low-, moderate-, high-, and very-high-risk categories, comprising 32.0%, 29.1%, 21.9%, and 17.0% of the participants, respectively.

RESULTS In the placebo arm, when compared with lower risk categories, patients at higher risk experienced a slower rate of decline in eGFR, but a higher risk of a composite kidney event. Empagliflozin reduced the risk of cardiovascular death or heart failure hospitalizations similarly in all KDIGO categories (HR: 0.81; 95% CI: 0.66-1.01 for low-; HR: 0.63; 95% CI: 0.52-0.76 for moderate-; HR: 0.82; 95% CI: 0.68-0.98 for high-; and HR: 0.84; 95% CI: 0.71-1.01 for very-high-risk groups; *P* trend = 0.30). Empagliflozin reduced the rate of decline in eGFR whether it was estimated by chronic slope, total slope, or unconfounded slope. When compared with the unconfounded slope, the magnitude of the effect on chronic slope was larger, and the effect on total slope was smaller. In EMPEROR-Reduced, patients at lowest risk experienced the largest effect of empagliflozin on eGFR slope; this pattern was not observed in EMPEROR-Preserved.

CONCLUSIONS The benefit of empagliflozin on major heart failure events was not influenced by KDIGO categories. The magnitude of the renal effects of the drug depended on the approach used to calculate eGFR slopes.

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Listen to this manuscript's audio summary by Editor-in-Chief Dr Valentin Fuster on www.jacc.org/journal/jacc.

ISSN 0735-1097 https://doi.org/10.1016/j.jacc.2023.03.390

Heart failure (HF) and chronic kidney disease (CKD) represent concurrent chronic disease conditions in which one syndrome increases the risk for development and progression of the other. Patients with both HF and CKD have a greater risk for morbidity and mortality, as compared with patients with only 1 disorder.[1-4] The effect of HF to decrease renal perfusion and increase renal congestion can accelerate the progression of CKD, and conversely, CKD can limit the efficacy of diuretics and foundational drug therapy.[5,6] It is not clear whether CKD influences the efficacy of sodium-glucose co-transporter-2 (SGLT2) inhibitors in patients with HF with a reduced or preserved ejection fraction.

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CKD is defined as reduced estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73 m^2 and/or one other marker of kidney damage (eg, albuminuria for ≥3 months).[7] However, such dichotomous classification precludes comprehensive risk assessment across the spectrum, and changes in eGFR and albuminuria may not be congruent. The Kidney Disease Improving Global Outcomes (KDIGO) classification separates patients into granular risk categories, considering both the eGFR (≥90, 60 to <90, 45 to <60, 30 to <45, and <30 mL/min/1.73 m^2) and the urine albumin-to-creatine ratio (UACR) (>300, 30-300, and <30 mg/g).[8]

The EMPEROR (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure) program studied 9,718 patients with chronic HF in 2 trials, one that enrolled participants with a reduced ejection fraction (EMPEROR-Reduced [Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Reduced Ejection Fraction]; NCT03057977) and one that focused on participants with a preserved ejection fraction (EMPEROR-Preserved [Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction]; NCT03057951).[9,10] Because patients were eligible with an eGFR as low as 20 mL/min/1.73 m^2 and albuminuria was not an exclusion criterion, the pooled data from both trials provide the opportunity to understand the cardiovascular and renal effects of empagliflozin across the risk spectrum of kidney disease.

METHODS

The EMPEROR program consisted of 2 international, multicenter, double-blind, randomized, parallel-group, placebo-controlled trials: the EMPEROR-Reduced and the EMPEROR-Preserved trials. Both trials were carried out by the same executive committee; events were adjudicated by the same endpoint adjudication committee, and the trials were overseen by the same independent data monitoring committee. The primary difference between the 2 trials was inclusion of patients with a left ventricular ejection fraction ≤40% in the EMPEROR-Reduced trial and >40% in the EMPEROR-Preserved trial.

PATIENT POPULATION. The design of both trials has been previously published.[11,12] In short, participants were men or women ≥18 years of age with chronic HF and New York Heart Association functional class II-IV symptoms for at least 3 months. Patients were also required to have an elevated N-terminal pro-B-type natriuretic peptide level (ie, >300 pg/mL if the ejection fraction was >40%; ≥2,500 pg/mL if the ejection fraction was 36% to 40%; ≥1,000 pg/mL if the ejection fraction was 31% to 35%; and ≥600 pg/mL if the ejection fraction was ≤30% or if patients had been hospitalized for HF within 12 months). These thresholds were doubled in EMPEROR-Reduced and tripled in EMPEROR-Preserved if patients had atrial fibrillation. In both trials, patients were randomized to receive either placebo or empagliflozin (10 mg daily), in addition to recommended therapy. Randomization was stratified by geographic region, diabetes status, and eGFR (<60 or ≥60 mL/min/1.73 m^2) in EMPEROR-Reduced and by the same variables and by left ventricular ejection fraction (<50% or ≥50%) in EMPEROR-Preserved. The protocol was approved by the ethical committee of each of the 622 participating sites in 23 countries, and all patients gave written informed consent.

ABBREVIATIONS AND ACRONYMS

CKD = chronic kidney disease

eGFR = estimated glomerular filtration rate

HF = heart failure

KCCQ-CSS = Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score

KDIGO = Kidney Disease Improving Global Outcomes

SGLT2 = sodium-glucose co-transporter-2

UACR = urine albumin-to-creatinine ratio

John McMurray, MD, served as Guest Associate Editor for this paper. Athena Poppas, MD, served as Guest Editor-in-Chief for this paper.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received August 24, 2022; revised manuscript received February 14, 2023, accepted March 7, 2023.

KDIGO CLASSIFICATION OF CKD. For this analysis, patients were categorized using baseline eGFR and UACR values into 4 categories according to the KDIGO classification system: low risk (eGFR ≥60 mL/min/1.73 m^2 and UACR <30 mg/g), moderate risk (eGFR ≥60 mL/ min/1.73 m^2 and UACR of 30-300 mg/g or eGFR 45 to <60 mL/min/1.73 m^2 and UACR <30 mg/g), high risk (eGFR ≥60 mL/min/1.73 m^2 and UACR >300 mg/g, eGFR 45 to <60 mL/min/1.73 m^2 and UACR 30-300 mg/g, or eGFR 30 to <45 mL/min/1.73 m^2 and UACR <30 mg/g), and very high risk (eGFR <60 mL/min/1.73 m^2 and UACR >300 mg/g, eGFR <45 mL/min/1.73 m^2 and UACR 30-300 mg/g, or eGFR <30 mL/min/1.73 m^2 regardless of UACR).

OUTCOMES. The principal HF outcomes for this analysis were time to cardiovascular death or HF hospitalization, total HF hospitalizations, time to first HF hospitalization, cardiovascular death, and health status assessed by Kansas City Cardiomyopathy Questionnaire (KCCQ) clinical summary score (CSS).

