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Empagliflozin Improves Cardiovascular and Renal Outcomes in Heart Failure Irrespective of Systolic Blood Pressure

Michael Böhm, MD,[a] Stefan D. Anker, MD, PhD,[b] Javed Butler, MD, MPH, MBA,[c] Gerasimos Filippatos, MD,[d] João Pedro Ferreira, MD, PhD,[e] Stuart J. Pocock, PhD,[f] Felix Mahfoud, MD,[a] Martina Brueckmann, MD,[g,h] Waheed Jamal, MD,[g] Anne Pernille Ofstad, MD, PhD,[i] Elke Schüler, Dipl.Math,[j] Piotr Ponikowski, MD,[k] Christoph Wanner, MD,[l] Faiez Zannad, MD, PhD,[e] Milton Packer, MD,[m,n] on behalf of the EMPEROR-Reduced Trial Committees and Investigators

ABSTRACT

BACKGROUND Empagliflozin reduces the risk of cardiovascular death or heart failure (HF) hospitalization in patients with reduced ejection fraction. Its interplay with systolic blood pressure (SBP) is not known.

OBJECTIVES The goal of this study was to evaluate the interplay of SBP and the effects of empagliflozin in EMPEROR-Reduced (Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction).

METHODS Study patients (N = 3,730) were randomly assigned to groups according to SBP at baseline (<110 mm Hg, n = 928; 110-130 mm Hg, n = 1,755; >130 mm Hg, n = 1,047). This study explored the influence of SBP on the effects of empagliflozin on cardiovascular death or HF hospitalization (primary outcome), as well as on total HF hospitalizations, rate of decline in estimated glomerular filtration rate, renal outcomes, and empagliflozin's effects and significance on SBP.

RESULTS Over a median of 16 months considering only patients receiving placebo, baseline SBP and the risk of cardiovascular death or hospitalization for HF (*P* trend = 0.0015) were inversely related. Corrected for placebo, a slight early increase was observed in SBP at <110 mm Hg, no change at 110-130 mm Hg, and a slight reduction at >130 mm Hg. These between-group differences were of borderline significance (*P* for interaction trend = 0.05-0.10) after 4 and 12 weeks but were not significant later. SBP at baseline did not influence the effect of empagliflozin to reduce the risk of HF events or renal endpoints. When treated with empagliflozin, patients with SBP <110 mm Hg did not have an increased rate of symptomatic hypotension.

CONCLUSIONS Empagliflozin was effective and safe, with no meaningful interaction between SBP and the effects of empagliflozin in the EMPEROR-Reduced trial. (Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction [EMPEROR-Reduced]; NCT03057977) (J Am Coll Cardiol 2021;78:1337–1348) © 2021 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

From the [a]Klinik für Innere Medizin III, Universitätsklinikum des Saarlandes, Saarland University, Homburg/Saar, Germany; [b]Department of Cardiology (CVK), and Berlin Institute of Health Center for Regenerative Therapies (BCRT), German Centre for Cardiovascular Research (DZHK) partner site Berlin, Charité Universitätsmedizin Berlin, Berlin, Germany; [c]Department of Medicine, University of Mississippi School of Medicine, Jackson, Mississippi, USA; [d]National and Kapodistrian University of Athens School of Medicine, Athens University Hospital Attikon, Athens, Greece; [e]Université de Lorraine, Centre d'Investigation Clinique-Plurithématique Inserm CIC-P 1433, Nancy, France Inserm U1116, CHRU Nancy Brabois, F-CRIN INI-CRCT (Cardiovascular and Renal Clinical Trialists), Nancy, France; [f]Department of Medical Statistics, London School of Hygiene & Tropical Medicine, London, United Kingdom; [g]Boehringer Ingelheim International, Ingelheim, Germany; [h]Faculty of Medicine Mannheim, University of Heidelberg, Mannheim, Germany; [i]Medical Department, Boehringer Ingelheim Norway KS, Asker, Norway; [j]mainanalytics GmbH, Sulzbach/Taunus, Germany; [k]Wroclaw Medical University, Wrocław, Poland; [l]Medizinische Klinik und Poliklinik 1, Schwerpunkt Nephrologie, Universitätsklinikum Würzburg, Würzburg, Germany; [m]Baylor University Medical Center, Dallas, Texas, USA; and the [n]Imperial College, London, United Kingdom.

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ABBREVIATIONS AND ACRONYMS

DBP = diastolic blood pressure

eGFR = estimated glomerular filtration rate

SBP = systolic blood pressure

SGLT2 = sodium-glucose cotransporter-2

Sodium-glucose cotransporter-2 (SGLT-2) inhibitors have been shown to reduce cardiovascular death and heart failure hospitalization in patients with diabetes (1-3) and with heart failure with reduced ejection fraction with and without diabetes (4-5). In addition, these drugs reduce systolic blood pressure (SBP) in patients with diabetes and hypertension (6,7). Because of fears that these heart failure medications may lower blood pressure, they are often not prescribed or are used at low doses, especially in patients with a low SBP at the start of treatment (8,9). There is an inverse relationship between SBP and the risk of cardiovascular death and hospitalization for heart failure in patients who have heart failure and a reduced ejection fraction (10). Thus, patients with the lowest SBP are at the highest risk but may be least likely to receive effective treatments.

Accordingly, we evaluated the interplay of baseline SBP and the effects of empagliflozin in patients enrolled in EMPEROR-Reduced (Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction), with a particular emphasis on patients with the lowest SBP.

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METHODS

STUDY DESIGN. The design and results of the EMPEROR-Reduced trial have been published previously (5,11). The ethics committees of each of the participating institutions approved the protocol, and all patients gave written informed consent. The registration identifier at ClinicalTrials.gov is NCT03057977.

STUDY PATIENTS AND PROCEDURES. Patients were screened and those fulfilling eligibility criteria were randomized double-blind in a 1:1 fashion to receive placebo or empagliflozin 10 mg daily in addition to their usual therapy for heart failure. Patients with or without diabetes were enrolled. During follow-up, all accompanying treatments could be altered or initiated according to the changes in the clinical status of the patients at the clinical discretion of the investigator.

