

ORIGINAL INVESTIGATIONS

Empagliflozin in Patients With Heart Failure, Reduced Ejection Fraction, and Volume Overload



EMPEROR-Reduced Trial

Milton Packer, MD,^{a,b} Stefan D. Anker, MD, PhD,^c Javed Butler, MD, MPH,^d Gerasimos Filippatos, MD,^e Joao Pedro Ferreira, MD,^f Stuart J. Pocock, PhD,^g Naveed Sattar, MD, PhD,^h Martina Brueckmann, MD,^{i,j} Waheed Jamal, MD,ⁱ Daniel Cotton, MS,^k Tomoko Iwata, MS,^l Faiez Zannad, MD, PhD,^f for the EMPEROR-Reduced Trial Committees and Investigators

ABSTRACT

BACKGROUND Investigators have hypothesized that sodium-glucose cotransporter 2 (SGLT2) inhibitors exert diuretic effects that contribute to their ability to reduce serious heart failure events, and this action is particularly important in patients with fluid retention.

OBJECTIVES This study sought to evaluate the effects of the SGLT2 inhibitor empagliflozin on symptoms, health status, and major heart failure outcomes in patients with and without recent volume overload.

METHODS This double-blind randomized trial compared the effects of empagliflozin and placebo in 3,730 patients with heart failure and a reduced ejection fraction, with or without diabetes. Approximately 40% of the patients had volume overload in the 4 weeks before study enrollment.

RESULTS Patients with recent volume overload were more likely to have been hospitalized for heart failure and to have received an intravenous diuretic agent in an outpatient setting in the previous 12 months, and to experience a heart failure event following randomization, even though they were more likely to be treated with high doses of a loop diuretic agent as an outpatient (all $p < 0.001$). When compared with placebo, empagliflozin reduced the composite risk of cardiovascular death or hospitalization for heart failure, decreased total hospitalizations for heart failure, and improved health status and functional class. Yet despite the predisposition of patients with recent volume overload to fluid retention, the magnitude of these benefits (even after 1 month of treatment) was not more marked in patients with recent volume overload (interaction p values > 0.05). Changes in body weight, hematocrit, and natriuretic peptides (each potentially indicative of a diuretic action of SGLT2 inhibitors) did not track each other closely in their time course or in individual patients.

CONCLUSIONS Taken together, study findings do not support a dominant role of diuresis in mediating the physiological changes or clinical benefits of SGLT2 inhibitors on the course of heart failure in patients with a reduced ejection fraction. (EMPAgliflozin outcomE tRial in Patients With chrOnic hearT Failure With Reduced Ejection Fraction [EMPEROR-Reduced]; [NCT03057977](https://clinicaltrials.gov/ct2/show/study/NCT03057977)) (J Am Coll Cardiol 2021;77:1381-92) © 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 license (<http://creativecommons.org/licenses/by/4.0/>).



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From the ^aBaylor Heart and Vascular Institute, Baylor University Medical Center, Dallas, Texas, USA; ^bImperial College, London, United Kingdom; ^cDepartment of Cardiology, Berlin Institute of Health Center for Regenerative Therapies, German Centre for Cardiovascular Research Partner Site Berlin, Charité Universitätsmedizin, Berlin, Germany; ^dDepartment of Medicine, University of Mississippi School of Medicine, Jackson, Mississippi, USA; ^eNational and Kapodistrian University of Athens School of Medicine, Athens University Hospital Attikon, Athens, Greece; ^fInvestigation Network Initiative-Cardiovascular and Renal Clinical Trialists, University Hospital, University of Lorraine, Nancy, France; ^gDepartment of Medical Statistics, London School of Hygiene and Tropical Medicine, London, United Kingdom; ^hBritish Heart Foundation Glasgow Cardiovascular Research Centre, University of

ABBREVIATIONS AND ACRONYMS

CI = confidence interval

eGFR = estimated glomerular
filtration rate

HR = hazard ratio

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

NYHA = New York Heart
Association

SGLT2 = sodium-glucose
cotransporter 2

The action of sodium-glucose cotransporter 2 (SGLT2) inhibitors to promote natriuresis and osmotic diuresis (1-4) has been proposed as a central mechanism by which these drugs reduce heart failure hospitalizations in large-scale trials (5-7). Sodium retention in patients with heart failure is related to increased sodium reabsorption in the proximal tubule (8), and by attenuating the sodium reabsorption at this site, SGLT2 inhibitors may potentiate the effect of diuretic agents acting at the loop of Henle (2,9,10). The effects of SGLT2 inhibitors to increase hematocrit and decrease body weight and circulating natriuretic peptides (6,7) have been linked by some investigators to an effect of diuresis to contract plasma and extracellular volume (11-13). However, the actions of SGLT2 inhibitors on these biomarkers can be explained by mechanisms that are independent of sodium and water excretion (14-17).