The principal renal effects of empagliflozin were assessed by the rate of decline in eGFR and by a composite of major adverse renal outcomes. Because SGLT2 inhibitors can influence eGFR by an intrarenal hemodynamic effect independent of their effect on the progression of kidney disease, the rate of decline in eGFR was assessed in 3 ways: 1) unconfounded slope, calculated by the annualized rate of decline in eGFR from baseline to 30 days following the withdrawal of randomized treatment at the end of the trial (with both measurements being performed in the absence of placebo or empagliflozin); 2) total slope, calculated by the rate of change from baseline to various time points on-treatment with the study drug; and 3) chronic slope, calculated by the rate of change from the on-treatment value at 4 weeks across all on-treatment values (thus excluding the initial dip in eGFR that represents the intrarenal hemodynamic effect of SGLT2 inhibitors). A negative value of eGFR slope denoted a decline in rate of change of eGFR in the treatment period The composite renal endpoint consisted of sustained reduction of ≥50% eGFR or end-stage kidney disease (chronic dialysis/renal transplant or sustained eGFR <15 mL/min/1.73 m^2 for patients with baseline eGFR ≥30 mL/min/1.73 m^2 or sustained eGFR <10 mL/min/1.73 m^2 for patients with baseline eGFR <30 mL/min/1.73 m^2) or renal death. This endpoint is the conventional endpoint from the assessment of renal outcomes and differs from that prespecified in the EMPEROR trial program.[13]

Safety outcomes included any adverse events, serious adverse events, any adverse events leading to discontinuation of trial drug, acute renal failure, volume depletion, urinary tract infection, bone fracture, confirmed hypoglycemia, and genital infection.

STATISTICAL ANALYSES. Baseline characteristics and differences between KDIGO risk categories were analyzed using descriptive statistics. Categorical variables were summarized as frequencies and percentages, continuous variables were summarized as mean ± SD and compared using ordinal regression likelihood ratio test. Time to first event analyses of HF outcomes and major renal outcomes were performed using Cox proportional hazard models adjusting for age, ejection fraction, region, sex, and diabetes status. Total (first and recurrent) hospitalizations for HF were evaluated using the joint frailty model with cardiovascular death as competing risk, adjusting for same covariates as the Cox model. Changes in KCCQ summary scores and eGFR were evaluated using a mixed model for repeated measurements. For the effect of treatment on eGFR slopes, the following methods were used:

1) Unconfounded slope. Annualized changes in eGFR from baseline to 30 days off-treatment period following the end of double-blind therapy were compared in the placebo and empagliflozin groups using a weighted analysis of covariance in patients with baseline, on-treatment, and post-treatment eGFR values. Weighting was implemented to account for the variance due to different durations of observation.
2) Total eGFR slope. Total eGFR slopes were estimated using 2-slope linear spline mixed effects model adjusting for same covariates as the Cox model and including time-by-treatment, and spline-by-treatment interaction and ensuring the inclusion of baseline and on-treatment values of eGFR. Because the observation period was longer in EMPEROR-Preserved than EMPEROR-Reduced, the total slope was estimated at week 124 for EMPEROR-Reduced and at week 124 and week 172 for EMPEROR-Preserved. Because there was a significant interaction for the effects of empagliflozin on total slopes between the 2 trials, total slopes were analyzed separately for each study and not for pooled.
3) Chronic eGFR slope. Chronic eGFR slopes were analyzed based on on-treatment data of change from baseline using a random coefficient model allowing intercept and slope to vary randomly between patients.

HRs, 95% CIs, and mean differences were calculated to estimate the treatment effect of empagliflozin vs placebo in each of the KDIGO risk categories,

TABLE 1 Characteristics of Participants by Baseline KDIGO Risk Categories in the EMPEROR Program

	Low Risk (n = 3,105)	Moderate Risk (n = 2,822)	High Risk (n = 2,131)	Very High Risk (n = 1,656)	*P* Trend
Age, y	68.0 (61.0-74.0)	70.1 (64.0-78.0)	74.0 (67.0-79.0)	74.0 (67.0-80.0)	<0.001
Women	1,052 (33.9)	1,052 (37.3)	833 (39.1)	632 (38.2)	<0.001
Race					0.490
Asian	492 (15.8)	457 (16.2)	308 (14.5)	239 (14.4)	
Black or African American	171 (5.5)	150 (5.3)	96 (4.5)	97 (5.9)	
White	2,261 (72.8)	2,067 (73.2)	1,621 (76.1)	1,219 (73.6)	
Other including mixed race	164 (5.3)	130 (4.6)	91 (4.3)	91 (5.5)	
Missing	17 (0.5)	18 (0.6)	15 (0.7)	10 (0.6)	
Geographic region					<0.001
Asia Pacific	361 (11.6)	383 (13.6)	256 (12.0)	179 (10.8)	
Western Europe	331 (10.7)	389 (13.8)	392 (18.4)	284 (17.1)	
Eastern Europe	1011 (32.6)	783 (27.7)	552 (25.9)	298 (18.0)	
North America	276 (8.9)	322 (11.4)	263 (12.3)	282 (17.0)	
Latin America	925 (29.8)	794 (28.1)	565 (26.5)	516 (31.2)	
Other	201 (6.5)	151 (5.4)	103 (4.8)	97 (5.9)	
eGFR, mL/min/1.73 m^2	75.5 (67.5-86.5)	60.5 (52.5-76.0)	48.0 (40.0-57.5)	35.0 (28.5-42.0)	<0.001
UACR, mg/g	8.8 (5.3-15.9)	30.1 (9.7-69.0)	39.8 (11.0-162.7)	132.6 (47.7-609.0)	<0.001
HF hospitalization within 1 y	733 (23.6)	696 (24.7)	608 (28.5)	483 (29.2)	<0.001
Body weight, kg	78.8 (67.0-92.2)	78.0 (66.3-92.5)	79 (67.9-92.0)	79.6 (67.1-93.7)	0.213
Ejection fraction, %	45 (30-55)	45 (30-56)	45 (30-56)	45 (30-58)	0.027
≤40	1,174 (37.8)	1,060 (37.6)	853 (40.0)	642 (38.8)	
41 to <50	705 (22.7)	581 (20.6)	404 (19.0)	290 (17.5)	
≥50	1,226 (39.5)	1,181 (41.8)	874 (41.0)	724 (43.7)	
NYHA functional class II	2,616 (84.3)	2,256 (79.9)	1,620 (76.0)	1,188 (71.7)	<0.001
KCCQ-CSS	77.7 (60.4-91.7)	75.2 (57.8-88.0)	70.8 (52.1-86.7)	68.8 (50.0-85.4)	<0.001
Systolic blood pressure, mm Hg	127 (115-138)	128 (115-140)	128 (116-140)	130 (118-143)	<0.001
Heart rate, beats/min	69 (62-78)	70 (62-79)	70 (62-79)	70 (62-78)	0.008
Hypertension	2,416 (77.8)	2,359 (83.6)	1,844 (86.5)	1,500 (90.6)	<0.001
Diabetes mellitus	1,269 (40.9)	1,343 (47.6)	1,132 (53.1)	1,046 (63.2)	<0.001
Atrial fibrillation	1,172 (37.7)	1,343 (47.6)	1,114 (52.3)	797 (48.1)	<0.001
Ischemic etiology	1,307 (42.1)	1,111 (39.4)	888 (41.7)	738 (44.6)	0.193
ACE inhibitor, ARB,[a] ARNI	2,665 (85.8)	2,395 (84.9)	1,775 (83.3)	1,287 (77.7)	<0.001
Diuretic[b]	2,396 (77.2)	2,331 (82.6)	1,843 (86.5)	1,484 (89.6)	<0.001
Loop or high-ceiling diuretics	2,059 (66.3)	2,058 (72.9)	1,691 (79.4)	1,393 (84.1)	<0.001
Thiazides or low-ceiling diuretics	507 (16.3)	433 (15.3)	319 (15.0)	265 (16.0)	0.442
Beta-blocker	2,781 (89.6)	2,528 (89.6)	1,910 (89.6)	1,478 (89.3)	0.823
MRA	1,629 (52.5)	1,464 (51.9)	1,104 (51.8)	706 (42.6)	<0.001
Uric acid, mg/dL	6.1 (5.1-7.3)	6.65 (5.3-7.8)	7.1 (5.7-8.5)	7.6 (6.1-9.1)	<0.001
Hemoglobin, g/dL	13.8 (12.9-14.8)	13.6 (12.5-14.6)	13.2 (12.2-14.4)	12.8 (11.6-13.8)	<0.001
NT-proBNP, pg/mL	927 (513-1,613)	1,253 (642-2,113)	1,577 (824-2,814)	1,992 (1,043-3,926)	<0.001
NT-proBNP, pg/mL (patients with AF/AF history)	1429 (1,011-1,997)	1680 (1,213-2,450)	2,082 (1,374-3,168)	2,526 (1,668-4,591)	<0.001
NT-proBNP, pg/mL (patients without AF/AFl history)	773 (428-1,424)	912 (498-1,866)	1,266 (615-2,529)	1,623 (805-3,591)	<0.001