At the screening visit, after the patient had rested quietly in the seated position for 5 minutes, 3 attended blood pressure measurements were recorded, and the mean of these 3 blood pressure values was used to determine eligibility. Blood pressure was recorded at every subsequent visit by using a standard manometer with an appropriate size cuff at the same arm in a sitting position after 5 minutes of rest.

Patients were assessed at study visits for major outcomes, vital signs, estimated glomerular filtration rate (eGFR) according to the Chronic Kidney Disease Epidemiology Collaboration equation, adverse events, and changes in medications or clinical status that reflected changes in the course of heart failure. All randomized individuals were followed up for the occurrence of pre-specified outcomes for the entire duration of the trial regardless of whether the study participants had taken the study medication or were adherent with the study procedures according to the intention-to-treat principle. At the end of double-blind therapy, treatment with the study medications was stopped, and patients underwent a follow-up visit, including assessment of eGFR 23 to 45 days later unconfounded by the presence of the study medication.

TRIAL OUTCOMES. The primary endpoint of the composite of adjudicated cardiovascular death or hospitalization for heart failure was analyzed as time-to-first event. The first secondary endpoint was the occurrence of all adjudicated hospitalizations for heart failure, including first and recurrent events. The second secondary endpoint was the analysis of the slope of the change in eGFR during double-blind treatment. We also analyzed the change in eGFR from baseline to the off-treatment values 23 to 45 days after discontinuation of double-blind treatment. In addition, we evaluated a renal composite endpoint, defined as the need for chronic dialysis or renal transplant or a ≥40% sustained decrease in eGFR or a sustained eGFR <15 mL/min/1.73 m^2 (if the baseline eGFR was ≥30 mL/min/1.73 m^2) or <10 mL/min/1.73 m^2 (if the baseline eGFR was <30 mL/min/1.73 m^2).

SBP ANALYSES. Patients were grouped according to their baseline SBP: <110 mm Hg, 110-130 mm Hg, and >130 mm Hg. We evaluated the risk of a serious heart failure and renal event in these groups in patients receiving placebo, and we compared the effects of empagliflozin versus placebo on efficacy variables in these SBP categories. Furthermore, to understand the influence of post-randomization changes in SBP in mediating the effects of empagliflozin, the treatment effects of empagliflozin were studied by using time-updated SBP as a covariate. The influence of baseline SBP on the occurrence of hypotension and symptomatic hypotension was examined in the placebo and empagliflozin groups.

STATISTICAL ANALYSES. The effect of empagliflozin compared with placebo on the time-to-first event analyses was examined by using Cox proportional hazards regression models with prespecified covariates of age, sex, geographical region, diabetes

TABLE 1 Baseline Characteristics According to Baseline SBP Group

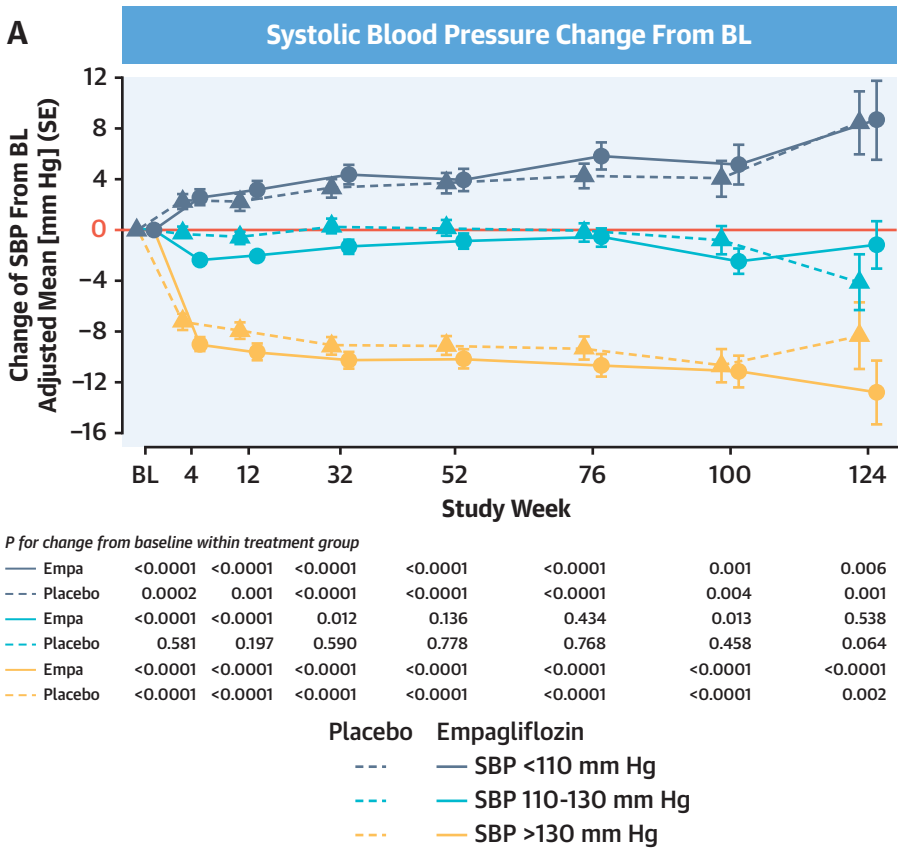
	SBP <110 mm Hg (n = 928)	SBP 110-130 mm Hg (n = 1,755)	SBP >130 mm Hg (n = 1,047)	*P* Value
Age, y	64.9 ± 11.4	66.9 ± 11.1	68.4 ± 10.3	<0.0001
Female	196 (21.1)	433 (24.7)	264 (25.2)	0.0392
Race				<0.0001
White	585 (63.0)	1251 (71.3)	793 (75.7)	
Black	77 (8.3)	119 (6.8)	61 (5.8)	
Asian	212 (22.8)	295 (16.8)	165 (15.8)	
Other, including mixed races	35 (3.8)	61 (3.5)	18 (1.7)	
Missing	19 (2.0)	29 (1.7)	10 (1.0)	
Region				<0.0001
North America	136 (14.7)	200 (11.4)	89 (8.5)	
Latin America	321 (34.6)	625 (35.6)	340 (32.5)	
Europe	260 (28.0)	639 (36.4)	454 (43.4)	
Asia	176 (19.0)	193 (11.0)	124 (11.8)	
Other	35 (3.8)	98 (5.6)	40 (3.8)	
NYHA functional class				0.1437
II	680 (73.3)	1,329 (75.7)	791 (75.5)	
III	243 (26.2)	421 (24.0)	246 (23.5)	
IV	5 (0.5)	5 (0.3)	10 (1.0)	
Body mass index, kg/m^2	26.6 ± 5.0	28.0 ± 5.3	28.8 ± 5.7	<0.0001
Heart rate, beats/min	71.0 ± 11.9	71.1 ± 11.6	71.8 ± 11.8	0.1059
SBP, mm Hg	104.0 ± 3.4	119.4 ± 6.4	142.3 ± 9.0	NA
DBP, mm Hg	66.6 ± 7.7	73.2 ± 9.0	81.4 ± 11.1	<0.0001
Left ventricular ejection fraction, %	26.1 ± 6.3	27.3 ± 5.9	28.9 ± 5.6	<0.0001
NT-proBNP, pg/mL	2,098.0 (1,235.5-3,905.5)	1,804.0 (1,074.0, 3,347.0)	1,851.0 (1,079.0, 3,244.0)	<0.0001[a]
Medical history				
Diabetes	412 (44.4)	879 (50.1)	565 (54.0)	<0.0001
Hospitalization for heart failure in last 12 mo	339 (36.5)	522 (29.7)	290 (27.7)	<0.0001
Atrial fibrillation[b]	350 (37.7)	642 (36.6)	377 (36.0)	0.3737
Hypertension	543 (58.5)	1,240 (70.7)	915 (87.4)	<0.0001
eGFR				
Mean, mL/min/1.73 m^2	62.2 ± 22.2	62.2 ± 21.4	61.5 ± 21.4	0.4330
eGFR <60 mL/min/1.73 m^2	468 (50.4)	826 (47.1)	505 (48.2)	0.3677
Device therapy				
Implantable cardioverter-defibrillator[c]	344 (37.1)	557 (31.7)	270 (25.8)	<0.0001
Cardiac resynchronization therapy[d]	133 (14.3)	212 (12.1)	97 (9.3)	0.0005
Heart failure medication				
ACE inhibitors/ARBs/ARNi	800 (86.2)	1,549 (88.3)	944 (90.2)	0.0064
ACE inhibitors/ARBs[e]	566 (61.0)	1,214 (69.2)	820 (78.3)	<0.0001
ARNi	237 (25.5)	353 (20.1)	137 (13.1)	<0.0001
Mineralocorticoid receptor antagonist	715 (77.0)	1,271 (72.4)	675 (64.5)	<0.0001
Beta-blocker	880 (94.8)	1,661 (94.6)	992 (94.7)	0.9450