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It has been proposed that if a diuretic action of SGLT2 inhibitors leads to a reduction in heart failure events, such a benefit would be particularly manifest in patients with heart failure who have fluid retention as a major feature of their history and clinical course (18,19). Typically, these patients manifest ongoing episodes of edema and other signs of organ congestion and volume overload, experience worse symptoms and clinical instability, and require repeated outpatient and inpatient interventions, especially the intensification of therapy with diuretic agents (20,21). This unfavorable course is often seen despite the use of high maintenance doses of oral diuretic agents, a finding suggesting a state of diuretic resistance (21,22). By acting on sodium reabsorption in the proximal tubule, SGLT2 inhibitors are poised to overcome resistance to loop diuretic agents that act more distally (23).

If the ability of SGLT2 inhibitors to potentiate the effect of loop diuretic agents is important, then patients who experience recent or repeated episodes of volume overload may be particularly likely to show a

reduction in heart failure events during long-term treatment with SGLT2 inhibitors. This hypothesis was specifically tested in a secondary analysis of the EMPEROR-Reduced (EMPagliflozin outcome tRial in Patients With chrOnic heaRt Failure With Reduced Ejection Fraction) trial, which evaluated the efficacy and safety of empagliflozin in patients with heart failure and a reduced ejection fraction.

METHODS

The design of the EMPEROR-Reduced trial has been described previously (8). Ethics approval was obtained at each study site, and all patients provided informed consent; the registration identifier at ClinicalTrials.gov is NCT03057977.

Participants had New York Heart Association (NYHA) functional class II to IV heart failure and an ejection fraction $\leq 40\%$, and they were receiving all appropriate treatments for heart failure. We preferentially enrolled patients with an ejection fraction of $\leq 30\%$ by requiring those patients with higher ejection fractions to have been hospitalized for heart failure within 12 months or to have markedly increased levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP) (i.e., $\geq 1,000$ pg/ml or $\geq 2,500$ pg/ml in patients with an ejection fraction of 31% to 35% or 36% to 40%, respectively); these thresholds were doubled in patients with atrial fibrillation. All patients were recruited as outpatients, but they were excluded if they had acute decompensation or a change in diuretic agents within 1 week before study enrollment.

Before randomization, investigators identified patients who had clinical evidence of volume overload in the 4 weeks before the first study visit and distinguished them from those patients who had been clinically euvolemic or volume depleted. Because there is no consensus on the definition of euvolemia, no guidance was provided to investigators on how to identify patients with volume overload. We assessed the baseline use of diuretic agents, and patients were categorized as receiving high or low doses of a loop diuretic agent, with the former defined as >40 mg daily of furosemide or its equivalent (24).

Glasgow, Glasgow, United Kingdom; ¹Boehringer Ingelheim International GmbH, Ingelheim, Germany; ²Faculty of Medicine Mannheim, University of Heidelberg, Mannheim, Germany; ³Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, Connecticut, USA; and the ⁴Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany.

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](#).

Patients were randomized and double blinded (in a 1:1 ratio) to receive placebo or empagliflozin 10 mg daily, in addition to their usual therapy for heart failure. Following randomization, all treatments for heart failure or other medical conditions could be initiated or altered at the discretion of the investigator. Patients were periodically assessed for major outcomes and functional capacity related to heart failure, intensification of diuretic therapy, vital signs, heart failure-pertinent biomarkers, and adverse events.

The primary endpoint was the composite of cardiovascular death or hospitalization for heart failure, analyzed as time to first event. The first secondary endpoint was the occurrence of all (first and recurrent) hospitalizations for heart failure. The second secondary endpoint was the slope of the change in estimated glomerular filtration rate (eGFR) during double-blind treatment. Serious adverse renal outcomes included long-term dialysis, renal transplantation, a sustained eGFR reduction of $\geq 40\%$, or a sustained eGFR < 15 ml/min/1.73 m² (if baseline eGFR was ≥ 30) or a sustained eGFR < 10 ml/min/1.73 m² (if baseline eGFR was < 30). Additional analyses included the following: 1) time to reported intensification of therapy with diuretic agents; 2) changes in the Kansas City Cardiomyopathy Questionnaire at 12 and 52 weeks; and 3) changes in NYHA functional class, hematocrit, uric acid, NT-proBNP, body weight, systolic blood pressure, serum sodium, and serum albumin at 4 and 52 weeks.