Values are median (IQR) or n (%). The *P* values for NT-proBNP and UACR were computed for log-transformed data. Race was self-reported. Those who identified with more than one race or with no race were classified as "other." [a]ARBs exclude valsartan when taken with sacubitril because sacubitril/valsartan is shown as an ARNI. [b]Excluding mineralocorticoid receptor antagonists.

ACE = angiotensin-converting enzyme; AF = atrial fibrillation; AFl = atrial flutter; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor neprilysin inhibitor; eGFR = estimated glomerular filtration rate; EMPEROR = Empagliflozin Outcome Trial in Patients with Chronic Heart Failure; HF = heart failure; KCCQ-CSS = Kansas City Cardiomyopathy Questionnaire-clinical summary score; KDIGO = Kidney Disease Improving Global Outcomes; MRA = mineralocorticoid receptor antagonist; NYHA = New York Heart Association; NT-proBNP = N-terminal pro–B-type natriuretic peptide; UACR = urine albumin-to-creatinine ratio.

including subgroup and subgroup-by-treatment interaction terms in each of the models. As prespecified, no HRs were calculated when there were fewer than 14 events in a subgroup. The effect of empagliflozin vs placebo across KDIGO risk categories was evaluated by *P* trend tests, which investigate the linearity of a trend across the KDIGO categories by including the subgroup as a numeric covariate. All

FIGURE 1 **Effects of Empagliflozin vs Placebo by Baseline KDIGO Risk Categories**

Endpoint	Empagliflozin n/N	Empagliflozin Events/ 100 py	Placebo n/N	Placebo Events/ 100 py	ARR (%)	HR (95% CI)	*P* Value for Trend
Cardiovascular death or first heart failure hospitalization							
All patients	776/4,860	9.31	973/4,858	12.03	−2.72	0.77 (0.70-0.84)	0.299
Low risk	151/1,528	5.52	190/1,577	6.78	−1.26	0.81 (0.66-1.01)	
Moderate risk	184/1,440	7.27	265/1,382	11.30	−4.03	0.63 (0.52-0.76)	
High risk	212/1,071	11.88	253/1,060	15.15	−3.27	0.82 (0.68-0.98)	
Very high risk	229/820	17.86	263/836	20.70	−2.84	0.84 (0.71-1.01)	
Total (first and recurrent) heart failure hospitalizations							
All patients	795		1,094			0.72 (0.63-0.82)	0.817
Low risk	132		195			0.73 (0.55-0.96)	
Moderate risk	197		265			0.70 (0.54-0.90)	
High risk	207		309			0.70 (0.54-0.91)	
Very high risk	259		325			0.79 (0.60-1.03)	
First heart failure hospitalization							
All patients	505/4,860	6.06	694/4,858	8.58	−2.52	0.70 (0.62-0.78)	0.186
Low risk	83/1,528	3.03	125/1,577	4.46	−1.43	0.68 (0.51-0.89)	
Moderate risk	116/1,440	4.58	180/1,382	7.68	−3.10	0.59 (0.47-0.74)	
High risk	142/1,071	7.96	186/1,060	11.14	−3.18	0.75 (0.60-0.93)	
Very high risk	164/820	12.79	203/836	15.98	−3.19	0.77 (0.63-0.95)	
Cardiovascular death							
All patients	406/4,860	4.58	446/4,858	5.02	−0.44	0.91 (0.80-1.05)	0.663
Low risk	91/1,528	3.20	88/1,577	2.98	0.22	1.07 (0.80-1.44)	
Moderate risk	101/1,440	3.79	135/1,382	5.31	−1.52	0.70 (0.54-0.91)	
High risk	104/1,071	5.40	108/1,060	5.69	−0.29	0.98 (0.75-1.29)	
Very high risk	110/820	7.67	113/836	7.60	0.07	1.01 (0.78-1.32)	
All-cause mortality							
All patients	671/4,860	7.56	693/4,858	7.80	−0.24	0.97 (0.87-1.08)	0.876
Low risk	143/1,528	5.02	138/1,577	4.68	0.34	1.08 (0.85-1.36)	
Moderate risk	176/1,440	6.60	186/1,382	7.31	−0.71	0.88 (0.72-1.09)	
High risk	168/1,071	8.72	174/1,060	9.17	−0.45	0.97 (0.79-1.20)	
Very high risk	184/820	12.83	193/836	12.98	−0.15	1.00 (0.81-1.22)	
Composite renal endpoint							
All patients	68/4,860	0.96	95/4,858	1.36	−0.40	0.70 (0.51-0.95)	0.761
Low risk	9/1,528	0.39	10/1,577	0.42	−0.03	0.95 (0.39-2.34)	
Moderate risk	12/1,440	0.56	23/1,382	1.16	−0.60	0.48 (0.24-0.97)	
High risk	14/1,071	0.93	21/1,060	1.41	−0.48	0.70 (0.36-1.38)	
Very high risk	33/820	2.97	41/836	3.63	−0.66	0.77 (0.49-1.22)	