Values are n, mean ± SD, n (%), or median (interquartile range). [a]Based on log-transformed results. [b]Defined as atrial fibrillation reported in any electrocardiogram before treatment intake or history of atrial fibrillation reported in medical history. [c]Implantable cardioverter-defibrillator with or without cardiac resynchronization therapy. [d]Cardiac resynchronization therapy with or without a defibrillator. [e]Excluding valsartan when taken with sacubitril because sacubitril/valsartan is shown as an angiotensin receptor blocker + neprilysin inhibitor (ARNi).

ACE = angiotensin-converting enzyme; ARBs = angiotensin receptor blockers; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; NT-proBNP = N-terminal pro-B-type natriuretic peptide; SBP = systolic blood pressure.

status at baseline, left ventricular ejection fraction, and eGFR at baseline. The interaction between (continuous) SBP and treatment group on the occurrence of the prespecified outcomes was tested by using a treatment-by-SBP interaction term (testing for a linear trend assuming ordered SBP categories). The first secondary outcome of total (first and recurrent) heart failure hospitalizations was evaluated with the use of the joint frailty model that accounted for informative censoring because of cardiovascular death. Changes in SBP and diastolic blood pressure (DBP) were analyzed in a mixed model with repeated

FIGURE 1 SBP and DBP Change According to Baseline SBP



Adjusted mean change in systolic blood pressure (SBP) **(A)** or diastolic blood pressure (DBP) **(B)** (ordinate) from baseline (BL) to 124 weeks of follow-up and placebo-corrected change in SBP **(C)** and DBP **(D)** from BL according to SBP at BL in patients treated with empagliflozin (Empa) (**solid lines**) or placebo **(dashed lines)**. CI = confidence interval.

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measures. Between-group differences in the slope of change in eGFR were analyzed by using a random intercept random slope model using on-treatment data. The slope, the joint frailty, and the mixed model with repeated measures models included the same covariates as the Cox model.

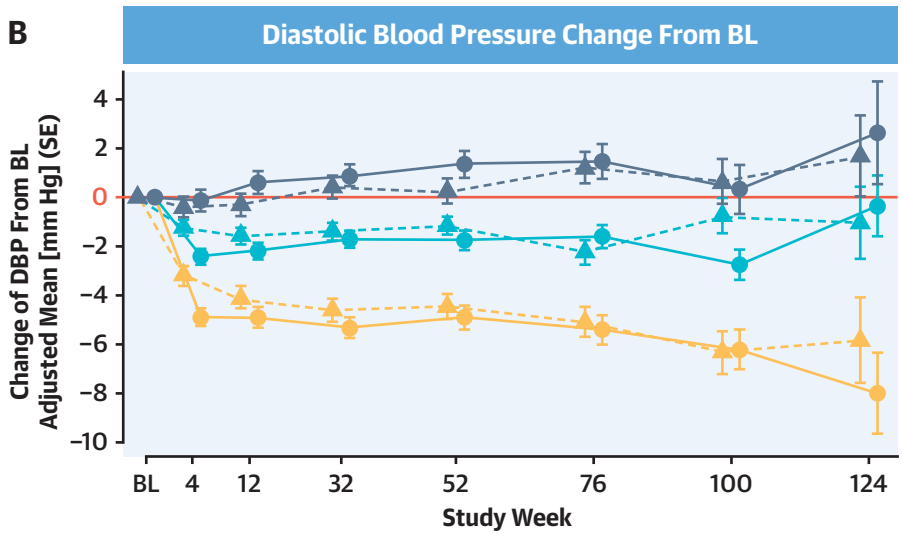
All analyses were performed by using SAS version 9.4 (SAS Institute, Inc). All P values reported are 2-sided, and $P < 0.05$ was considered as statistically significant in all cases. No adjustments for multiple testing were made from the exploratory nature of the study.