OUTCOME MEASURES AND STATISTICAL ANALYSIS.

For time-to-first-event analyses, between-group differences were assessed using a Cox proportional hazards model, with pre-specified covariates of age, sex, region, diabetes, ejection fraction, and eGFR at baseline. For the analysis of total events, between-group differences were assessed using a joint frailty model, with cardiovascular death as a competing risk, and changes in NYHA functional class were evaluated by logistic regression. Both analyses used the same covariates as the time-to-first event analyses and included baseline NYHA functional class for the analysis of NYHA functional class. The eGFR slope analysis was determined on the basis of on-treatment data using a random coefficient model, with age and baseline eGFR as linear covariates and sex, region, ejection fraction, diabetes, baseline eGFR, time, and recent volume overload interaction terms as fixed effects.

For vital signs and laboratory measurements, treatment effects were assessed using a mixed model for repeated measures, with age and baseline eGFR as linear covariates and baseline score by visit, visit by treatment, sex, region, ejection fraction, individual

last projected visit, and diabetes as fixed effects. All analyses of changes in NT-proBNP were performed on log-transformed data.

Interaction p values were used to compare the magnitude of the effect of empagliflozin on pre-specified outcomes in groups defined by the presence or absence of recent volume overload. To assess differences in the course of the patients with or without recent volume overload at baseline, analyses were performed on placebo recipients only, by using the same covariate adjustments.

RESULTS

Of the 3,730 randomized patients, 1,477 patients (39.6%) had volume overload in the previous 4 weeks. A total of 2,128 patients were reported to have been euvolemic for the entire previous 4 weeks, and 121 had experienced volume depletion; these 2,249 patients were grouped together and were considered to have had no recent volume overload. Four patients with missing data for volume overload are not considered in this report.

CLINICAL CHARACTERISTICS AND CLINICAL COURSE.

The baseline characteristics of the patients with or without recent volume overload were similar with respect to ejection fraction and eGFR, but patients with recent volume overload were more likely to have a history of hypertension, diabetes, and atrial fibrillation. Patients with recent volume overload were also more likely to have had worsening NYHA functional class within 3 months, to have been hospitalized for heart failure and to have received an intravenous diuretic agent as an outpatient within the previous 12 months, and to have NYHA functional class III or IV symptoms at randomization (all $p < 0.0001$). Furthermore, patients with recent volume overload had higher serum levels of NT-proBNP, even though they were more likely to be receiving high doses of a loop diuretic agent (both $p < 0.0001$). The 2 groups were similar with respect to the use of beta-blockers and mineralocorticoid receptor antagonists, but patients with recent volume overload were less likely to have undergone implantable cardioverter-defibrillator or cardiac resynchronization therapy (all $p < 0.0001$). Serum chloride was lower in patients with recent volume overload; other baseline characteristics are shown in [Table 1](#). Of note, patients recruited in Asia or who were of Asian descent were more likely to have recent volume overload.

Despite similarities in ejection fraction, renal function, and the use of neurohormonal antagonists, when treated with placebo, patients with recent

TABLE 1 Baseline Characteristics of Patients With or Without Recent Volume Overload at Baseline