Endpoint	Empagliflozin Mean ± SE	Placebo Mean ± SE	Difference (95% CI)	*P* Value for Trend
KCCQ-CSS change from baseline at 52 weeks				
All patients	4.74 ± 0.25	3.17 ± 0.25	1.56 (0.86 to 2.27)	
Low risk	4.94 ± 0.45	3.31 ± 0.44	1.63 (0.41 to 2.85)	
Moderate risk	4.74 ± 0.46	3.20 ± 0.48	1.54 (0.23 to 2.85)	0.949
High risk	5.07 ± 0.55	3.88 ± 0.55	1.19 (−0.33 to 2.71)	
Very high risk	4.69 ± 0.63	2.74 ± 0.63	1.95 (0.19 to 3.70)	

Annualized absolute risk reduction (ARR) is expressed as events prevented per 100 person-years (py) of follow-up. Event rates are presented as per 100 py. The primary outcome was the composite of cardiovascular death or hospitalization for heart failure (HF). Empagliflozin reduced the risk of cardiovascular death or hospitalizations for HF similarly in all Kidney Disease Improving Global Outcomes (KDIGO) risk categories. When treated with placebo, patients in higher risk KDIGO categories were at increased risk for adverse HF and renal outcomes and worsening health status over time, as compared with patients in lower risk categories. KCCQ-CSS = Kansas City Cardiomyopathy Questionnaire-clinical summary score.

analyses were conducted using SAS, version 9.4 (SAS Institute). A *P* value of 0.05 was considered statistically significant.

RESULTS

BASELINE CHARACTERISTICS. The EMPEROR-Reduced trial included 3,730 participants, of whom 3,728 (99.9%) had eGFR and 3,710 (99.5%) had UACR values at baseline. The EMPEROR-Preserved trial included 5,988 participants, of whom 5,986 (99.9%) had eGFR and 5,963 (99.6%) had UACR values at baseline. Patients with missing UACR value were categorized as UACR <30. The proportion of overall participants in the low-, moderate-, high-, and very-high-risk KDIGO categories was 32.0%, 29.1%, 21.9%, and 17.0%, respectively. A similar distribution was observed in the EMPEROR-Reduced and EMPEROR-Preserved cohorts (Supplemental Figure 1). When compared with patients in lower risk categories, patients in higher KDIGO risk categories were older; more likely to be women and have a history of diabetes mellitus, hypertension, and atrial fibrillation; and more likely to have a lower KCCQ score, worse New York Heart Association functional class, and higher levels of natriuretic peptides (**Table 1**). The higher risk categories had greater use of diuretics but less use of inhibitors of the renin-angiotensin system or mineralocorticoid receptor antagonists. These patterns were observed when EMPEROR-Reduced and EMPEROR-Preserved were analyzed separately (Supplemental Tables 1 and 2).

OUTCOMES BY BASELINE KDIGO RISK CATEGORIES IN THE PLACEBO ARM. Patients in higher KDIGO risk categories had a greater risk of cardiovascular death or hospitalization for HF (6.78 for low-, 11.30 for moderate-, 15.15 for high-, and 20.70 for very-high-risk group per 100 patient-years at risk; *P* trend < 0.001). A similar pattern was seen for total HF hospitalization (6.69 for low-, 10.56 for moderate-, 16.60 for high-, and 22.16 for very-high-risk per 100 patient-years at risk; *P* trend < 0.001), first HF hospitalization (4.46 for low-, 7.68 for moderate-, 11.14 for high-, and 15.98 for very-high-risk groups per 100 patient-years at risk; *P* trend < 0.001), and cardiovascular death (2.98 for low-, 5.31 for moderate-, 5.69 for high-, and 7.60 for very-high-risk groups per 100 patient-years at risk; *P* trend < 0.001) (Supplemental Figure 2).

The magnitude of improvement in KCCQ-CSS over time was least in the patients in the highest KDIGO risk categories (4.06 in low-, 3.22 in moderate-, 2.98 in high-, and 1.14 in very-high-risk group at week 52; *P* trend = 0.001) (Supplemental Figure 2). Similar results were seen when the EMPEROR-Reduced and EMPEROR-Preserved cohorts were analyzed separately (Supplemental Figures 3 and 4).

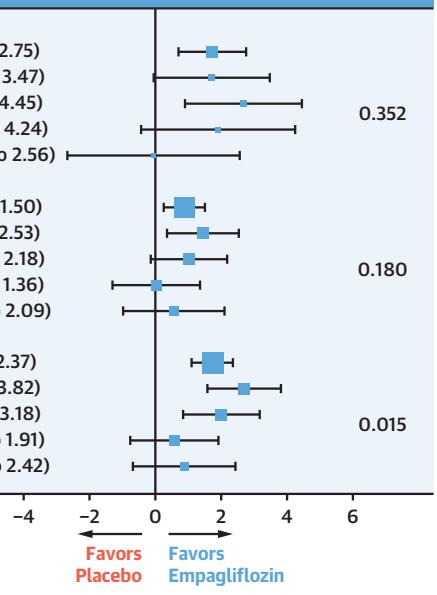
When compared with the lower risk categories, eGFR declined less rapidly in the higher KDIGO risk categories. Based on unconfounded slope, the rate of decline in eGFR averaged 0.5 to 1.5 mL/min/1.73 m^2 in the patients in the highest risk categories and 2.5 to 4.0 mL/min/1.73 m^2 per year in the lowest risk categories (*P* < 0.0001 for *P* trend) (Supplemental Figure 5). Similar results were seen for total slope and chronic slope, and the results were consistent in EMPEROR-Reduced and EMPEROR-Preserved (Supplemental Figures 6 and 7); however, in contrast with the pattern on eGFR slopes, patients in higher baseline KDIGO risk categories had a higher risk of experiencing the composite kidney endpoint (0.42 for low-risk, 1.16 for moderate-risk, 1.41 for high-risk, and 3.63 for very-high-risk per 100 patient-years at risk; *P* trend < 0.0001) (Supplemental Figure 2). Consistent results were seen in the EMPEROR-Reduced and EMPEROR-Preserved cohorts (Supplemental Figures 3 and 4).