DATA-SHARING STATEMENT. Data will be made available upon request in adherence with transparency conventions in medical research and through requests to the executive committee. The executive committee of EMPEROR-Reduced has developed a comprehensive analysis plan and numerous prespecified analyses, which will be presented in future scientific meetings and publications. At a later time point, the full database will be made available in adherence with the transparency policy of the sponsor.

RESULTS

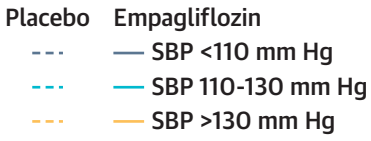
PATIENT CHARACTERISTICS. A total of 3,730 patients were randomly assigned to receive either empagliflozin (n = 1,863, 10 mg once daily) or placebo (n = 1,867) (Supplemental Figure 1). **Table 1** presents the baseline characteristics of patients in the 3 baseline SBP categories. Those with lower SBP had a greater severity of heart failure, as evidenced by a lower ejection fraction, higher N-terminal pro-B-type natriuretic peptide plasma concentrations, and a higher likelihood of having experienced a heart

FIGURE 1 Continued



P for change from baseline within treatment group

Empa	0.759	0.198	0.085	0.015	0.038	0.746	0.210
Placebo	0.337	0.498	0.382	0.635	0.061	0.479	0.309
Empa	<0.0001	<0.0001	<0.0001	<0.0001	0.001	<0.0001	0.772
Placebo	<0.0001	<0.0001	<0.0001	0.003	<0.0001	0.279	0.475
Empa	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Placebo	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	0.001



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failure hospitalization in the last 12 months. Patients with lower SBP were more likely to be treated with a neprilysin inhibitor or have received an implanted cardioverter-defibrillator and/or cardiac resynchronization therapy device.

ASSOCIATION OF BLOOD PRESSURE WITH OUTCOMES. The relationship of baseline SBP to the severity of heart failure was further investigated by calculating incidence rates for major endpoints in patients receiving placebo. The incidence rate per 100 patient years of follow-up for the primary endpoint increased from 16.5 in patients with SBP >130 mm Hg to 20.8 in patients with SBP of 110-130 mm Hg, and to 26.3 in patients with SBP <110 mm Hg (*P* trend = 0.0015). The event rate per 100 patient years of follow-up for total hospitalizations for heart failure increased from 17.9 in patients with SBP >130 mm Hg to 22.0 in patients with SBP of 110-130 mm Hg and to 28.1 in patients with SBP <110 mm Hg (*P* trend = 0.0075).

EFFECT OF EMPAGLIFLOZIN ON BLOOD PRESSURE. The time course of SBP and DBP in the 2 treatment groups according to baseline SBP categories is shown in Figure 1A (SBP) and Figure 1B (DBP). When corrected for placebo, we observed a slight early increase in blood pressure in the <110 mm Hg group, no change in the 110-130 mm Hg group, and a slight reduction in the >130 mm Hg group. These between-group differences were of borderline significance (*P* for interaction trend = 0.05-0.10) after 4 and 12 weeks but were not significant at later time points (Figures 1C and 1D).

SAFETY ASSESSMENTS. The incidence of symptomatic hypotension in the placebo group increased from 2.9 per 100 patient years of follow-up in patients with SBP >130 mm Hg, to 4.0 in those with SBP 110-130 mm Hg, and to 8.2 in patients with SBP <110 mm Hg (Table 2). A similar pattern was observed with hypotension. Treatment with empagliflozin did not increase the risk of hypotension or symptomatic hypotension.