	Patients Without Recent Volume Overload (n = 2,249)		Patients With Recent Volume Overload (n = 1,477)		p Value
	Placebo (n = 1,110)	Empagliflozin (n = 1,139)	Placebo (n = 754)	Empagliflozin (n = 723)	
Age, yrs	66.4 ± 11.2	66.7 ± 10.8	66.6 ± 11.3	67.9 ± 10.8	0.088
Women	280 (25.2)	282 (24.8)	174 (23.1)	155 (21.4)	0.058
Race					
White	781 (70.4)	813 (71.4)	522 (69.2)	511 (70.7)	<0.001
Black	76 (6.8)	74 (6.5)	58 (7.7)	49 (6.8)	
Asian	178 (16.0)	189 (16.6)	157 (20.8)	148 (20.5)	
Region					
North America	145 (13.1)	149 (13.1)	68 (9.0)	62 (8.6)	<0.001
Latin America	385 (34.7)	390 (34.2)	259 (34.4)	251 (34.7)	
Europe	399 (35.9)	414 (36.3)	276 (36.6)	262 (36.2)	
Asia	123 (11.1)	122 (10.7)	122 (16.2)	126 (17.4)	
Clinical course of heart failure					
Duration of heart failure, yrs	4.4 (1.7, 9.2)	3.8 (1.5, 8.7)	3.7 (1.3, 8.8)	3.8 (1.2, 8.8)	0.431
NYHA functional class III-IV	221 (19.9)	243 (21.3)	244 (32.4)	221 (30.6)	<0.001
Worsening NYHA functional class within 3 months	36 (3.2)	37 (3.2)	92 (12.2)	67 (9.3)	<0.001
Hospitalization for HF within 12 months	282 (25.4)	293 (25.7)	291 (38.6)	283 (39.1)	<0.001
Outpatient IV diuretic agents within 12 months	123 (11.1)	124 (10.9)	129 (17.1)	117 (16.2)	<0.001
Body mass index, kg/m ²	27.7 ± 5.1	27.8 ± 5.3	28.0 ± 5.6	28.2 ± 5.7	0.055
LV ejection fraction, %	27.1 ± 5.9	27.8 ± 5.8	27.4 ± 6.4	27.6 ± 6.2	0.747
Systolic blood pressure, mm Hg	121.6 ± 15.5	122.2 ± 15.7	121.1 ± 15.1	123.1 ± 16.2	0.741
Heart rate, beats/min	71.0 ± 11.3	70.3 ± 11.5	72.4 ± 12.4	72.0 ± 11.9	<0.001
NT-proBNP, pg/ml	1,772 (1,074-3,155)	1,805 (1,032-3,191)	2,079 (1,256-4,002)	2,045 (1,152-3,934)	<0.001
Serum sodium, mEq/l	140.7 ± 2.9	140.6 ± 3.1	140.4 ± 3.1	140.6 ± 3.1	0.255
Serum chloride, mEq/l	100.8 ± 3.5	100.9 ± 3.7	100.4 ± 3.8	100.6 ± 3.9	0.004
Estimated GFR, mL/min/1.73 m ²	62.6 ± 21.3	62.0 ± 21.4	61.6 ± 22.0	61.6 ± 22.3	0.358
Cardiovascular history					
Hypertension	796 (71.7)	801 (70.3)	551 (73.1)	547 (75.7)	0.026
Previous myocardial infarction	491 (44.2)	535 (47.0)	292 (38.7)	303 (41.9)	0.001
Atrial fibrillation or atrial flutter	416 (37.5)	414 (36.3)	321 (42.6)	288 (39.8)	0.006
Diabetes mellitus	528 (47.6)	545 (47.8)	400 (53.1)	382 (52.8)	0.002
Treatment of heart failure					
High doses of loop diuretic agents	223 (20.1)	219 (19.2)	196 (26.0)	191 (26.4)	<0.001
Beta-blocker	1,053 (94.9)	1,078 (94.6)	712 (94.4)	687 (95.0)	0.964
Mineralocorticoid receptor antagonist	793 (71.4)	797 (70.0)	560 (74.3)	508 (70.3)	0.288
Nephrilysin inhibitor	249 (22.4)	219 (19.2)	137 (18.2)	121 (16.7)	0.012
Cardiac glycosides	186 (16.8)	177 (15.5)	125 (16.6)	106 (14.7)	0.683
Implantable cardioverter-defibrillator*	396 (35.7)	391 (34.3)	195 (25.9)	186 (25.7)	<0.001
Cardiac resynchronization therapy†	145 (13.1)	156 (13.7)	77 (10.2)	64 (8.9)	<0.001

Values are mean ± SD, n (%), or median (interquartile range). The p values refer to the difference between patients with or without recent volume overload, combining the 2 randomized treatment groups. Patients who self-identified with ≥1 race or with no race are classified as "other"; data for "other" or missing for both race and region are not shown. *Implantable cardioverter-defibrillator with or without cardiac resynchronization therapy. †Cardiac resynchronization therapy with or without a defibrillator.

GFR = glomerular filtration rate; HF = heart failure; IV = intravenous; LV = left ventricular; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association.