EFFECT OF EMPAGLIFLOZIN ACCORDING TO KDIGO RISK CATEGORIES. Cardiovascular outcomes. Empagliflozin reduced the risk of cardiovascular death or hospitalizations for HF similarly in all KDIGO risk categories (HR: 0.81; 95% CI: 0.66-1.01 for low-; HR: 0.63; 95% CI: 0.52-0.76 for moderate-; HR: 0.82; 95% CI: 0.68-0.98 for high-; and HR: 0.84; 95% CI: 0.71-1.01 for very-high-risk groups; *P* trend = 0.30) (**Figure 1**). Similarly, KDIGO risk categories did not influence the benefits of empagliflozin on total HF hospitalizations (*P* trend = 0.82) or time to first HF hospitalization (*P* trend = 0.19). Empagliflozin did not reduce the risk of cardiovascular death (*P* trend = 0.683) or all-cause mortality (*P* trend = 0.876) regardless of the KDIGO risk category. Empagliflozin improved KCCQ-CSS similarly in all KDIGO risk categories at 52 weeks. For all HF endpoints, the pattern of responses was similar in EMPEROR-Reduced and EMPEROR-Preserved (Supplemental Figures 8 and 9).

eGFR slope and renal outcomes. The effect of empagliflozin on eGFR at various time points according to KDIGO category for the pooled data and for the individual trials is shown in Supplemental Figures 10 to 12. The effect of the drug on unconfounded eGFR slope, total eGFR slope, and chronic eGFR slope is shown separately for EMPEROR-Reduced and EMPEROR-Preserved in **Figures 2 and 3**. The effect of empagliflozin on total eGFR slope was significantly larger in EMPEROR-Reduced than in EMPEROR-

FIGURE 2 Effect of Empagliflozin vs Placebo on eGFR Slope (EMPEROR-Reduced)

Endpoint	Empagliflozin Mean ± SE	Placebo Mean ± SE	Difference (95% CI)	*P* Value for Trend
Unconfounded eGFR slope change				
All patients	−0.71 ± 0.37	−2.43 ± 0.37	1.72 (0.70 to 2.75)	
Low risk	−1.92 ± 0.63	−3.63 ± 0.65	1.71 (−0.05 to 3.47)	
Moderate risk	−0.34 ± 0.63	−3.02 ± 0.65	2.68 (0.91 to 4.45)	0.352
High risk	1.00 ± 0.86	−0.90 ± 0.83	1.90 (−0.43 to 4.24)	
Very high risk	−0.72 ± 0.97	−0.65 ± 0.94	−0.06 (−2.69 to 2.56)	
eGFR total slope change at week 124				
All patients	−1.90 ± 0.22	−2.77 ± 0.23	0.87 (0.25 to 1.50)	
Low risk	−2.31 ± 0.40	−3.74 ± 0.39	1.43 (0.34 to 2.53)	
Moderate risk	−2.11 ± 0.41	−3.13 ± 0.43	1.02 (−0.14 to 2.18)	0.180
High risk	−1.95 ± 0.49	−1.98 ± 0.48	0.03 (−1.31 to 1.36)	
Very high risk	−0.72 ± 0.55	−1.27 ± 0.56	0.56 (−0.98 to 2.09)	
eGFR chronic slope change per year				
All patients	−0.55 ± 0.23	−2.28 ± 0.23	1.73 (1.10 to 2.37)	
Low risk	−0.50 ± 0.41	−3.20 ± 0.40	2.70 (1.58 to 3.82)	
Moderate risk	−0.57 ± 0.41	−2.58 ± 0.43	2.01 (0.85 to 3.18)	0.015
High risk	−0.81 ± 0.49	−1.39 ± 0.48	0.57 (−0.77 to 1.91)	
Very high risk	−0.34 ± 0.55	−1.21 ± 0.57	0.87 (−0.68 to 2.42)	



Unconfounded estimated glomerular filtration rate (eGFR slope), eGFR total slope at weeks 124 and 172, and eGFR chronic slope per year by baseline. The effect of empagliflozin on total eGFR slope was significantly larger in EMPEROR-Reduced (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Reduced Ejection Fraction) than in EMPEROR-Preserved (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction) overall. Empagliflozin reduced the risk for cardiovascular death or hospitalizations for heart failure and slowed the rate of decline in eGFR in all baseline Kidney Disease Improving Global Outcomes risk categories.

Preserved overall (0.87 vs 0.10 mL/min/1.73 m^2 per year estimated at week 124), interaction $P = 0.023$, and therefore, the data for total eGFR slopes were not pooled.

For the analysis of unconfounded eGFR slope, empagliflozin had a significant effect to reduce the rate of decline in both EMPEROR-Reduced and EMPEROR-Preserved, with a similar effect across KDIGO categories (P trend = 0.35 for EMPEROR-Reduced and P trend = 0.57 for EMPEROR-Preserved). In all analyses, as compared with the effect on unconfounded eGFR slopes, the magnitude of the effect of the drug on total eGFR slopes was smaller; however, the magnitude of the effect of the drug on chronic eGFR slopes was similar to or larger than the unconfounded eGFR slope, in EMPEROR-Reduced and EMPEROR-Preserved, respectively (**Figures 2 and 3**). For chronic eGFR slopes, empagliflozin exerted a smaller effect in higher risk KDIGO categories than in lower risk categories in EMPEROR-Reduced (P trend = 0.015), but not in EMPEROR-Preserved (P trend = 0.62). There was no apparent influence of KDIGO categories on the response to empagliflozin using other definitions of eGFR slope in either trial (**Figures 2 and 3**).

For the pooled data across both trials, the effect of empagliflozin on composite kidney endpoint was smallest in the patients in the lowest risk category (HR: 0.95; 95% CI: 0.39-2.34), but the number of events in each risk category was small, and the P trend was not significant (P = 0.76). The data in individual trials were too sparse to allow for an assessment of the influence of KDIGO risk category on the composite kidney endpoint (Supplemental Figures 8 and 9).

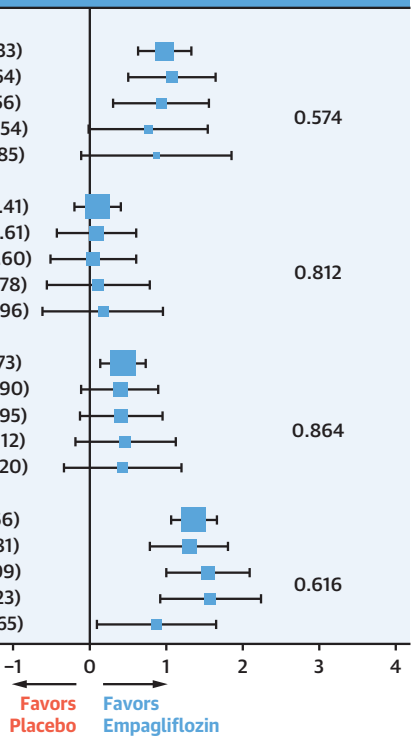
Safety outcomes. The effect of empagliflozin on safety outcomes across the KDIGO categories is outlined in Supplemental Table 3. There was no influence of KDIGO risk categories on the effect of empagliflozin on any adverse event that was observed.