FIGURE 1 Continued

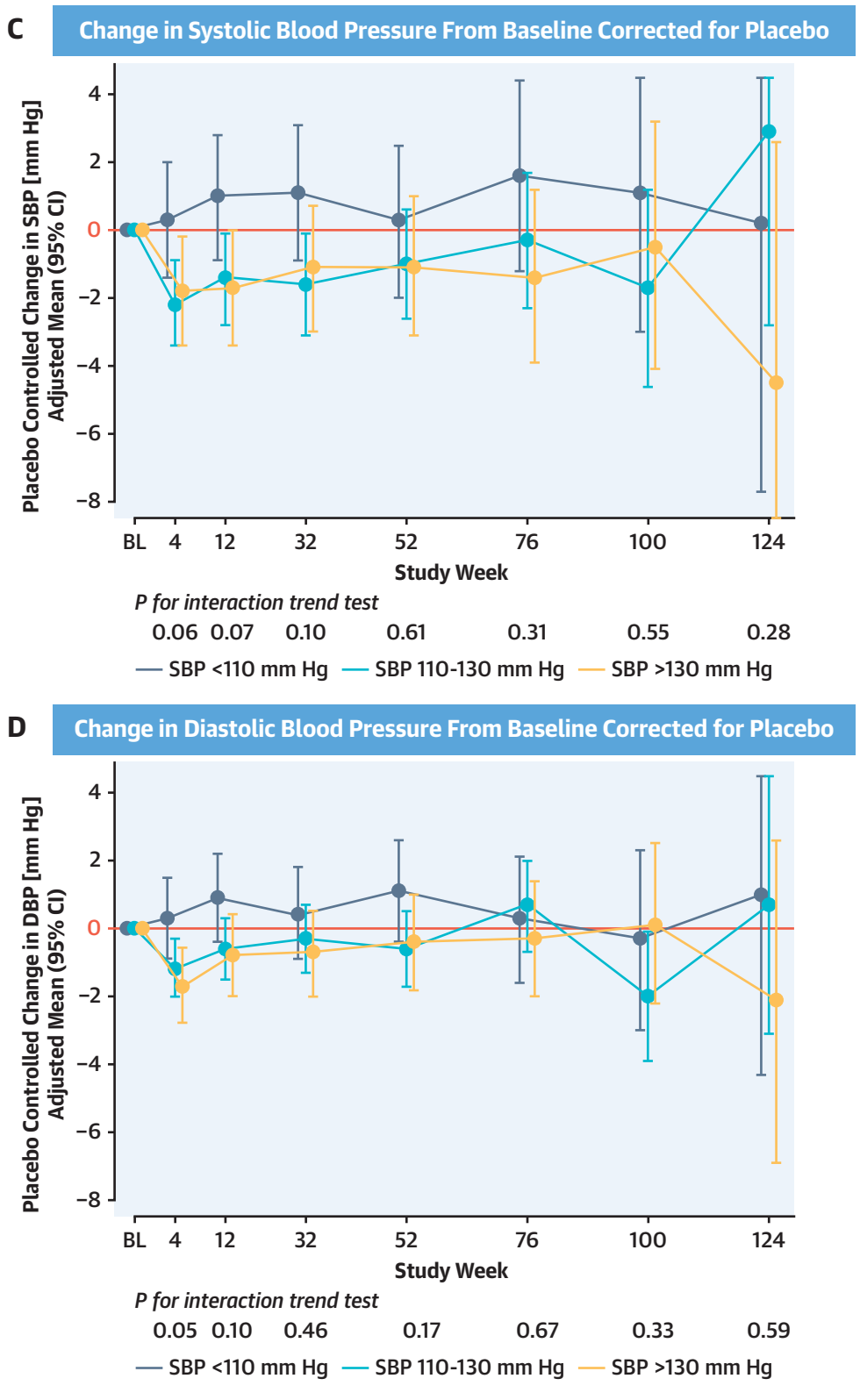


TABLE 2 Adverse Events According to Baseline SBP

	SBP <110 mm Hg (n = 927)				SBP 110-130 mm Hg (n = 1,752)				SBP >130 mm Hg (n = 1,047)			
	Placebo (n = 489)		Empagliflozin (n = 438)		Placebo (n = 875)		Empagliflozin (n = 877)		Placebo (n = 499)		Empagliflozin (n = 548)	
	n (%)	IR/100	n (%)	IR/100	n (%)	IR/100	n (%)	IR/100	n (%)	IR/100	n (%)	IR/100
Hypotension[a]	62 (12.7)	11.8	58 (13.2)	12.4	66 (7.5)	6.6	88 (10.0)	8.6	35 (7.0)	5.9	30 (5.5)	4.6
Symptomatic hypotension[b]	44 (9.0)	8.2	35 (8.0)	7.3	41 (4.7)	4.0	51 (5.8)	4.9	18 (3.6)	2.9	20 (3.6)	3.0

[a]Based on pre-selected adverse events. [b]Investigator defined.
IR/100 = incidence rate per 100 patient years; SBP = systolic blood pressure.

EFFECT OF EMPAGLIFLOZIN ON EFFICACY OUTCOMES. The cumulative incidence functions of the primary outcome (cardiovascular death or heart failure hospitalization) according to baseline SBP are shown in Supplemental Figure 2. The relative risk reduction of the primary outcome by empagliflozin was similar across all SBP groups (*P* for interaction trend = 0.83) (**Figure 2**). When we investigated the treatment effects from week 4 onward using SBP as a time-updated covariate, changes in SBP did not influence the effect of empagliflozin on the primary endpoint (*P* for interaction trend = 0.43) (Supplemental Figure 3). SBP also did not influence the magnitude of the risk reduction produced by empagliflozin on total (first and recurrent) hospitalizations for heart failure (*P* for interaction trend = 0.96).

Empagliflozin attenuated the slope of eGFR decline similarly in all SBP categories (*P* for interaction trend = 0.68) (**Figure 3A**). Because the eGFR slope could be influenced by the early eGFR changes on empagliflozin but not on placebo, we evaluated the eGFR change from baseline to the off-treatment values at 23 to 45 days after discontinuation of randomized treatments. There were no differences in the treatment effect of empagliflozin in the SBP groups on the eGFR change from baseline to off-treatment (*P* for interaction trend = 0.63) (**Table 3**). The effect of SBP on the ability of empagliflozin to reduce the risk of the renal composite was somewhat greater in patients with SBP <110 mm Hg, but the *P* for interaction trend was borderline significant (*P* = 0.088) (**Figure 3B**), and this analysis is based on sparse events.