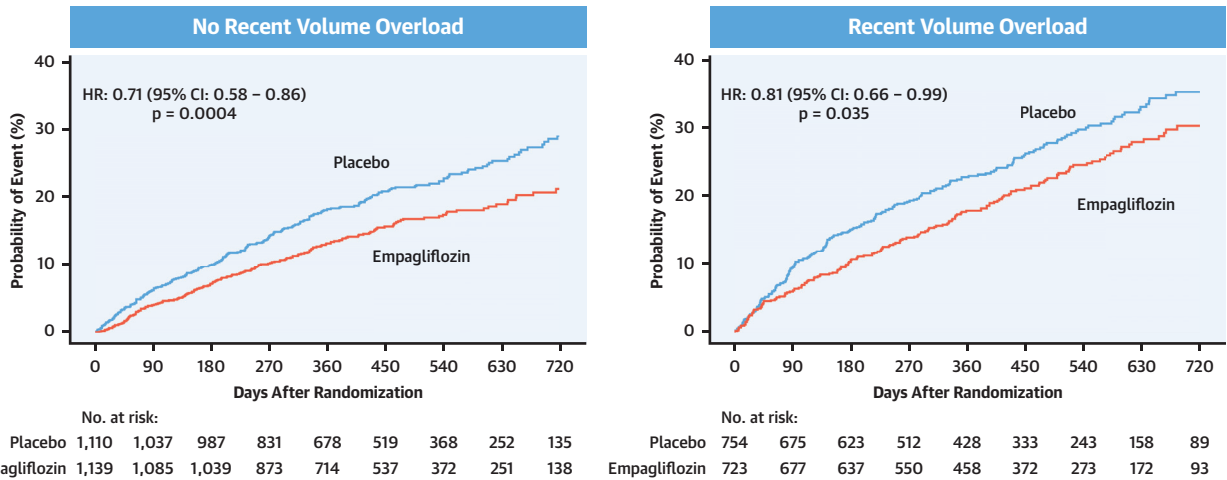
volume overload were more likely to experience the composite endpoint of cardiovascular death or hospitalization for heart failure (hazard ratio [HR]: 1.31; 95% confidence interval [CI]: 1.09 to 1.57; $p = 0.0044$) and had a higher number of total hospitalizations for heart failure (HR: 1.36; 95% CI: 1.06 to 1.75; $p = 0.016$). Additionally, when treated with placebo, patients with recent volume overload were more likely than those without recent volume overload to require

intensification of treatment with diuretic agents following randomization (HR: 1.22; 95% CI: 1.00 to 1.48; $p = 0.047$).

EFFECT ON HEART FAILURE AND RENAL OUTCOMES.

When compared with placebo, empagliflozin reduced the combined risk of cardiovascular death or hospitalization for heart failure in patients with and without recent volume overload (HR: 0.81; 95% CI: 0.66 to 0.99 and HR: 0.71; 95% CI: 0.58 to

CENTRAL ILLUSTRATION Effect of Empagliflozin on the Combined Risk of Cardiovascular Death or Hospitalization for Heart Failure in Patients With or Without Recent Volume Overload at Baseline



Packer, M. et al. *J Am Coll Cardiol.* 2021;77(11):1381-92.

Cumulative incidence plots, with hazard ratio (HR), 95% confidence interval (CI), and p value for the comparison of empagliflozin and placebo. Interaction p value for the difference in the effect of empagliflozin on the left and right is 0.34.

0.86, respectively; interaction $p = 0.34$) (Central Illustration, Table 2). The effect of empagliflozin to reduce the total number of hospitalizations for heart failure was somewhat less compelling in patients with as compared with patients without recent volume overload (16% vs. 40% risk reduction, respectively; HR: 0.84; 95% CI: 0.63 to 1.12 and HR: 0.60; 95% CI: 0.47 to 0.78;,, respectively; interaction $p = 0.09$) (Figure 1 and Table 2). For these endpoints, the incidence plots separated immediately in patients without recent volume overload, but this separation occurred after 30 to 45 days in the patients with recent volume overload.

When compared with placebo, empagliflozin slowed the rate of decline in eGFR in patients with and without recent volume overload to a similar degree. Similarly, empagliflozin reduced the risk of a serious adverse renal outcome in patients with and without recent volume overload HRs of 0.49 (95% CI: 0.26 to 0.92) and 0.51 (95% CI: 0.27 to 0.91), respectively (Table 2), with no difference between the volume overload subgroups (interaction $p = 0.95$). The influence of recent volume overload on other outcome measures is summarized in Table 2.

