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## ORIGINAL RESEARCH

### HEART FAILURE

# Efficacy and Safety of Empagliflozin According to Background Diuretic Use in HFrEF



## Post-Hoc Analysis of EMPEROR-Reduced

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### ABSTRACT

**BACKGROUND** The EMPEROR-Reduced (EMPagliflozin outcome tRial in Patients With chrOnic hearT Failure With Reduced Ejection Fraction) trial established the efficacy of empagliflozin in reducing heart failure (HF) outcomes among patients with heart failure with reduced ejection fraction (HFrEF).

**OBJECTIVES** The authors examined the outcomes of EMPEROR-Reduced as a function of background diuretic therapy.

**METHODS** The EMPEROR-Reduced trial was a double-blind, randomized controlled trial of placebo vs empagliflozin 10 mg among 3,730 HFrEF patients. Herein, the population was stratified into 4 groups: no diuretic and diuretic dose equivalent to furosemide <40, 40, and >40 mg daily at baseline.

**RESULTS** A total of 3,656 patients from the EMPEROR-Reduced trial were available for analysis. Of those patients, 482 (13.2%) were receiving no diuretic therapy, and 731 (20.0%), 1,411 (38.6%), and 1,032 (28.2%) were receiving <40 mg, 40 mg, and >40 mg, respectively. The efficacy of empagliflozin on the primary outcome (time to first event of hospitalization for HF or cardiovascular [CV] death) was consistent regardless of background diuretic therapy (>40 mg: HR: 0.88 [95% CI: 0.71-1.10]; 40 mg: HR: 0.65 [95% CI: 0.51-0.82]; <40 mg: HR: 0.65 [95% CI: 0.46-0.92]); no diuretic agents: HR: 0.78 [95% CI: 0.47-1.29];  $P_{\text{trend test}} = 0.192$ ). Baseline diuretic doses did not influence the effect of empagliflozin on body weight, systolic blood pressure, NT-proBNP, or hematocrit at 52 weeks. The safety profile of empagliflozin vs placebo was unaffected by baseline diuretic dose; however, independently of treatment allocation, total rates of adverse events were higher among patients with higher baseline doses of diuretic agents.

**CONCLUSIONS** Empagliflozin exhibits a consistent effect on time to CV death or HF hospitalization and an unaltered safety profile regardless of baseline diuretic therapy. (EMPagliflozin outcome tRial in Patients With chrOnic hearT Failure With Reduced Ejection Fraction [EMPEROR-Reduced]; [NCT03057977](https://doi.org/10.1016/j.jchf.2023.06.036)) (J Am Coll Cardiol HF 2024;12:35-46) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

## ABBREVIATIONS AND ACRONYMS

**CKD** = chronic kidney disease

**CV** = cardiovascular

**eGFR** = estimated glomerular filtration rate

**HF** = heart failure

**HFrEF** = heart failure with reduced ejection fraction

**KCCQ** = Kansas City Cardiomyopathy Questionnaire

**MMRM** = mixed model with repeated measures

**MRA** = mineralocorticoid receptor antagonist

**NT-proBNP** = N-terminal pro-B-type natriuretic peptide

**SGLT2** = sodium glucose co-transporter 2

In patients with heart failure with reduced ejection fraction (HFrEF), the sodium glucose co-transporter 2 (SGLT2) inhibitors empagliflozin and dapagliflozin reduce the rates of cardiovascular (CV) death or heart failure (HF) hospitalization by about 25%.<sup>1-4</sup> These benefits are observed independently of glycemic status<sup>5,6</sup> and down to an eGFR of 20 mL/min/1.73 m<sup>2</sup>. These data have led to changes in the clinical practice guidelines that now recommend SGLT2 inhibitors as a Class I indication in HFrEF.<sup>7-10</sup>

Although SGLT2 inhibitors have been suggested to promote diuresis and natriuresis, this effect is short-lived and likely not a significant mechanistic component of their long-term protective effects on cardiorenal outcomes.<sup>11-13</sup> Nevertheless, given that patients with HFrEF are often prescribed diuretic agents for sign and symptom control, understanding whether the clinical efficacy of SGLT2 inhibitors varies by baseline use and intensity of diuretic agents is an important and unanswered question that we address in this post hoc analysis from the EMPEROR-Reduced (EMPagliflozin outcome tRIal in Patients With chrOnic hearT Failure With Reduced Ejection Fraction) trial.

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## METHODS

**TRIAL DESIGN.** The design and methods of the EMPEROR-Reduced trial have been previously reported.<sup>1,14</sup> To summarize, patients with HFrEF  $\leq 40\%$  and NYHA functional class II-IV symptoms were

randomized in a double-blind fashion to the addition of either empagliflozin 10 mg daily or placebo to existing guideline-directed therapy. Inclusion furthermore required an N-terminal pro-B-type natriuretic peptide (NT-proBNP) of  $\geq 600$ , 1,000, and 2,500 pg/mL for patients with an ejection fraction  $\leq 30\%$ , 31%-35%, and 36%-40%, respectively. The only exception was patients who had been hospitalized within 12 months, for whom an NT-proBNP threshold of  $\geq 600$  pg/mL was used regardless of ejection fraction. For patients with atrial fibrillation, the aforementioned thresholds were doubled to 1,200, 2,000, and 5,000 pg/mL. Symptomatic hypotension and/or a systolic blood pressure  $< 100$  mm Hg and estimated glomerular filtration rate (eGFR)  $< 20$  mL/min/1.73 m<sup>2</sup> represented the key exclusion criteria. Individual physicians had discretion to modify background HF therapy as indicated throughout the duration of the trial.

**STUDY OUTCOMES.** EMPEROR-Reduced was adjudicated using a composite primary endpoint of time-to-first of hospitalization for HF or CV death. Key secondary outcomes assessed in the primary investigation, as well as in the current subanalysis, include total hospitalizations for HF (first and recurrent), components of the primary outcome, and time to all-cause mortality. Patient-reported health status was assessed with the Kansas City Cardiomyopathy Questionnaire (KCCQ). Finally, other outcomes of interest including changes in body weight, blood pressure, NT-proBNP levels, hematocrit, and adverse outcomes were collected throughout the study follow-up.

**DIURETIC SUBGROUPS.** The purpose of the present subanalysis was to assess the potential modification

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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](#).