DISCUSSION

In this analysis of the EMPEROR-Pooled, we show several key findings (**Central Illustration**). First, when

FIGURE 3 Effect of Empagliflozin vs Placebo on eGFR Slope (EMPEROR-Preserved)

Endpoint	Empagliflozin Mean ± SE	Placebo Mean ± SE	Difference (95% CI)	*P* Value for Trend
Unconfounded eGFR slope change				
All patients	−1.45 ± 0.13	−2.43 ± 0.13	0.98 (0.63 to 1.33)	
Low risk	−2.28 ± 0.21	−3.35 ± 0.20	1.07 (0.50 to 1.64)	
Moderate risk	−1.50 ± 0.22	−2.44 ± 0.23	0.94 (0.31 to 1.56)	
High risk	−0.79 ± 0.28	−1.56 ± 0.28	0.76 (−0.02 to 1.54)	0.574
Very high risk	−0.02 ± 0.36	−0.90 ± 0.35	0.87 (−0.11 to 1.85)	
eGFR total slope change at week 124				
All patients	−2.57 ± 0.11	−2.67 ± 0.11	0.10 (−0.20 to 0.41)	
Low risk	−3.25 ± 0.19	−3.34 ± 0.19	0.09 (−0.43 to 0.61)	
Moderate risk	−2.73 ± 0.20	−2.77 ± 0.20	0.04 (−0.52 to 0.60)	
High risk	−1.97 ± 0.24	−2.08 ± 0.24	0.11 (−0.56 to 0.78)	0.812
Very high risk	−1.60 ± 0.29	−1.76 ± 0.28	0.17 (−0.62 to 0.96)	
eGFR total slope change at week 172				
All patients	−2.22 ± 0.11	−2.65 ± 0.11	0.43 (0.13 to 0.73)	
Low risk	−2.84 ± 0.18	−3.23 ± 0.18	0.40 (−0.11 to 0.90)	
Moderate risk	−2.32 ± 0.19	−2.74 ± 0.20	0.41 (−0.13 to 0.95)	
High risk	−1.70 ± 0.23	−2.16 ± 0.24	0.46 (−0.19 to 1.12)	0.864
Very high risk	−1.39 ± 0.28	−1.81 ± 0.27	0.43 (−0.34 to 1.20)	
eGFR chronic slope change per year				
All patients	−1.25 ± 0.11	−2.62 ± 0.11	1.36 (1.06 to 1.66)	
Low risk	−1.75 ± 0.19	−3.05 ± 0.18	1.30 (0.79 to 1.81)	
Moderate risk	−1.30 ± 0.19	−2.84 ± 0.20	1.55 (1.00 to 2.09)	
High risk	−0.84 ± 0.24	−2.42 ± 0.24	1.58 (0.92 to 2.23)	0.616
Very high risk	−0.87 ± 0.29	−1.74 ± 0.28	0.87 (0.09 to 1.65)	

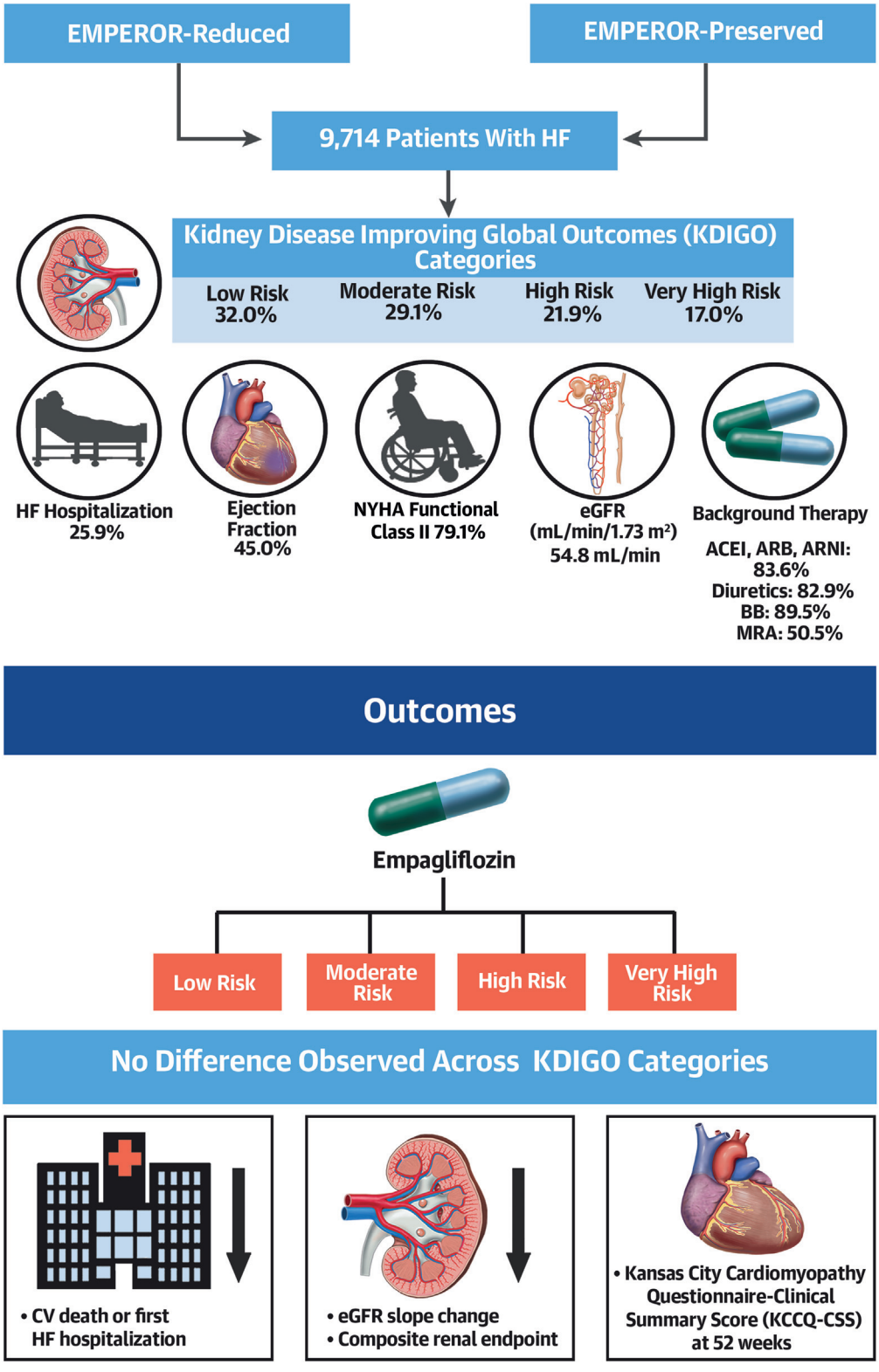


Unconfounded eGFR slope, eGFR total slope at weeks 124 and 172, and eGFR chronic slope per year by baseline. The effect of empagliflozin on total eGFR slope was significantly larger in EMPEROR-Reduced than in EMPEROR-Preserved overall. Empagliflozin reduced the risk for cardiovascular death or hospitalizations for heart failure and slowed the rate of decline in eGFR in all baseline KDIGO risk categories. Abbreviations as in Figures 1 and 2

treated with placebo, patients in higher risk KDIGO risk categories were at increased risk for adverse HF and renal outcomes and worsening health status over time, as compared with patients in lower risk categories. Second, empagliflozin reduced the risk for cardiovascular death or hospitalizations for HF and slowed the rate of decline in eGFR in all baseline KDIGO risk categories; the findings were consistent in EMPEROR-Reduced and EMPEROR-Preserved. Third, conclusions based on the calculation of eGFR slopes were highly dependent on the method used to calculate slopes.