EFFECT ON USE OF DIURETIC AGENTS, HEALTH STATUS AND FUNCTIONAL CLASS. When compared with the placebo group, patients in the empagliflozin group were less likely to require intensification of

treatment with diuretic agents, with an HR of 0.68 (95% CI: 0.55 to 0.85) in the patients with recent volume overload and an HR of 0.67 (95% CI: 0.55 to 0.82) in the patients without recent volume overload (interaction $p = 0.88$) (Figure 2, Table 2). Empagliflozin improved the Kansas City Cardiomyopathy Questionnaire clinical summary score at 12 weeks to a similar degree in patients with and without recent volume overload (interaction $p = 0.65$); these benefits were sustained during double-blind therapy in both volume-defined subgroups.

For changes in NYHA functional class at 4 weeks, empagliflozin-treated patients had a higher odds of showing improvement, odds ratios of 1.43 (95% CI: 1.04 to 1.97) and 1.34 (95% CI: 0.99 to 1.82) for patients with or without recent volume overload, respectively. At this time, empagliflozin-treated patients also had a lower odds of showing worsening NYHA functional class, with odds ratios of 0.79 (95% CI: 0.41 to 1.54) and 0.50 (95% CI: 0.29 to 0.85) with and without recent volume overload, respectively. For both improvement and worsening, the responses to empagliflozin in the 2 volume overload groups did not differ (interaction $p = 0.78$ and $p = 0.29$, respectively). Similar patterns were seen for changes in functional class at 52 weeks (Table 2).

EFFECT ON VITAL SIGNS, BIOMARKERS, AND SAFETY. As compared with placebo, NT-proBNP

TABLE 2 Effects of Empagliflozin in Patients With or Without Recent Volume Overload at Baseline

Outcomes	Patients Without Recent Volume Overload (n = 2,249)		Patients With Recent Volume Overload (n = 1,477)		Interaction p Value
	Placebo (n = 1,110)	Empagliflozin (n = 1,139)	Placebo (n = 754)	Empagliflozin (n = 723)	
Cardiovascular death or adjudicated hospitalization for heart failure	246 (22.2)	182 (16.0)	214 (28.4)	179 (24.8)	0.34
	0.71 (0.58-0.86), p = 0.0004		0.81 (0.66-0.99), p = 0.035		
Total (first and recurrent adjudicated hospitalizations for heart failure)	275	181	274	207	0.09
	0.60 (0.47-0.78), p = 0.0002		0.84 (0.63-1.12), p = 0.24		
Slope of decline in eGFR (ml/min/1.73 m ² /yr)	-2.1 ± 0.3	-0.6 ± 0.3	-2.6 ± 0.4	-0.5 ± 0.3	0.38
	+1.49 ± 0.42, p = 0.0005		+2.06 ± 0.50, p < 0.0001		
Composite of serious adverse renal outcomes	28 (2.5)	15 (1.3)	30 (4.0)	15 (2.1)	0.95
	0.51 (0.27-0.95), p = 0.034		0.49 (0.26-0.92), p = 0.025		
Time to first adjudicated hospitalization for heart failure	185 (16.7)	123 (10.8)	155 (20.6)	123 (17.0)	0.24
	0.63 (0.50-0.80), p < 0.0001		0.77 (0.61-0.98), p = 0.033		
Cardiovascular death	104 (9.4)	93 (8.2)	98 (13.0)	94 (13.0)	0.71
	0.89 (0.67-1.17), p = 0.40		0.96 (0.72-1.27), p = 0.76		
Patients requiring intensification of diuretic agents (time-to-event-analysis)	224 (20.2)	160 (14.0)	188 (24.9)	137 (18.9)	0.88
	0.67 (0.55-0.82), p = 0.0001		0.68 (0.55-0.85), p = 0.0008		
NYHA functional class at 4 weeks					
Odds ratio for improvement	1.34 (0.99-1.82), p = 0.055		1.43 (1.04-1.97), p = 0.028		0.78
Odds ratio for worsening	0.50 (0.29-0.85), p = 0.0098		0.79 (0.41-1.54), p = 0.49		0.29
NYHA functional class at 52 weeks					
Odds ratio for improvement	1.25 (0.96-1.64), p = 0.10		1.44 (1.06-1.95), p = 0.02		0.51
Odds ratio for worsening	0.51 (0.31-0.85), p = 0.01		0.81 (0.46-1.43), p = 0.47		0.23
KCCQ clinical summary score at 12 weeks	+1.74 (0.47-3.01), p = 0.007		+2.21 (0.64-3.78), p = 0.006		0.65
KCCQ clinical summary score at 52 weeks	+1.16 (-0.42-2.75), p = 0.15		+2.32 (0.38-4.26), p = 0.019		0.37