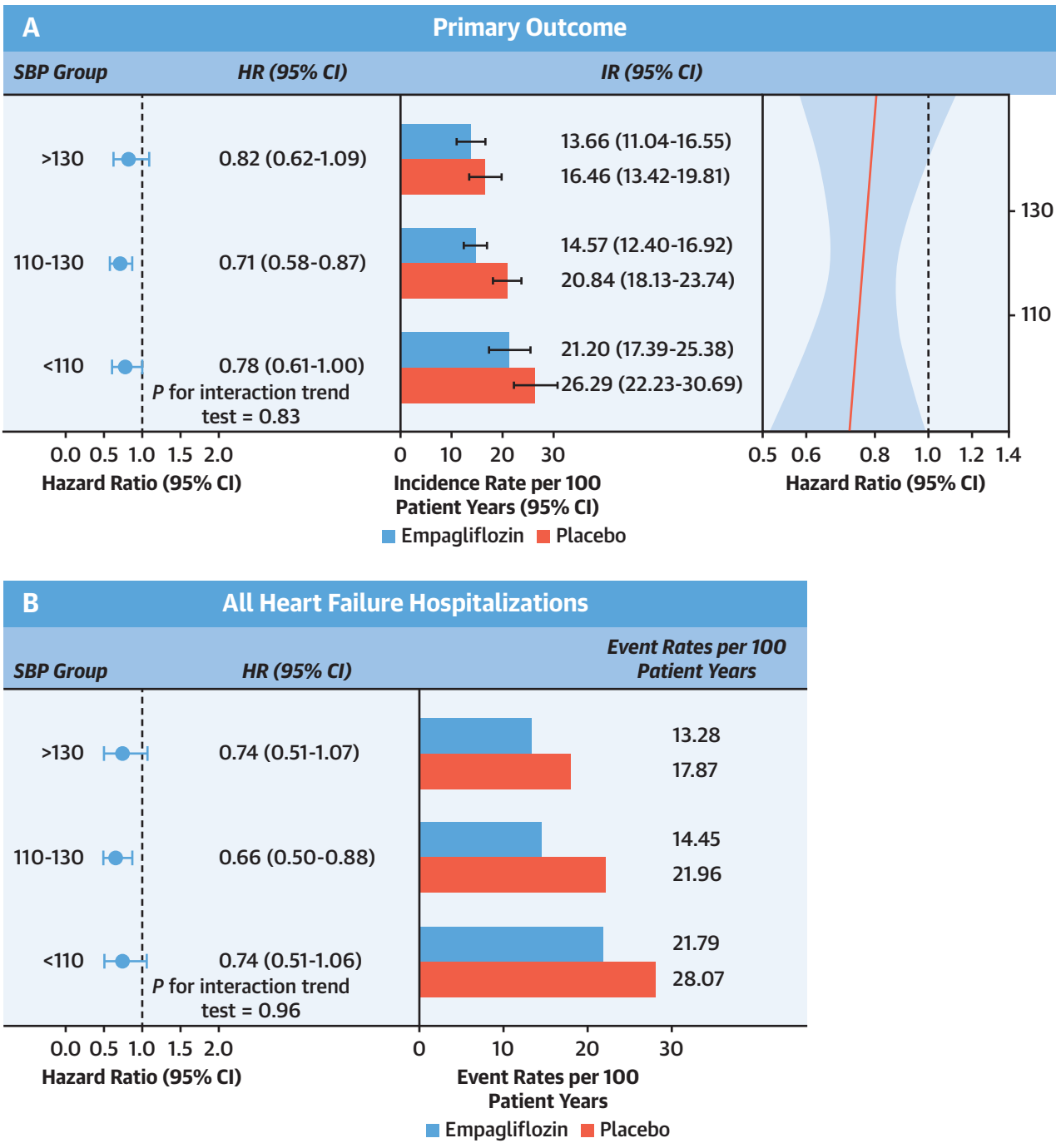
DISCUSSION

We show an inverse relationship between SBP and the risk of major cardiovascular outcomes in patients with heart failure with reduced ejection fraction in the EMPEROR-Reduced trial. Empagliflozin reduced the risk of the primary outcome independently of baseline SBP and SBP during the trial. Moreover, empagliflozin reduced the number of total hospitalizations for heart failure, slowed eGFR decline, and reduced the risk of a composite renal outcome consistently across baseline SBP categories. Empagliflozin had only minor effects on SBP and did not produce hypotension or symptomatic hypotension, even in the patients with the lowest baseline SBP (ie, <110 mm Hg).

Our finding that low baseline SBP is accompanied by increased risk of serious heart failure outcomes have previously been reported in several registries (12) and trials such as PARADIGM-HF (13) and DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) (14) involving patients with chronic heart failure. Progression of renal function decline according to SBP with a nadir of 120 to 130 mm Hg has been observed in hypertension (15) as well as in secondary prevention (16). However, we found that renal function declined by ~2 mL/min/1.73 m^2 per year on placebo irrespective of blood pressure.

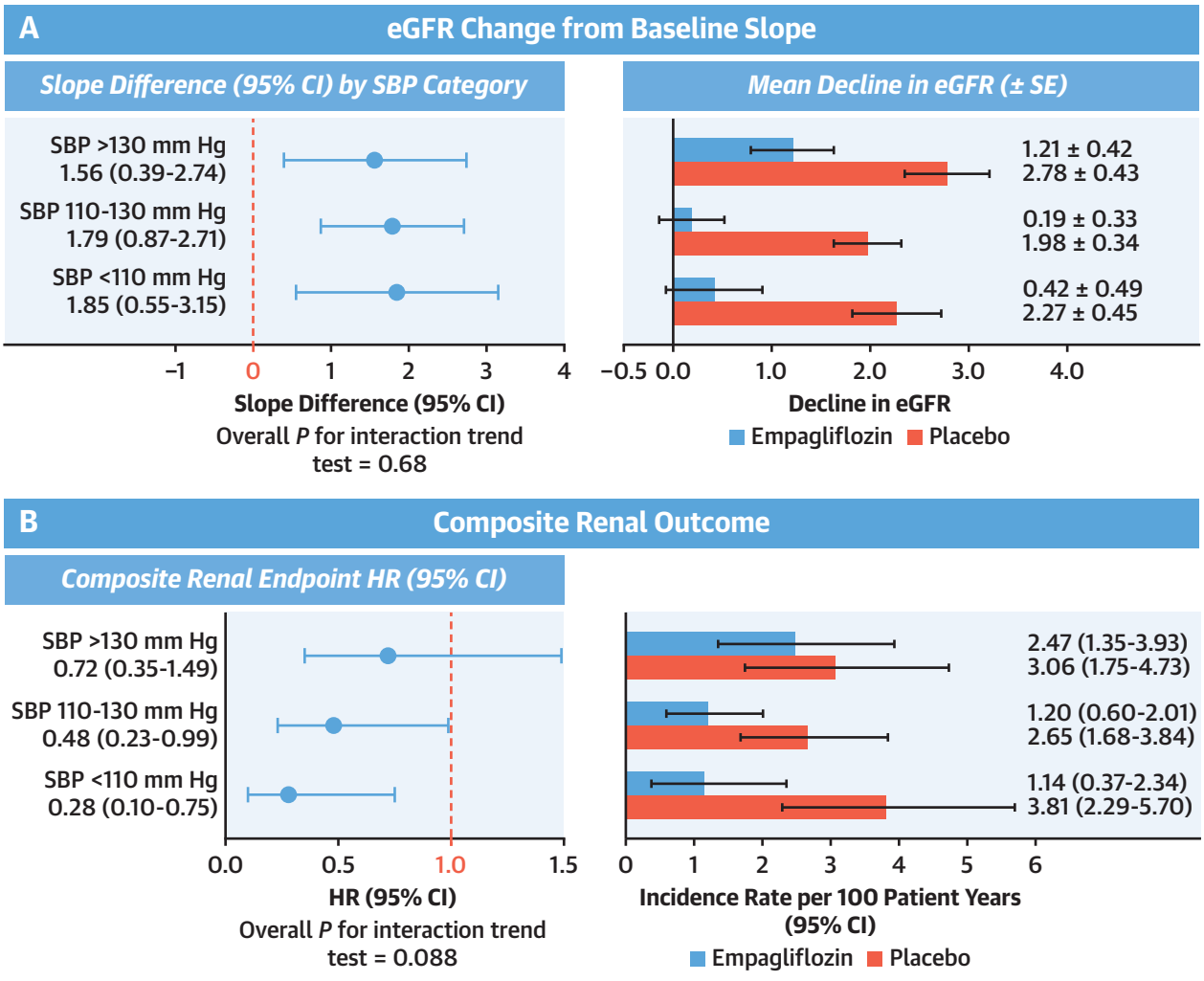
Empagliflozin reduced the risk of heart failure outcomes independently of baseline SBP and SBP during the trial. DAPA-HF assessed the effects of dapagliflozin on heart failure outcomes and mortality across 4 baseline SBP categories and adjusted for updated mean SBP, and found results similar to ours (14). We extend the findings from DAPA-HF by also reporting renal effects according to SBP: baseline SBP did not influence the reduction in renal function decline by empagliflozin. Moreover, we observed a consistent reduction in renal composite events across baseline SBP. The effects of empagliflozin on the eGFR slope, on the change in eGFR from baseline to off-treatment, and the renal composite endpoints were concordant and were not different between the SBP subgroups. In prespecified analyses, it was already shown that consistent effects on cardiorenal outcomes in EMPEROR-Reduced were observed in patients with or without chronic kidney disease (eGFR >60 mL/min/1.73 m^2 and eGFR ≤60 mL/min/1.73 m^2) (17) and with or without diabetes (18). Here, we extend these results by showing that SBP is not an effect modifier for the cardiorenal effects of empagliflozin.