No previous clinical trial in patients with HF has studied clinical outcomes according to KDIGO risk categories. Patients with a baseline eGFR (<60 vs ≥60 mL/min/1.73 m^2) showed similar responses to sacubitril/valsartan or spironolactone in the PARAGON-HF (Prospective Comparison of ARNI With ARB Global Outcomes in HF With Preserved Ejection Fraction) trial, PARADIGM-HF (Prospective comparison of Angiotensin Receptor-neprilysin inhibitor with Angiotensin converting enzyme inhibitor to Determine Impact on Global Mortality and morbidity in Heart Failure) trial, and TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist) trial, respectively.[14-16] A baseline eGFR (<60 vs ≥60 mL/min/1.73 m^2) also did not influence the effect of SGLT2 inhibition in 2 large-scale trials of SGLT2 inhibitors (DAPA-HF [Study to Evaluate the Effect of Dapagliflozin on the Incidence of

CENTRAL ILLUSTRATION **Patient Baseline Characteristics and Outcomes in EMPEROR-Pooled by KDIGO Categories**



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Worsening Heart Failure or Cardiovascular Death in Patients With Chronic Heart Failure With Reduced Ejection Fraction] and DELIVER [Dapagliflozin Evaluation to Improve the LIVEs of Patients With Preserved Ejection Fraction Heart Failure]).[17,18] Of note, these studies excluded patients with the most advanced kidney disease (eGFR <30 mL/min/1.73 m^2), and UACR was collected only in the PARADIGM-HF trial. In contrast, the EMPEROR program (EMPEROR-Reduced and EMPEROR-Preserved) measured UACR and included patients with an eGFR as low as 20 mL/min/1.73 m^2. Therefore, our analysis is the first to apply KDIGO risk categories to a large-scale trial in HF.

Four large-scale cardiovascular outcomes trials have evaluated the influence of KDIGO categories on the response to SGLT2 inhibitors in patients with type 2 diabetes or CKD.[19-22] In the 3 trials of patients with type 2 diabetes (EMPA-REG OUTCOME [BI 10773 (Empagliflozin) Cardiovascular Outcome Event in Type 2 Diabetes Mellitus Patients], CANVAS [CANagliflozin cardioVascular Assessment Study], and VERTIS-CV [Cardiovascular Outcomes Following Ertugliflozin Treatment in Type 2 Diabetes Mellitus Participants With Vascular Disease]), patients at the higher KDIGO categories were more likely to experience a major HF or adverse renal event, as compared with patients in lower risk KDIGO subgroups. However, in the EMPA-REG OUTCOME and CANVAS trials,[19,20] the relative risk reduction for HF and kidney outcomes produced by SGLT2 was similar regardless of baseline KDIGO risk, and thus, treatment-related absolute risk reductions were greatest in patients at high and very high risk.[20] However, in the VERTIS-CV trial, baseline KDIGO category exerted a significant influence on the relative risk reduction with ertugliflozin for cardiovascular death and hospitalization for HF, with minimal treatment effect being apparent in patients in the low-risk KDIGO category (treatment-by-KDIGO category interaction $P = 0.03$).[21] The DAPA-CKD trial did not note an influence of KDIGO risk on the effect of dapagliflozin in CKD,[22] but that trial did not enroll patients at lowest risk. In the EMPEROR trial program, KDIGO risk category did not modify the effect of empagliflozin on HF or renal outcomes in patients with HF, a response pattern similar to that reported in EMPA-REG OUTCOME and in the CANVAS trials. Further, improvement in health-related quality of life was observed across all KDIGO risk categories. This is consistent with results observed with other HF therapeutics, such as angiotensin receptor neprilysin inhibitors.

Under circumstances in which trials may be underpowered for an evaluation of major renal outcomes, investigators have proposed that the magnitude of the effect of treatment on the rate of decline in eGFR be used as a surrogate metric. It has been hoped that analyses that examine between-group differences in eGFR slopes can discern a drug effect in trials that are meaningfully smaller and shorter than those designed to evaluate major renal events. Some have proposed that a between-group difference of 0.5 to 1.0 mL/min/1.73 m^2 can be used to predict a 30% reduction in the risk of an adverse renal outcome.[23] However, there are numerous possible approaches to the calculation of eGFR slopes; the available models differ substantially in their exclusion of data and underlying assumptions; and commonly used models can yield markedly different results that can show important discrepancies with observed outcomes.[24] In fact, some have suggested that the analysis of eGFR slope performs well only when the pretreatment eGFR is high, when the treatment has no immediate effect on eGFR, and when the duration of the trial is sufficiently long for a reliable estimation of slope.[24,25]

None of these prerequisites for the reliability of eGFR slopes applies to patients with chronic HF who have been enrolled in large-scale trials of SGLT2 inhibitors. The typical patients with mild-to-moderate HF have an eGFR of approximately 60 to 65 mL/min/1.73 m^2, the duration of follow-up averages only 1.5 to 2.5 years, and SGLT2 inhibitors have an immediate reversible effect to reduce eGFR due to an intrarenal hemodynamic action. Therefore, to

CENTRAL ILLUSTRATION Continued

A total of 9,714 patients with HF from EMPEROR-Reduced and EMPEROR-Preserved were stratified into KDIGO risk categories with 32.0% at low risk, 29.1% at moderate risk, 21.9% at high risk, and 17.0% at very-high risk. Key baseline characteristics for the pooled population are described. In all baseline KDIGO risk categories empagliflozin reduced the risk for cardiovascular death or first HF hospitalization, slowed the rate of decline in eGFR, and increased the KCCQ-CSS score at 52 weeks. ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor neprilysin inhibitor; BB = beta-blocker; CV = cardiovascular; eGFR = estimated glomerular filtration rate; EMPEROR = Empagliflozin Outcome Trial in Patients with Chronic Heart Failure; MRA = mineralocorticoid receptor antagonist; NYHA = New York Heart Association; HF = heart failure.

calculate eGFR slopes, some investigators have excluded this early dip, thus basing the estimation of eGFR slope on on-treatment values only and excluding the baseline value—an approach that is referred to as "chronic slope." Others have forced the inclusion of the baseline value and attempted to calculate "total slope" using a 2-compartment model. Even though linearity is not present, the calculation yields a single value for a yearly decline (at a specific time point), which does not represent either the underlying data or pathophysiology. Importantly, the model also fails to account for the reversible depression of all on-treatment values of eGFR in the patients treated with an SGLT2 inhibitor. In analyzing the data from the EMPEROR trials, we were able to avoid the difficulties inherent in both the "chronic slope" and "total slope" models because we measured eGFR during a 30-day off-treatment period. A comparison of this off-treatment value with the baseline value allowed an assumption-free estimation of the annualized change in eGFR that was unconfounded by the presence of the drug. In this paper, we refer to this approach as the "unconfounded eGFR slope."