**TABLE 1 Diuretic Agent Dose Equivalents**

Furosemide Doses	Equivalents
Furosemide 40 mg IV or 80 mg PO	Bumetanide 1 mg Torseamide 20 mg Azoseamide 60 mg Etacrynic acid 100 mg

If not taking a loop diuretic, dose was considered 0 mg (ie, patients taking a nonloop diuretic agent only were included in the <40 mg group). MRA was not classified as a diuretic agent.  
 IV = intravenous; MRA = mineralocorticoid receptor antagonists; PO = per oreum (orally).

of empagliflozin’s efficacy and safety based on background diuretic therapy. In particular, randomized patients were divided into 4 major groups based on their baseline diuretic use: no diuretic therapy, and oral furosemide-equivalent daily doses of <40 mg, 40 mg, or >40 mg. **Table 1** demonstrates the diuretic dose equivalents considered in this study, which were determined on the basis of previous published reports;<sup>15,16</sup> doses for nonloop diuretic agents were considered 0 mg (ie, <40 mg), and mineralocorticoid receptor antagonists (MRAs) were not considered diuretic agents for the purposes of this investigation. Changes made to diuretic dosage during the investigation were documented throughout the trial.

**STATISTICAL ANALYSIS.** Baseline characteristics per furosemide equivalence dose of diuretic agents (no diuretic, <40 mg, 40 mg, and >40 mg) were presented descriptively using post hoc analyses with an ordinal regression likelihood ratio test to evaluate whether there is a linear trend across categories. Time-to-event analyses were performed using a multivariable Cox proportional hazards model to derive HR and 95% CI. Total (first and recurrent) hospitalizations endpoint was analyzed with a joint frailty model together with CV death to obtain HR and 95% CI. Both multivariable models included the following baseline characteristics as covariates: left ventricular ejection fraction (LVEF), age, sex, eGFR, diabetes status, and region. Endpoints related to change in diuretic agents therapy were analyzed as time-to-first occurrence of the event of interest. For changes in KCCQ scores and physiological outcomes analyses, mixed model with repeated measures (MMRM) was used. This MMRM model included age and baseline eGFR as linear covariates and sex, baseline LVEF, region, diabetes status at baseline, visit by treatment by baseline diuretic agents interaction, and baseline value by visit interaction as fixed effects.

The treatment effect of empagliflozin (compared with placebo) by diuretic agents therapy was assessed

for each outcome; therefore, the subgroup of diuretic agents use or dose and all necessary interactions were added to the model, where applicable. HRs and mean differences were compared across subgroups by adding *P* value for trend across all subgroups. Values of *P* < 0.05 are described as significant; *P* values and 95% CIs presented here were not adjusted for multiplicity. All analyses were performed with SAS version 9.4 (SAS Institute).

**STUDY APPROVAL.** Written informed consent was obtained from all patients included in this trial. Approval for the trial was received from each trial center’s respective ethics committee. Boehringer Ingelheim and Eli Lilly were the sponsors of the trial.

**RESULTS**

**BASELINE CHARACTERISTICS.** A total of 3,656 patients from the EMPEROR-Reduced trial were available for analysis. **Table 2** presents their demographics and clinical characteristics according to baseline diuretic dosage. Of the studied patients, 482 (13.2%) were receiving no diuretic therapy, 731 (20.0%) were receiving <40 mg, 1,411 (38.6%) were receiving 40 mg, and 1,032 (28.2%) were receiving >40 mg furosemide equivalent dose. The majority of patients receiving diuretic agents were receiving loop diuretic agents only (>40 mg: 898 [87.0%]; 40 mg: 1,286 [91.1%]; <40 mg: 593 [81.1%], and the median furosemide equivalent doses at baseline were 80.0 mg, 40.0 mg, and 20.0 mg, in the >40 mg, 40 mg, and <40 mg groups, respectively.

Broadly, patients prescribed higher diuretic doses at baselines had more advanced clinical HF syndromes. This manifested as higher baseline median NT-pro-BNP levels (>40 mg: 2,175 [IQR: 1,335-4,386]; 40 mg: 1,926 [IQR: 1,101-3,450]; <40 mg: 1,714 [IQR: 1,072-3,106]; no diuretic agents: (1,555 [IQR: 940-2,636]), higher rates of hospitalization for HF in the previous 12 months (>40 mg: 410 [39.7%]; 40 mg: 406 [28.8%]; <40 mg: 211 [28.9%]; no diuretic agents: 97 [20.1%]), and worse baseline KCCQ-CSS scores: median (IQR) (>40 mg: 67.7 [IQR: 49.0-83.6]; 40 mg: 72.9 [IQR: 53.6-89.3]; <40 mg: 81.0 [IQR: 66.4-91.7]; no diuretic agents: 82.3 [IQR: 63.0-92.7]). These patients also tended to have higher rates of diabetes (>40 mg: 618 [59.9%], 40 mg: 693 [49.1%], <40 mg: 318 [43.5%], no diuretic agents: 196 [40.7%]) and chronic kidney disease (CKD) (>40 mg: 658 [63.8%]; 40 mg: 730 [51.7%]; <40 mg: 361 [49.4%]; no diuretic agents: 188 [39.0%]). Baseline eGFR was lower among patients taking higher doses of diuretic agents (>40 mg:

**TABLE 2 Baseline Characteristics by Baseline Diuretic Agent Dose**

	No Diuretic Agent (n = 482)	<40 mg Equivalents (n = 731)	=40 mg Equivalents (n = 1,411)	>40 mg Equivalents (n = 1,032)	P <sub>trend test</sub>
<b>Demographics</b>					
Female	133 (27.6)	170 (23.3)	351 (24.9)	220 (21.3)	0.027
<b>Race/ethnicity</b>					
White	344 (71.4)	409 (56.0)	1,051 (74.5)	767 (74.3)	<0.001
Black/African American	29 (6.0)	29 (4.0)	106 (7.5)	90 (8.7)	
Asian	78 (16.2)	269 (36.8)	187 (13.3)	127 (12.3)	
Other including mixed race	24 (5.0)	19 (2.6)	54 (3.8)	17 (1.6)	
Missing	7 (1.5)	5 (0.7)	13 (0.9)	31 (3.0)	
<b>Region</b>					
North America	61 (12.7)	81 (11.1)	135 (9.6)	122 (11.8)	<0.001
Latin America	210 (43.6)	169 (23.1)	629 (44.6)	269 (26.1)	
Europe	129 (26.8)	212 (29.0)	464 (32.9)	520 (50.4)	
Asia	57 (11.8)	217 (29.7)	132 (9.4)	80 (7.8)	
Other	25 (5.2)	52 (7.1)	51 (3.6)	41 (4.0)	
Age, y	68.0 (60.0-74.0)	69.0 (62.0-77.0)	68.0 (60.0-75.0)	68.0 (59.0-75.0)	0.405
<b>Baseline heart failure metrics</b>					
LVEF, %	28.1 ± 5.6	28.3 ± 5.8	27.3 ± 6.1	26.8 ± 6.2	<0.001
Baseline NT-pro-BNP, pg/mL	1,555.00 (940.00- 2,636.00)	1,714.00 (1,072.00- 3,106.00)	1,926.00 (1,101.00- 3,450.00)	2,175.00 (1,335.00- 4,385.50)	<0.001
Baseline SBP, mm Hg	124.1 ± 15.3	122.8 ± 16.4	122.2 ± 15.6	120.5 ± 15.3	<0.001
Baseline DBP, mm Hg	74.8 ± 10.9	73.8 ± 11.2	74.2 ± 10.5	73.3 ± 10.7	0.028
Baseline weight, kg	75.37 ± 17.41	73.95 ± 18.10	79.41 ± 18.26	82.61 ± 18.77	<0.001
Baseline BMI, kg/m <sup>2</sup>	27.01 ± 5.01	26.42 ± 5.16	28.22 ± 5.43	28.79 ± 5.43	<0.001
History of hospitalization for HF in the past 12 mo	97 (20.1)	211 (28.9)	406 (28.8)	410 (39.7)	<0.001
Baseline hematocrit, %	42.7 ± 4.8	42.0 ± 4.9	42.2 ± 4.9	41.8 ± 5.2	0.017
Baseline diabetes	196 (40.7)	318 (43.5)	693 (49.1)	618 (59.9)	<0.001
Use of insulin <sup>a</sup>	34 (17.3)	56 (17.6)	167 (24.1)	207 (33.5)	<0.001
<b>NYHA functional class</b>					
II	398 (82.6)	591 (80.8)	1,088 (77.1)	673 (65.2)	<0.001
III	83 (17.2)	136 (18.6)	315 (22.3)	352 (34.1)	
IV	1 (0.2)	4 (0.5)	8 (0.6)	7 (0.7)	
<b>Cause of HF</b>					
Ischemic	241 (50.0)	362 (49.5)	700 (49.6)	585 (56.7)	0.002
Nonischemic	241 (50.0)	369 (50.5)	711 (50.4)	447 (43.3)	
Baseline KCCQ-TSS	85.4 (68.8-97.9)	83.3 (68.8-93.8)	77.1 (58.3-93.8)	74.0 (52.1-89.6)	<0.001
Baseline KCCQ-CSS	82.3 (63.0-92.7)	81.0 (66.4-91.7)	72.9 (53.6-89.3)	67.7 (49.0-83.6)	<0.001
Baseline KCCQ-OSS	78.6 (60.4-89.6)	76.0 (62.0-87.8)	69.0 (49.7-84.9)	64.8 (44.8-80.5)	<0.001
<b>Baseline renal metrics</b>					
Baseline eGFR, mL/min/1.73 m <sup>2</sup>	68.2 ± 19.9	63.9 ± 20.9	62.7 ± 21.8	57.0 ± 21.8	<0.001
Serum creatinine	99.6 ± 29.5	107.2 ± 33.9	110.9 ± 36.3	123.2 ± 41.1	<0.001
Prevalence of CKD at baseline (eGFR <60 mL/min/1.73 m <sup>2</sup> or UACR >300 mg/g)	188 (39.0)	361 (49.4)	730 (51.7)	658 (63.8)	<0.001

Continued on the next page

57.0 ± 21.8 mL/min/1.73 m<sup>2</sup>; 40 mg: 62.7 ± 21.8 mL/min/1.73 m<sup>2</sup>; <40 mg: 63.9 ± 20.9 mL/min/1.73 m<sup>2</sup>; no diuretic agents: 68.2 ± 19.9 mL/min/1.73 m<sup>2</sup>).

Similar rates of baseline use of guideline-directed medical therapies for HF<sub>rEF</sub> were recorded regardless of baseline diuretic dose, except for MRAs, which were prescribed more commonly among patients taking higher doses of diuretic agents (>40 mg: 760 [73.6%], 40 mg: 1,041 [73.8%], <40 mg: 509 [69.6%], no diuretic agents: 297 [61.6%]). There were higher rates of cardiac resynchronization therapy/

defibrillator use among patients with higher baseline diuretic doses (≥40 mg: 168 [16.3%], 40 mg: 122 [8.6%], <40 mg: 51 [7.0%], no diuretic agents: 28 [5.8%]).

**PRIMARY AND SECONDARY OUTCOME MEASURES.** The results of EMPEROR-Reduced stratified by background diuretic doses are displayed in [Figure 1](#). With respect to the primary outcome of time to first event of hospitalization for HF or CV death, a consistent benefit of empagliflozin was documented in all patients regardless of baseline diuretic dose (>40 mg

**TABLE 2 Continued**

	No Diuretic Agent (n = 482)	<40 mg Equivalents (n = 731)	=40 mg Equivalents (n = 1,411)	>40 mg Equivalents (n = 1,032)	<i>P</i> <sub>trend test</sub>
Baseline diuretic information, IV therapy, and volume status					
Frequency of patients receiving loop diuretic agents only	0 (0)	593 (81.1)	1,286 (91.1)	898 (87.0)	<0.001
Frequency of patients receiving nonloop diuretic agents only	0 (0)	98 (13.4)	0 (0)	0 (0)	<0.001
Frequency of patients receiving both loop and nonloop diuretic agents	0 (0)	40 (5.5)	125 (8.9)	134 (13.0)	<0.001
Use of furosemide without azosemide, bumetanide, and torsemide at baseline	0 (0)	487 (66.6)	1,149 (81.4)	654 (63.4)	<0.001
Furosemide equivalent dose at baseline in mg, median	NA	20.0	40.0	80.0	<0.001
IV therapy for HF during most recent hospitalization	109 (22.6)	196 (26.8)	422 (29.9)	428 (41.5)	<0.001
IV therapy for HF (other than during a hospital admission) during the year before visit 1	39 (8.1)	65 (8.9)	188 (13.3)	191 (18.5)	<0.001
Volume overloaded with edema or organ congestion 4 wks before visit	41 (8.5)	84 (11.5)	227 (16.1)	186 (18.0)	<0.001 <sup>b</sup>
Baseline HFrEF therapies					
Medical therapy					
ACEI/ARB/ARNI	434 (90.0)	644 (88.1)	1,254 (88.9)	897 (86.9)	0.126
BB	452 (93.8)	684 (93.6)	1,356 (96.1)	972 (94.2)	0.449
MRA	297 (61.6)	509 (69.6)	1,041 (73.8)	760 (73.6)	<0.001
ACEI/ARB/ARNI + BB/ivabradine	417 (86.5)	615 (84.1)	1,222 (86.6)	855 (82.8)	0.132
ACEI/ARB/ARNI + BB/ivabradine + MRA	260 (53.9)	442 (60.5)	905 (64.1)	651 (63.1)	0.002
Device therapy					
ICD	122 (25.3)	137 (18.7)	266 (18.9)	303 (29.4)	<0.001
CRT-D	28 (5.8)	51 (7.0)	122 (8.6)	168 (16.3)	<0.001
CRT-P	4 (0.8)	12 (1.6)	25 (1.8)	23 (2.2)	0.075