FIGURE 2 Treatment Effects According to Baseline SBP



Hazard ratios (HRs) **(left)**, incidence rate per 100 patient years **(middle),** and HRs modeled as a continuous variable **(right)** for empagliflozin compared with placebo according to baseline SBP for the primary outcome (composite of heart failure hospitalization or cardiovascular death) **(A)** and first and recurrent heart failure hospitalization **(B)**. IR = incidence rate per 100 patient years; other abbreviations as in Figure 1.

FIGURE 3 eGFR Change From Baseline According to Baseline SBP



Effect of empagliflozin compared with placebo on slope of change in estimated glomerular filtration rate (eGFR) (adjusted mean differences, mL/min/1.73 m^2/year) **(left)** and mean eGFR declines **(right) (A)** and the effect of empagliflozin compared with placebo on the risk of the composite renal outcomes (chronic dialysis, renal transplant, 40% sustained decrease in eGFR or a sustained eGFR <15 mL/min/1.73 m^2 [if baseline eGFR ≥30 mL/min/1.73 m^2] or <10 mL/min/1.73 m^2 [if baseline eGFR <30 mL/min/1.73 m^2]) **(left)** and incidence rates **(right) (B)**. eGFR was calculated by using the Chronic Kidney Disease Epidemiology Collaboration equation. Abbreviations as in Figures 1 and 2.

This is important, as EMPEROR-Reduced included patients with eGFR as low as 20 mL/min/1.73 m^2 and SBP as low as 100 mm Hg at baseline, thus involving subgroups of more vulnerable patients. Similar consistent reductions in renal events across SBP categories were already reported with canagliflozin in patients with type 2 diabetes and chronic kidney disease in the CREDENCE (Canagliflozin and Renal Events in Diabetes and Nephropathy Clinical Evaluation) trial (19), but the lowest SBP category included in those analyses was <130 mm Hg. Thus, we extend the evidence for the use of SGLT2 inhibitors to patients

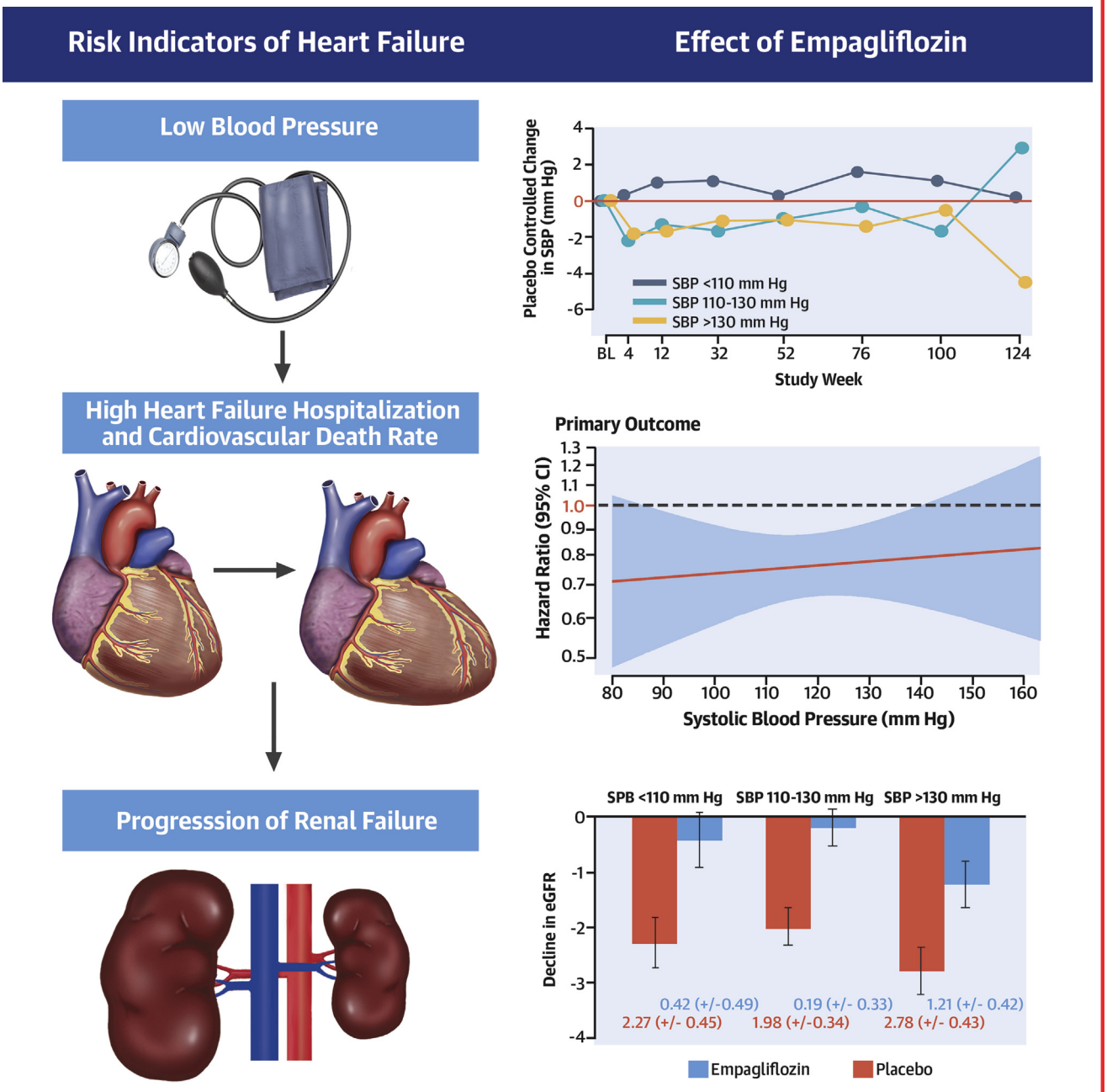
TABLE 3 Change in eGFR From Baseline to Off-Treatment