Based on our ability to calculate unconfounded slope, we were able to perform a comprehensive assessment of the value of chronic and total slopes in our patients. In the placebo group, when compared with low-risk patients, eGFR slope declined substantially more slowly in the patients at highest risk of an adverse renal outcome, reaffirming the recommendation that the absolute changes in eGFR slope are unreliable in patients with compromised renal function.[24] More importantly, we noted that, as compared with the effect on unconfounded eGFR slopes, the magnitude of the effect of empagliflozin on total eGFR slopes was smaller, whereas the magnitude of its effect on chronic eGFR slopes was typically larger. This observation indicates that total slope models are likely to significantly underestimate the true treatment effect of SGLT2 inhibitors. Finally, across KDIGO categories, the effect of empagliflozin on eGFR slopes did not track closely with the effect of the drug on renal outcomes, although this observation is limited by the small number of renal events, especially in low-risk patients. These findings, taken together, highlight the important difficulties in trying to extrapolate from observations on conventionally calculated eGFR slopes to conclusions about major adverse renal outcomes in patients with chronic HF.

STUDY STRENGTHS AND LIMITATIONS. The major strength is its ability to measure unconfounded slope, a metric of the rate of decline in eGFR that is not affected by the expected acute effect of empagliflozin on eGFR. The major limitation of the current analysis is the relatively short duration of double-blind therapy, which limited our ability to link changes in eGFR with the occurrence of major adverse kidney outcomes.

CONCLUSIONS

Empagliflozin reduced the risk for cardiovascular death or HF hospitalization in all KDIGO risk categories, whether the data in EMPEROR-Reduced and EMPEROR-Preserved were pooled or analyzed separately. Empagliflozin slowed the decline in eGFR in all KDIGO groups, but the magnitude of these effects varied according to the model used to calculate eGFR slopes. The nonlinear nature of total slopes and their predilection to be confounded by an ongoing intrarenal hemodynamic effect of the drugs limits their utility in assessing the effects of SGLT2 inhibitors. For both total and chronic slopes, treatment-related changes in eGFR slopes in patients with HF should be interpreted cautiously.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Boehringer Ingelheim and Eli Lilly and Company funded EMPEROR-Reduced and EMPEROR-Preserved. The manuscript was sponsored by the Boehringer Ingelheim and Eli Lilly and Company Diabetes Alliance. Dr Butler has received payment or honoraria for lectures, presentations, Speakers Bureau, manuscript writing, or educational events from Abbott, Adrenomed, Amgen, Applied Therapeutics, Array, AstraZeneca, Bayer, BerlinCures, Cardior, CVRx, Foundry, G3 Pharma, Imbria, Impulse Dynamics, Innolife, Janssen, LivaNova, Luitpold, Medtronic, Merck, Novartis, Novo Nordisk, Relypsa, Roche, Sanofi, Sequana Medical, Occlutech, and Vifor; and is a Trial Executive Committee member of Boehringer Ingelheim & Eli Lilly and Company Diabetes Alliance (trial sponsor). Dr Packer has received consulting fees from AbbVie, Actavis, Amgen, Amarin, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Casana, CSL Behring, Cytokinetics, Johnson & Johnson, Eli Lilly and Company, Moderna, Novartis, ParatusRx, Pfizer, Relypsa, Salamandra, Synthetic Biologics, and Theravance; and is a Trial Executive Committee member of the Boehringer Ingelheim & Eli Lilly and Company Diabetes Alliance (trial sponsor). Dr Böhm is supported by the Deutsche Forschungsgemeinschaft (German Research Foundation; TTR 219, project number 322900939); and has received personal fees from Abbott, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Cytokinetics, Medtronic, Novartis, Servier, and Vifor during the conduct of the study. Dr Januzzi is a trustee of the American College of Cardiology; is a board member of Imbria Pharmaceuticals; has received grant support from Applied Therapeutics, Innolife, Novartis Pharmaceuticals, and Abbott Diagnostics; has received consulting income from Abbott, Janssen, Novartis, and Roche Diagnostics; and participates in clinical endpoint committees/data safety monitoring boards for Abbott, AbbVie, Amgen, Bayer, CVRx, Janssen, MyoKardia, and Takeda. Dr Verma has received research and/or speaking honoraria from Amgen, Amarin, AstraZeneca, Bayer, CMS, Janssen, HLS, Sanofi, Novo Nordisk, Novartis, Merck, and PhaseBio; has received personal fees from Boehringer Ingelheim; is president of the Canadian Medical and Surgical Knowledge Translation Research Group; and holds the Tier 1 Canada Research Chair in Cardiovascular Surgery. Dr Wanner has

received personal fees from Boehringer Ingelheim during the conduct of the study; and has received personal fees from Akebia, AstraZeneca, Bayer, Eli Lilly and Company, GSK, Gilead, MSD, Mundipharma, Sanofi-Genzyme, and Vifor Fresenius. Dr Ferreira has received consulting fees from Boehringer Ingelheim; and is a Trial Executive Committee member of the Boehringer Ingelheim & Eli Lilly and Company Diabetes Alliance (trial sponsor). Dr Pocock has received consulting fees and payment or honoraria for lectures, presentations, Speakers Bureau, manuscript writing, or educational events from Boehringer Ingelheim; and is a Trial Executive Committee member of the Boehringer Ingelheim & Eli Lilly and Company Diabetes Alliance (trial sponsor). Dr Filippatos has received payment or honoraria for lectures, presentations, Speakers Bureau, manuscript writing, or educational events from Boehringer Ingelheim, Medtronic, Vifor, Servier, and Novartis; and is a Trial Executive Committee member of the Boehringer Ingelheim & Eli Lilly and Company Diabetes Alliance (trial sponsor). Dr Anker has received grants from Abbott Vascular and Vifor (International) Ltd; has received consulting fees from Abbott Vascular, Bayer, Brahms GmbH, Cardiac Dimensions, Cordio, Novartis, Servier, and Vifor (International) Ltd; and is a Trial Executive Committee member of the Boehringer Ingelheim & Eli Lilly and Company Diabetes Alliance (trial sponsor). Dr Zannad has recieved payment or honoraria for lectures, presentations, Speakers Bureau, manuscript writing, or educational events from Boehringer Ingelheim, Amgen, CVRx, AstraZeneca, Vifor Fresenius, Cardior, Cereno Pharmaceutical, Applied Therapeutics, Merck, and Bayer; other financial or nonfinancial interests in CVCT and Cardiorenal; and is a Trial Executive Committee member of the Boehringer Ingelheim & Eli Lilly and Company Diabetes Alliance (trial sponsor). Drs Brueckmann and Gergei, and Tomoko Iwata are employees of Boehringer Ingelheim, the manufacturer of empagliflozin. Dr Siddiqi has reported that he has no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Treatment with empagliflozin reduces the risk of HF hospitalization or cardiovascular death and slows the decline of renal function in patients with HF across a broad range of renal risk, including those with eGFR down to 20 mL/min/1.73 m^2, irrespective of albuminuria.

TRANSLATIONAL OUTLOOK: Measures of renal function other than eGFR should be explored as predictors of adverse outcomes in patients with HF and renal impairment and as potential indications for treatment with empagliflozin or another SGLT2 inhibitor.

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KEY WORDS cardiovascular disease, chronic kidney disease, congestive heart failure, KDIGO category, SGLT2 inhibitor

APPENDIX For supplemental tables and figures, please see the online version of this paper.