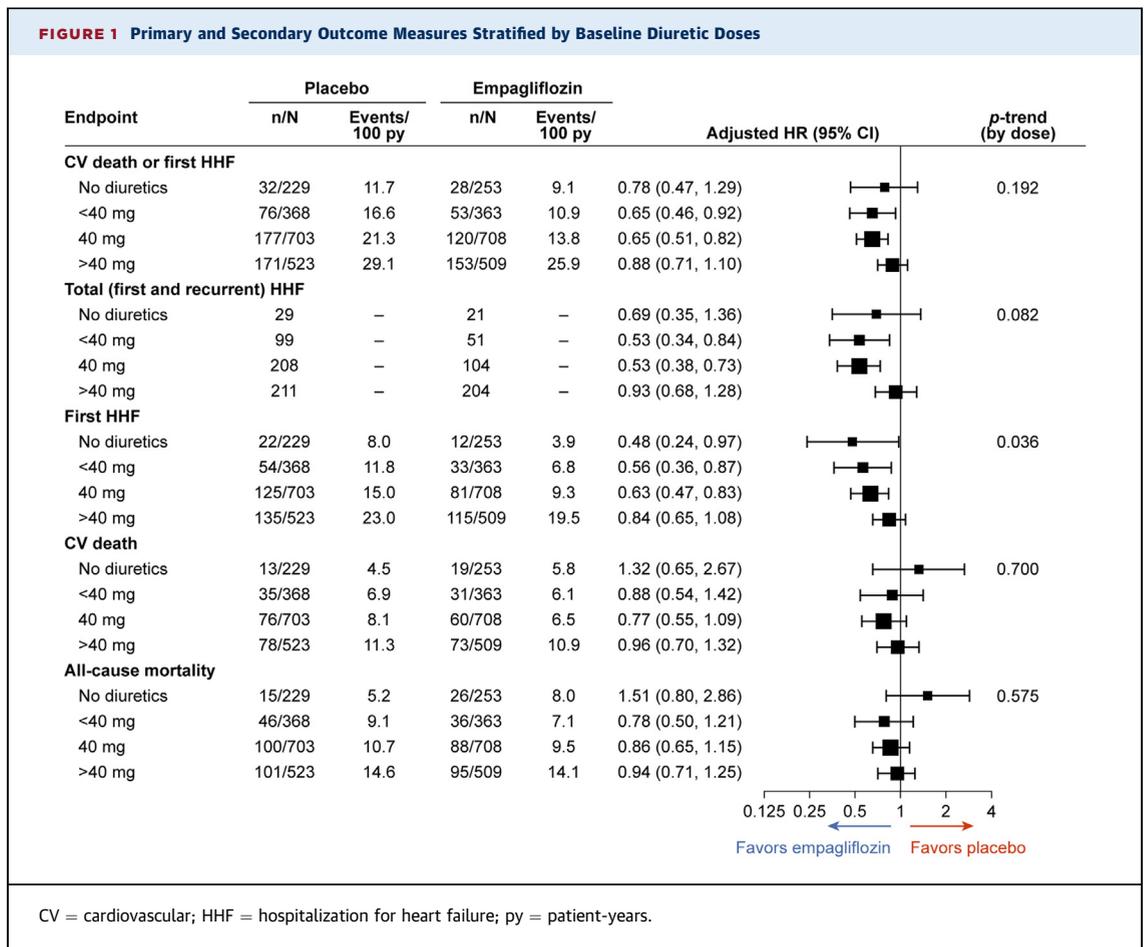
Values are n (%), mean ± SD, or median (Q1-Q3). <sup>a</sup>Percentages from diabetic patients at baseline. <sup>b</sup>*P*<sub>trend test</sub> included all possible answers in the case report form.

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; BB = beta-blocker; BMI = body mass index; CKD = chronic kidney disease; CRT-D = cardiac resynchronization therapy defibrillator; CRT-P = cardiac resynchronization therapy pacemaker; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; ICD = implantable cardioverter-defibrillator; IV = intravenous; KCCQ-CSS = Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score; KCCQ-OSS = Kansas City Cardiomyopathy Questionnaire-Overall Summary Score; KCCQ-TSS = Kansas City Cardiomyopathy Questionnaire-Total Symptom Score; LVEF = left ventricular ejection fraction; NA = not applicable; NT-pro-BNP = N-terminal pro-B type natriuretic peptide; Q1 = quartile 1; Q3 = quartile 3; SBP = systolic blood pressure; UACR = urine albumin-creatinine ratio; other abbreviation as in [Table 1](#).

[HR: 0.88; 95% CI: 0.71-1.10]; 40 mg [HR: 0.65; 95% CI: 0.51-0.82]; <40 mg: [HR: 0.65; 95% CI: 0.46-0.92]; no diuretic agents: [HR: 0.78; 95% CI: 0.47-1.29]; *P*<sub>trend test</sub> = 0.192) (**Central Illustration**). However, a trend toward diminished efficacy of empagliflozin among those receiving the highest doses of diuretic agents at baseline was documented for total (first and recurrent) hospitalizations for HF (>40 mg: [HR: 0.93; 95% CI: 0.68-1.28]; 40 mg: [HR: 0.53; 95% CI: 0.38-0.73]; <40 mg: [HR: 0.53; 95% CI: 0.34-0.84]; no diuretic agents: [HR: 0.69; 95% CI: 0.35-1.36]; *P*<sub>trend test</sub> = 0.082), with this trend reaching significance for time to first hospitalization for HF (>40 mg: [HR: 0.84; 95% CI: 0.65-1.08]; 40 mg: [HR: 0.63; 95% CI: 0.47-0.83]; <40 mg: [HR: 0.56; 95% CI: 0.36-0.87]; no diuretic agents: [HR: 0.48; 95% CI: 0.24-0.97]; *P*<sub>trend test</sub> = 0.036). In addition, a *P*<sub>interaction</sub> test was used to assess for subgroup differences, the results of which are shown in [Supplemental Table 1](#). Except that the difference in subgroups for time to first hospitalization for HF no longer reached

statistical significance (*P*<sub>interaction</sub> = 0.202), there were no changes in the interpretation of the results. Given the potential attenuation, an analysis was conducted with patients using the highest doses of diuretic agents further stratified into those with a diuretic dose equivalent >80 mg and those with a diuretic dose equivalent >40 mg but ≤80 mg ([Supplemental Table 2](#)). For outcomes related to hospitalization for HF, the HRs were lower for patients with a diuretic dose equivalent >80 mg than for those with a diuretic dose equivalent >40 mg but ≤80 mg (total hospitalizations for HF: >40 mg and ≤80 mg: [HR: 0.96; 95% CI: 0.64-1.45]; >80 mg: [HR: 0.89; 95% CI: 0.54-1.46]; and time to first hospitalization for HF: >40 mg and ≤80 mg: [HR: 0.87; 95% CI: 0.62-1.21]; >80 mg: [HR: 0.77; 95% CI: 0.53-1.13]). The statistical tests for heterogeneity across subgroups did not materially change with the addition of the fifth subgroup.