Values are n (%), mean ± SD, HR (95% CI), unless otherwise indicated. For NYHA functional class, a benefit of empagliflozin is indicated by odds ratios >1.0 for improvement and <1.0 for worsening. CI = confidence interval; eGFR = estimated glomerular filtration rate; HR = hazard ratio; KCCQ = Kansas City Cardiomyopathy Questionnaire; other abbreviations as in [Table 1](#).

declined in the empagliflozin-treated group, modestly after 4 weeks and to a greater degree after 52 weeks, but these decreases were not influenced by the presence or absence of recent volume overload (interaction p = 0.38 and p = 0.67, respectively) ([Table 3](#)). Systolic blood pressure declined by a mean of 1 to 2 mm Hg after 4 weeks, and it decreased by 0 to 1 mm Hg after 52 weeks, without an effect of recent volume overload (interaction p = 0.17 and p = 0.51, respectively). Body weight declined by ~1.0 kg throughout double-blind treatment, but it decreased similarly in patients with and without recent volume overload. Empagliflozin increased hematocrit after 4 weeks and 52 weeks, and this effect did not vary according to volume overload. Treatment with empagliflozin was accompanied by very small increases in serum albumin without changes in serum sodium, with similar effects in the volume overload groups ([Table 3](#)). Importantly, changes in body weight were poorly correlated with changes in NT-proBNP or with changes in hematocrit in individual patients

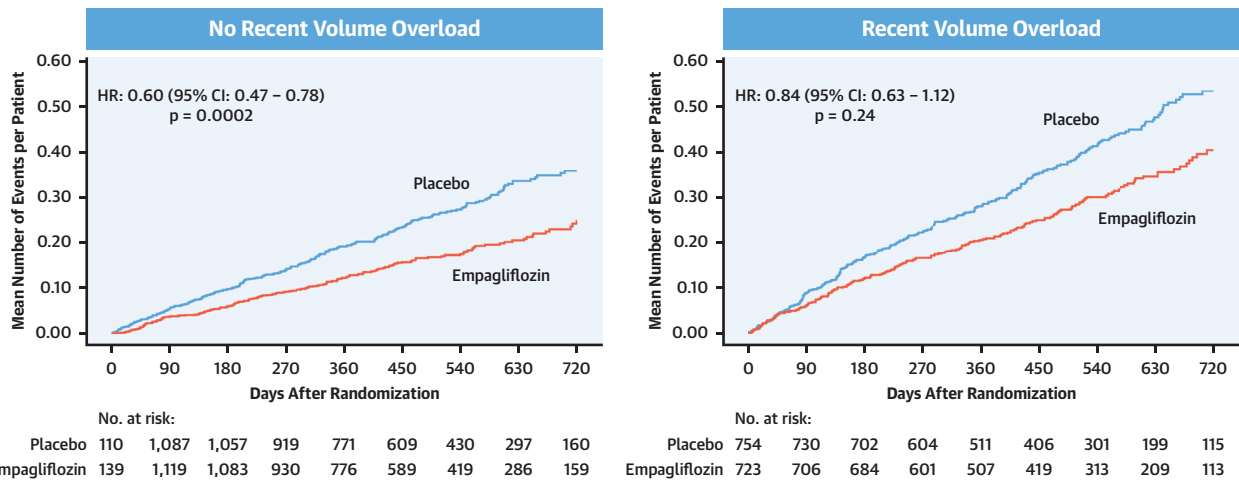
treated with empagliflozin (r = 0.12 and r = -0.17, respectively, at 4 weeks; and r = -0.14 and r = 0.045, respectively, at 52 weeks).

Additionally, the frequency of reports of adverse events related to symptomatic hypotension, volume depletion, or worsening renal function was not increased by empagliflozin, either in patients with or without recent volume overload. The incidence of volume depletion was somewhat higher and the incidence of hyperkalemia somewhat lower in empagliflozin-treated patients with recent volume overload ([Supplemental Table 1](#)), but the between-group differences in the number of events were small.