SBP Group	Adjusted Change From Baseline, Mean ± SE		Adjusted Mean (95% CI) Treatment Comparison At Follow-Up	*P* Value
	Placebo	Empagliflozin		
<110 mm Hg	-4.4 ± 1.1	-1.6 ± 1.1	2.8 (-0.2 to 5.9)	0.0690
110-130 mm Hg	-4.1 ± 0.8	0.2 ± 0.8	4.3 (2.1 to 6.5)	0.0001
>130 mm Hg	-4.3 ± 1.0	-2.1 ± 0.9	2.1 (-0.5 to 4.8)	0.1112

P for interaction = 0.63. Based on analysis of covariance with the following factors: baseline eGFR (according to the Chronic Kidney Disease Epidemiology Collaboration equation) (continuous), age (continuous), region, sex, left ventricular ejection fraction (categorical), baseline diabetes status, baseline SBP (categorical), treatment, and baseline SBP*treatment interaction.

Abbreviations as in Table 1.

CENTRAL ILLUSTRATION **Effect of Empagliflozin on Blood Pressure and Outcomes**



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Placebo-corrected effect of empagliflozin on systolic blood pressure (SBP) according to baseline SBP **(top)**, effect of empagliflozin on the primary outcome over the spectrum of baseline SBP **(middle)**, and effect of empagliflozin and placebo on decline of estimated glomerular filtration rate according to baseline SBP **(bottom)**.

with heart failure and reduced ejection fraction with SBP <110 mm Hg, showing a benefit also in terms of a reduction in serious adverse renal events.

In patients receiving placebo, we observed a slight initial increase of SBP in the low SBP group and a slight initial decline of SBP in patients with high SBP at baseline, followed by stabilization in both groups. This phenomenon has been shown previously in heart failure trials (13,20-23) and may suggest regression to the mean. However, it is noteworthy that, during the first 4 to 12 weeks, empagliflozin produced a slight increase in SBP in patients with a SBP <110 mm Hg and a slight decrease in SBP in those with a SBP >130 mm Hg (*P* for interaction trend = 0.06-0.07), with little change in SBP thereafter. Changes in SBP postrandomization did not influence the effect of empagliflozin on the primary endpoint, suggesting that empagliflozin does not produce its benefits on heart failure events through an effect to reduce SBP. One might speculate that the slight increase on empagliflozin compared with placebo could reflect an improvement of the heart failure syndrome.

We observed that baseline SBP did not influence the magnitude of the effect of empagliflozin to reduce the risk of cardiovascular death or hospitalization for heart failure. The hazard ratio in patients with SBP <110 mm Hg was 0.78, similar to the effect seen in the overall trial (0.75). However, because patients with SBP <110 mm Hg represent a high-risk subgroup, the absolute risk reduction with empagliflozin in patients with SBP <110 mm Hg tended to be greater than in patients with SBP >130 mm Hg. Because patients with SBP <110 mm Hg did not experience a decline in SBP or an increased risk of hypotension or symptomatic hypotension with empagliflozin, the benefit-to-risk relationship for empagliflozin would seem to be particularly favorable in patients with SBP <110 mm Hg. These observations are relevant, as physicians are often reluctant to initiate treatment with outcome-modifying drugs in patients with heart failure whose SBP is low (24).

STUDY LIMITATIONS. The major limitation of our analysis is that the results are confined to those patients who did not meet exclusion criteria such as an eGFR <20 mL/min/1.73 m^2, symptomatic hypotension, or an SBP <100 mm Hg, as these patients were not included in the EMPEROR-Reduced trial.

CONCLUSIONS

We confirmed in our analysis that patients with heart failure with reduced ejection fraction and low SBP (ie, <110 mm Hg) had the highest risk of heart failure outcomes. Empagliflozin reduced the risk of heart failure and renal outcomes independently of baseline SBP. Patients in the low SBP group tolerated empagliflozin treatment well and experienced no decline in SBP and no increased rates of symptomatic hypotension (**Central Illustration**).

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ADDRESS FOR CORRESPONDENCE: Dr Michael Böhm, Universitätsklinikum des Saarlandes, Klinik für Innere Medizin III, Saarland University, Kardiologie, Angiologie und Internistische Intensivmedizin, Kirrberger Str. 1, 66421 Homburg/Saar, Germany. E-mail: michael.boehm@uks.eu. Twitter: @FelixMahfoud.

PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: In patients with heart failure and reduced left ventricular ejection fraction, empagliflozin reduces major adverse cardiovascular outcomes and preserves renal function independently of SBP.

TRANSLATIONAL OUTLOOK: Additional studies are required to elucidate the role of empagliflozin in high-risk patients with heart failure and reduced ejection fraction.

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