**KCCQ AND OTHER CLINICAL OUTCOMES.** [Table 3](#) details the KCCQ results according to diuretic dose subgroups and randomized therapy at 12 weeks and

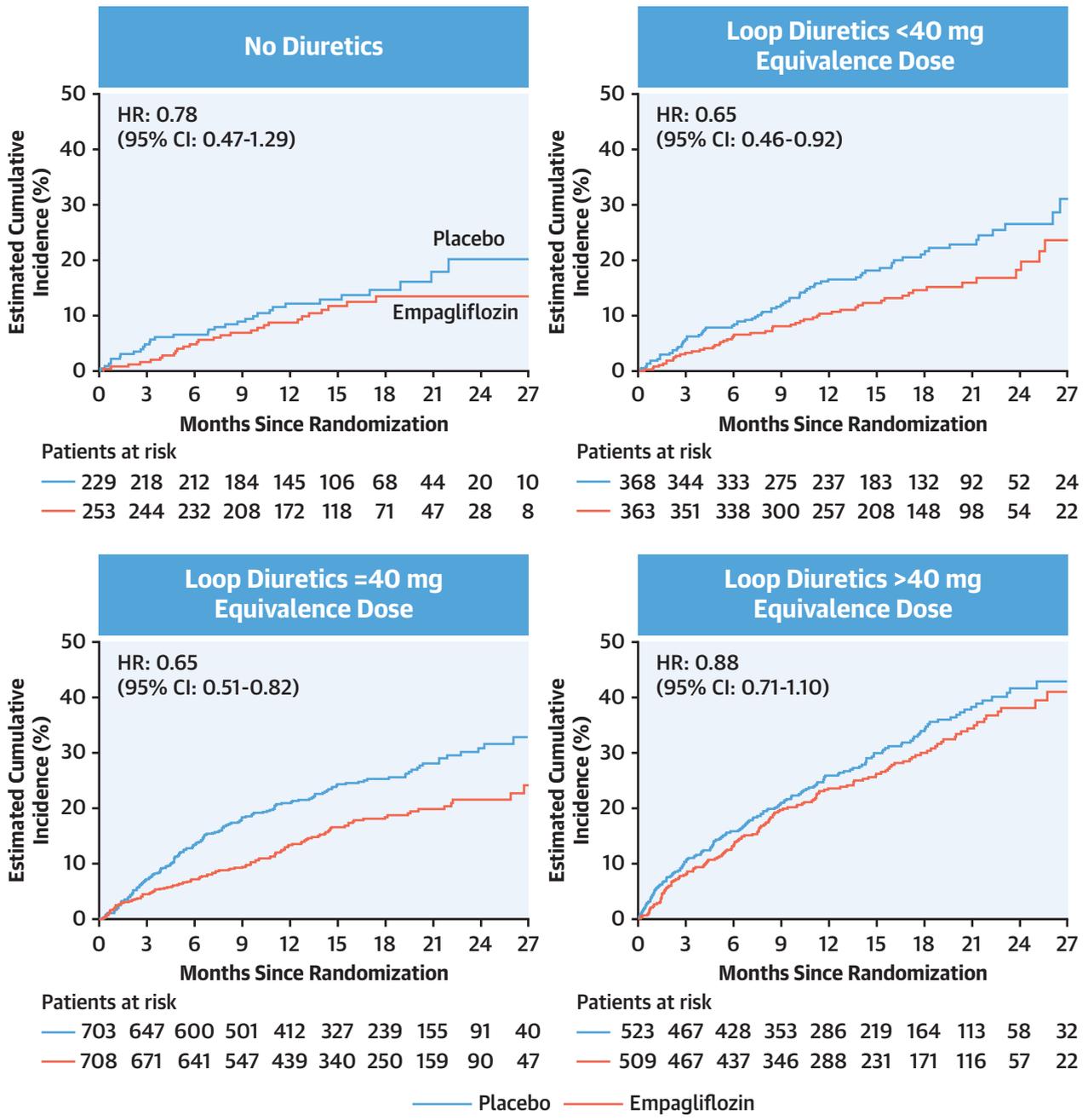


52 weeks. The treatment effect of empagliflozin in improving KCCQ scores was similar regardless of baseline diuretic doses. Similarly, as shown in [Supplemental Table 3](#), there was no influence of baseline diuretic doses on the effect of empagliflozin on systolic blood pressure, NT-proBNP, or hematocrit at week 12 and week 52. Patients taking higher doses of diuretic agents had smaller decreases in body weight with empagliflozin vs placebo after 12 weeks of treatment; the statistical significance of this trend disappeared at 52 weeks. Patients taking lower doses of diuretic agents had more profound decreases in uric acid levels with empagliflozin vs placebo at 52 weeks compared with those taking higher doses of diuretic agents ( $P_{\text{trend test}} = 0.026$ ).

**CHANGE IN DIURETIC AGENT DOSING.** Empagliflozin lengthened the time to first diuretic dose increase in all patients taking diuretic agents at baseline (HR: 0.68 [95% CI: 0.58-0.80];  $P < 0.001$ ), with a suggestion of reduced efficacy for those taking the highest doses of diuretic agents at baseline (>40 mg: [HR: 0.85; 95% CI: 0.66-1.08]; 40 mg: [HR: 0.58;

95% CI: 0.44-0.76]; <40 mg: [HR: 0.59; 95% CI: 0.43-0.83];  $P_{\text{trend test}} = 0.054$ ) ([Figure 2](#), [Supplemental Figure 1](#)). Similarly, time to diuretic initiation among patients taking no diuretic agents at baseline was lengthened with randomization to empagliflozin (HR: 0.62 [95% CI: 0.44-0.88];  $P < 0.01$ ) ([Figure 2](#), [Supplemental Figure 2](#)). Although no difference was seen between empagliflozin and placebo groups in all patients taking diuretic agents at baseline for time to first discontinuation of diuretic agents (HR: 0.86 [95% CI: 0.69-1.07];  $P = 0.183$ ) or time to permanent discontinuation of diuretic agents (HR: 1.24 [95% CI: 0.91-1.68];  $P = 0.171$ ) patients taking a furosemide-equivalent dose <40 mg randomized to empagliflozin had an increased likelihood of diuretic discontinuation (both in time to first and permanent discontinuation) compared with placebo: Time to first discontinuation: >40 mg: (HR: 0.84; 95% CI: 0.57-1.23); 40 mg: (HR: 0.59; 95% CI: 0.41-0.84); <40 mg: (HR: 1.55; 95% CI: 1.01-2.37); ( $P_{\text{trend test}} = 0.040$ ); and Time to permanent discontinuation: >40 mg: (HR: 1.17; 95% CI: 0.66-2.07); 40 mg: (HR: 0.74; 95% CI:

**CENTRAL ILLUSTRATION** Time to Primary Outcome Measure Stratified by Baseline Diuretic Agent Doses in EMPEROR-Reduced



P trend across diuretic dose groups: 0.192

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A consistent effect of empagliflozin on time to heart failure hospitalization or cardiovascular death was documented irrespective of baseline diuretic agent doses.

**TABLE 3 KCCQ Outcomes Stratified by Diuretic Agent Doses**

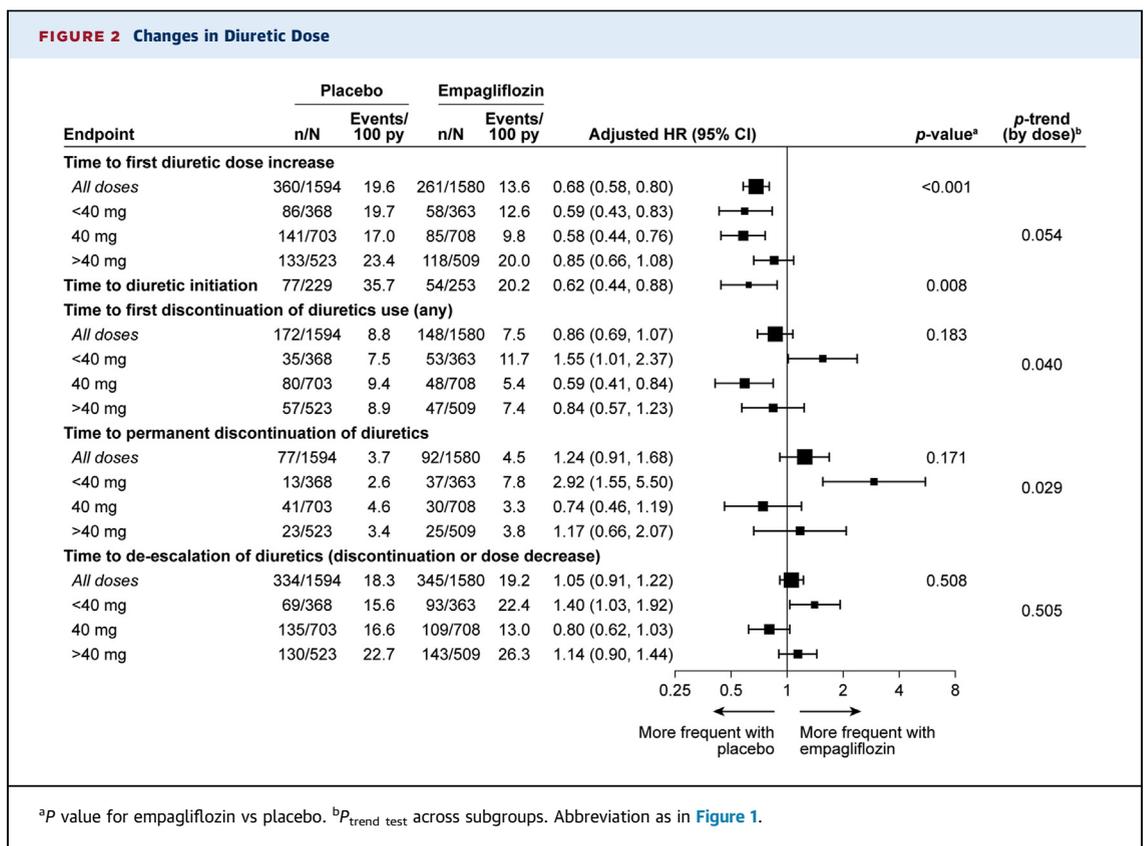
Time Point	Empagliflozin vs Placebo				$P_{\text{trend test Across All Subgroups}}$
	No Diuretic Agents	<40 mg Equivalents	40 mg Equivalents	>40 mg Equivalents	
KCCQ-CSS adjusted mean difference to placebo (95% CI)					
12 wks	2.15 (−0.58 to 4.89)	1.35 (−0.86 to 3.56)	2.66 (1.05 to 4.26)	1.36 (−0.52 to 3.25)	0.841
52 wks	1.85 (−1.52 to 5.21)	2.26 (−0.43 to 4.95)	1.83 (−0.17 to 3.84)	0.63 (−1.75 to 3.01)	0.431
KCCQ-TSS adjusted mean difference to placebo (95% CI)					
12 wks	3.21 (0.24 to 6.17)	2.29 (−0.10 to 4.68)	3.05 (1.31 to 4.79)	1.72 (−0.33 to 3.76)	0.517
52 wks	2.52 (−1.03 to 6.07)	1.90 (−0.94 to 4.73)	1.97 (−0.15 to 4.08)	0.37 (−2.14 to 2.89)	0.315

Abbreviations as in Table 2.

0.46-1.19); <40 mg: (HR: 2.92; 95% CI: 1.55-5.50); ( $P_{\text{trend test}} = 0.029$ ). There was no benefit of empagliflozin compared with placebo on time to diuretic de-escalation (discontinuation or dose decrease) among all patients taking diuretic agents at baseline (HR: 1.05 [95% CI: 0.91-1.22];  $P = 0.508$ ), nor within each subgroup (Figure 2).

**SAFETY.** Regardless of randomization to empagliflozin or placebo, patients with higher baseline diuretic doses experienced higher total rates of

adverse events: >40 mg: 447 (85.8%) with placebo, 422 (82.9%) with empagliflozin; 40 mg: 541 (77.0%) with placebo, 516 (72.9%) with empagliflozin; <40 mg: 276 (75.2%) with placebo, 278 (76.6%) with empagliflozin; no diuretic agents: 168 (73.7%) with placebo, 181 (71.5%) with empagliflozin. Similarly, patients taking the highest baseline doses of diuretic agents also had higher rates of adverse events leading to treatment discontinuation compared with patients taking lower doses of diuretic agents, irrespective of



randomized therapy: >40 mg: 121 (23.2%) with placebo, 124 (24.4%) with empagliflozin; 40 mg: 116 (16.5%) with placebo, 112 (15.8%) with empagliflozin; <40 mg: 56 (15.3%) with placebo, 46 (12.7%) with empagliflozin; no diuretic agents: 30 (13.2%) with placebo, 36 (14.2%) with empagliflozin. However, rates of acute kidney injury, volume depletion, hypotension, hyperkalemia, genital infections, and confirmed hypoglycemia were similar across diuretic subgroups in the placebo and empagliflozin groups, and there was no ketoacidosis in any group, as shown in [Supplemental Table 4](#).

## DISCUSSION

The present subanalysis of the EMPEROR-Reduced trial has 3 central findings. First, as expected, patients taking higher baseline diuretic doses have considerably more advanced HF syndromes, manifesting as higher baseline NT-pro-BNP levels, higher rates of recent HF hospitalization, and worse baseline KCCQ scores. Second, empagliflozin demonstrated a consistent benefit on the primary composite outcome of HF hospitalization or CV death in patients across the spectrum of furosemide equivalent doses studied. For the outcomes of time to first and total HF hospitalizations, there was a suggestion of potential attenuation of the efficacy of empagliflozin in patients receiving the highest doses of diuretic agents. Third, empagliflozin exhibited a diuretic-sparing effect, delaying the time to first diuretic dose increase (in all except those taking the highest doses of diuretic agents) and diuretic initiation (in those not taking diuretic agents at baseline). Patients taking the lowest doses of diuretic agents randomized to empagliflozin also had an increased likelihood of diuretic discontinuation. The present findings of a consistency of effect of empagliflozin on the primary outcome of CV death or HF hospitalization in HFrEF irrespective of baseline diuretic doses mirrors previous findings from DAPA-HF (Dapagliflozin in Patients With Heart Failure and Reduced Ejection Fraction).<sup>16</sup> However, unlike the analysis from DAPA-HF, in which total HF hospitalization rates and time to first HF hospitalization were not assessed, this analysis also demonstrates a potential attenuated efficacy of empagliflozin on HF hospitalizations among patients taking the highest doses of diuretic agents. Although this interaction was nominally significant only for the time to first HF hospitalization, multiple theories could explain this effect.

First, this finding could be the result of important differences between baseline diuretic groups that may have modulated the efficacy of empagliflozin. As

mentioned earlier, patients taking higher doses of diuretic agents at baseline had higher rates of comorbidities. These differences could have confounded the results, given that the relevant HRs reported here were adjusted for only 6 covariates. Similarly, this attenuation could be a product of the more advanced clinical HF syndromes seen in patients with higher baseline doses of diuretic agents, with the more severe stages of disease being harder to modify. It should be highlighted that compared with DAPA-HF, the EMPEROR-Reduced population was enriched with patients with more advanced HF syndromes, given the NT-proBNP inclusion criteria, which could explain why an attenuation was seen in the present analysis but not in the corresponding analysis with dapagliflozin.<sup>1,2</sup> However, this theory is less likely, considering that previous published reports have extensively documented empagliflozin's consistent benefit in HFrEF across various subgroups, with concordant efficacy being demonstrated regardless of diabetes,<sup>5</sup> ejection fraction from <25% to <65%,<sup>17</sup> eGFR,<sup>18</sup> baseline NT-proBNP,<sup>19</sup> KCCQ scores,<sup>20</sup> and background foundational therapies.<sup>21</sup> Second, the possible attenuation of effect could theoretically be a result of mechanistic overlap, with high pre-existing loop diuretic use leading to a dampening of the osmotic diuretic effects of empagliflozin.<sup>22,23</sup> However, clinical and experimental studies have been unable to demonstrate a long-term diuretic effect associated with SGLT2 inhibitors,<sup>24</sup> likely as a result of renal adaptation leading to maintained volume and sodium balance.<sup>25</sup> Indeed, although some studies have shown increases in fractional glucose excretion and plasma osmolality after 30 days of treatment,<sup>22</sup> these increases have not been accompanied by sustained changes in sodium excretion, urine osmolality, plasma volume, or extracellular water.<sup>22,26-28</sup> Furthermore, in prior work, the natriuretic effect of SGLT2 inhibitors was most apparent in patients receiving high doses of furosemide,<sup>29</sup> a finding that is inconsistent with our current observations, if our results were to be attributed to a diuretic effect of these drugs. Therefore, taken together, in concert with the consistency of effect of empagliflozin regardless of diabetes or CKD, the available evidence suggests that diuresis is not a significant component of the mechanism of action of empagliflozin.<sup>24</sup> Indeed, the cardiorenal protective effects of SGLT2 inhibitors seem to be more directly mediated by their enhancement of nutrient deprivation signaling and autophagic flux.<sup>11,30</sup> Finally, given the higher rates of treatment discontinuation among patients taking the highest doses of diuretic agents compared with those taking lower doses, a finding

that was unaffected by treatment with empagliflozin or placebo, the attenuation could be a result of a regression toward the null hypothesis in this subgroup.

It should be noted that changes in diuretic doses are likely caused by the effects of SGLT2 inhibitor on the clinical course of HF, understanding that diuretic intensification commonly occurs after hospitalization for HF, an event that occurred less frequently in patients receiving empagliflozin. It is also likely that diuretic agents may be reduced or discontinued in patients who are demonstrating a favorable symptomatic response to SGLT2 inhibitors, especially if they have been taking low doses of loop diuretic agents. It is mathematically far more difficult for patients to stop diuretic agents completely if they are taking high doses rather than low doses of furosemide.

**STUDY LIMITATIONS.** The present findings should be interpreted in the context of inherent limitations. Whereas changes in diuretic dosage throughout the trial were recorded as either intensifications or decreases in doses, the actual magnitude of diuretic dosing changes was not collected. As such, changes in diuretic doses were statistically assessed as events rather than continuous variables. In addition, changes in diuretic doses were not collected at regular intervals but rather were probed by investigators at every subsequent visit, each of which had variable lengths of interval time. Most importantly, these analyses were post hoc, they were not corrected for multiplicity, and some findings were not observed in DAPA-HF; therefore, many of our findings could be the result of chance.

## CONCLUSIONS

In summary, empagliflozin in EMPEROR-Reduced demonstrated a consistent effect on the primary composite outcome of hospitalization for HF or CV death, along with a comparable safety profile, regardless of baseline diuretic doses.

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**Data Sharing Statement:** To ensure independent interpretation of clinical study results and enable authors to fulfil their role and obligations under the ICMJE criteria, Boehringer Ingelheim grants all external authors access to relevant clinical study data. In adherence with the Boehringer Ingelheim Policy on Transparency and Publication of Clinical Study Data, scientific and medical researchers can request access to clinical study data after publication of the primary manuscript and secondary analyses in a peer-reviewed journal and regulatory and reimbursement activities are completed, normally within 1 year after the marketing application has been granted by major Regulatory Authorities. Researchers should use <https://vivli.org/> to request access to study data and visit <https://www.mystudywindow.com/msw/datasharing> for further information.

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## PERSPECTIVES

**COMPETENCY IN MEDICAL KNOWLEDGE:** Empagliflozin's benefit on time to first HF hospitalization or CV death is not altered by baseline diuretic use.

**COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS:** For patients with HFrEF, empagliflozin should be considered an important pharmacologic option irrespective of background diuretic therapy.

**TRANSLATIONAL OUTLOOK:** Based on the present post hoc analysis of EMPEROR-Reduced, empagliflozin exhibits a consistent effect on hospitalization for HF or CV death among HFrEF patients irrespective of baseline diuretic doses.

## REFERENCES

1. Packer M, Anker SD, Butler J, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med*. 2020;383(15):1413-1424.
2. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med*. 2019;381(21):1995-2008.
3. Verma S, McGuire DK, Kosiborod MN. Two tales: one story: EMPEROR-Reduced and DAPA-HF. *Circulation*. 2020;142(23):2201-2204.
4. Bhatt DL, Verma S, Braunwald E. The DAPA-HF trial: a momentous victory in the war against heart failure. *Cell Metab*. 2019;30(5):847-849.
5. Anker SD, Butler J, Filippatos G, et al. Effect of empagliflozin on cardiovascular and renal outcomes in patients with heart failure by baseline diabetes status: results from the EMPEROR-Reduced trial. *Circulation*. 2021;143(4):337-349.
6. Petrie MC, Verma S, Docherty KF, et al. Effect of dapagliflozin on worsening heart failure and cardiovascular death in patients with heart failure with and without diabetes. *JAMA*. 2020;323(14):1353-1368.
7. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2021;42(36):3599-3726.
8. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on clinical practice guidelines. *J Am Coll Cardiol*. 2022;79(17):e263-e421.
9. Verma S, Anker SD, Butler J, Bhatt DL. Early initiation of SGLT2 inhibitors is important, irrespective of ejection fraction: SOLOIST-WHF in perspective. *ESC Heart Fail*. 2020;7(6):3261-3267.
10. Verma S, Dhingra NK, Bhatt DL, Marx N, Cosentino F. One size fits all: the story of SGLT2 inhibitors in heart failure. *Med*. 2022;3(11):735-739.
11. Packer M. Critical reanalysis of the mechanisms underlying the cardiorenal benefits of SGLT2 inhibitors and reaffirmation of the nutrient deprivation signaling/autophagy hypothesis. *Circulation*. 2022;146(18):1383-1405.
12. Lopaschuk GD, Verma S. Mechanisms of cardiovascular benefits of sodium glucose cotransporter 2 (SGLT2) inhibitors: a state-of-the-art review. *J Am Coll Cardiol Basic Trans Science*. 2020;5(6):632-644.
13. Packer M. Autophagy stimulation and intracellular sodium reduction as mediators of the cardioprotective effect of sodium-glucose cotransporter 2 inhibitors. *Eur J Heart Fail*. 2020;22(4):618-628.
14. Packer M, Butler J, Filippatos GS, et al. Evaluation of the effect of sodium-glucose cotransporter 2 inhibition with empagliflozin on morbidity and mortality of patients with chronic heart failure and a reduced ejection fraction: rationale for and design of the EMPEROR-Reduced trial. *Eur J Heart Fail*. 2019;21(10):1270-1278.
15. Testani JM, Brisco MA, Turner JM, et al. Loop diuretic efficiency: a metric of diuretic responsiveness with prognostic importance in acute decompensated heart failure. *Circ Heart Fail*. 2014;7(2):261-270.
16. Jackson AM, Dewan P, Anand IS, et al. Dapagliflozin and diuretic use in patients with heart failure and reduced ejection fraction in DAPA-HF. *Circulation*. 2020;142(11):1040-1054.
17. Butler J, Packer M, Filippatos G, et al. Effect of empagliflozin in patients with heart failure across the spectrum of left ventricular ejection fraction. *Eur Heart J*. 2022;43(5):416-426.
18. Zannad F, Ferreira JP, Pocock SJ, et al. Cardiac and kidney benefits of empagliflozin in heart failure across the spectrum of kidney function: insights from EMPEROR-Reduced. *Circulation*. 2021;143(4):310-321.
19. Januzzi JL Jr, Zannad F, Anker SD, et al. Prognostic importance of NT-proBNP and effect of empagliflozin in the EMPEROR-Reduced trial. *J Am Coll Cardiol*. 2021;78(13):1321-1332.
20. Butler J, Anker SD, Filippatos G, et al. Empagliflozin and health-related quality of life outcomes in patients with heart failure with reduced ejection fraction: the EMPEROR-Reduced trial. *Eur Heart J*. 2021;42(13):1203-1212.
21. Verma S, Dhingra NK, Butler J, et al. Empagliflozin in the treatment of heart failure with reduced ejection fraction in addition to background therapies and therapeutic combinations (EMPEROR-Reduced): a post-hoc analysis of a randomised, double-blind trial. *Lancet Diabetes Endocrinol*. 2022;10(1):35-45.
22. Boorsma EM, Beusekamp JC, Ter Maaten JM, et al. Effects of empagliflozin on renal sodium and glucose handling in patients with acute heart failure. *Eur J Heart Fail*. 2021;23(1):68-78.
23. Mordi NA, Mordi IR, Singh JS, McCrimmon RJ, Struthers AD, Lang CC. Renal and cardiovascular effects of SGLT2 inhibition in combination with loop diuretics in patients with type 2 diabetes and chronic heart failure: the RECODE-CHF trial. *Circulation*. 2020;142(18):1713-1724.

24. Packer M, Anker SD, Butler J, et al. Empagliflozin in patients with heart failure, reduced ejection fraction, and volume overload: EMPEROR-Reduced trial. *J Am Coll Cardiol*. 2021;77(11):1381-1392.
25. Scholtes RA, Muskiet MHA, van Baar MJB, et al. The adaptive renal response for volume homeostasis during 2 weeks of dapagliflozin treatment in people with type 2 diabetes and preserved renal function on a sodium-controlled diet. *Kidney Int Rep*. 2022;7(5):1084-1092.
26. Schork A, Saynisch J, Vosseler A, et al. Effect of SGLT2 inhibitors on body composition, fluid status and renin-angiotensin-aldosterone system in type 2 diabetes: a prospective study using bioimpedance spectroscopy. *Cardiovasc Diabetol*. 2019;18(1):46.
27. Scholtes RA, Muskiet MHA, van Baar MJB, et al. Natriuretic effect of two weeks of dapagliflozin treatment in patients with type 2 diabetes and preserved kidney function during standardized sodium intake: results of the DAPASALT trial. *Diabetes Care*. 2021;44(2):440-447.
28. Sha S, Polidori D, Heise T, et al. Effect of the sodium glucose co-transporter 2 inhibitor canagliflozin on plasma volume in patients with type 2 diabetes mellitus. *Diabetes Obes Metab*. 2014;16(11):1087-1095.
29. Griffin M, Rao VS, Ivey-Miranda J, et al. Empagliflozin in heart failure: diuretic and cardiorenal effects. *Circulation*. 2020;142(11):1028-1039.
30. Zannad F, Ferreira JP, Butler J, et al. Effect of empagliflozin on circulating proteomics in heart failure: mechanistic insights into the EMPEROR programme. *Eur Heart J*. 2022;43(48):4991-5002.
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- KEY WORDS** diuretic agents, empagliflozin, heart failure with reduced ejection fraction
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- APPENDIX** For supplemental figures and tables, please see the online version of this paper.