DISCUSSION

Patients who had volume overload in the 4 weeks before enrollment in the EMPEROR-Reduced trial had a history of clinical instability and remained at elevated risk for heart failure events during follow-up. Patients with recent volume overload were

FIGURE 1 Effect of Empagliflozin on Total (First and Recurrent) Hospitalizations for Heart Failure in Patients With or Without Recent Volume Overload at Baseline



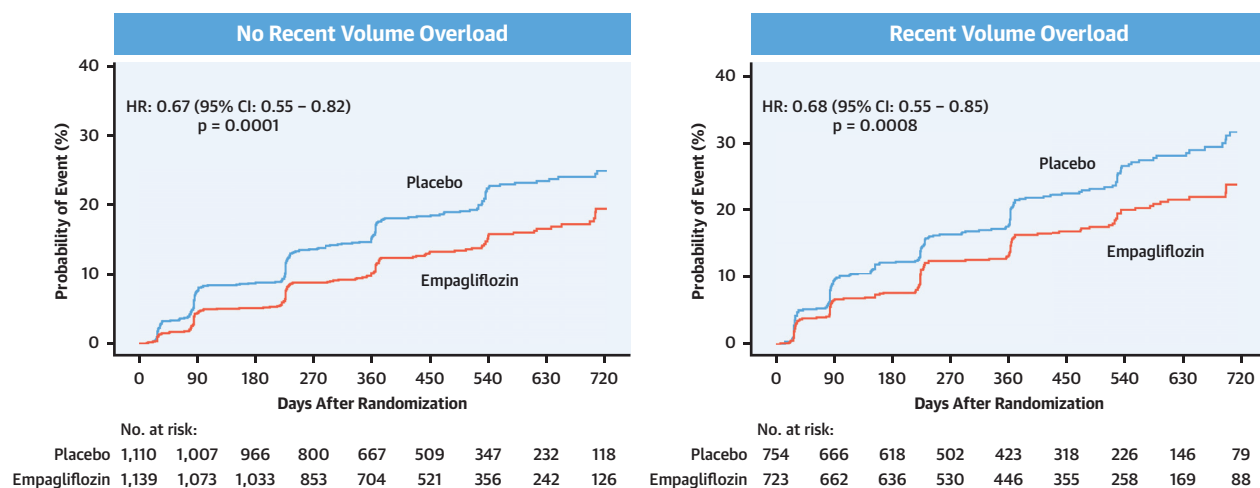
Cumulative function plots, with hazard ratios (HR), 95% confidence intervals (CIs), and p values for the comparison of empagliflozin and placebo. The interaction p value for the difference in the effect of empagliflozin on the **left and right** is 0.09.

likely to have been hospitalized for heart failure and to have received an intravenous diuretic agent as an outpatient within the previous 12 months, to have worsening NYHA functional class within 3 months, and to have class III to IV symptoms at the time of randomization. These patients were also more likely to experience the composite endpoint of cardiovascular death or hospitalization for heart failure. These clinical features were apparent even though these patients were more likely to have received high doses of a loop diuretic agent as an outpatient and to require intensification of diuretic therapy following randomization, thus indicating a degree of diuretic resistance, a finding supported by the lower values of serum chloride in these patients (25). The predisposition of these patients to fluid retention and clinical instability could not be explained by ejection fraction, systolic blood pressure, or renal function. Interestingly, patients with recent volume overload represented 40% of the patients in the trial, which was specifically enriched for those patients with markedly elevated levels of natriuretic peptides (6).

SGLT2 inhibitors may potentiate the effects of loop diuretic agents, and it has been proposed that these drugs are particularly effective in promoting fluid excretion in patients with volume overload before treatment (2,9,10,18,19). However, in the EMPEROR-Reduced trial, empagliflozin reduced the combined risk of cardiovascular death or hospitalization for heart failure in patients with and without recent volume overload, with no difference between

the 2 groups. In fact, the effect of empagliflozin to reduce the total number of hospitalizations for heart failure was somewhat less compelling in patients with recent volume overload as compared with patients without recent volume overload (16% vs. 40% risk reduction, respectively), and for both endpoints, the benefits of empagliflozin seemed to emerge more rapidly in patients without recent volume overload. In parallel with the benefits on the course of heart failure, empagliflozin reduced the need for intensification of diuretic agents and improved Kansas City Cardiomyopathy Questionnaire and NYHA functional class, but the magnitude of these benefits was similar in patients with or without recent volume overload.

In some mechanistic studies, SGLT2 inhibitors have been reported to produce changes in urinary sodium, glucose, and water excretion and decreases in plasma volume within the first several days of treatment (1-4). In other reports, however, meaningful changes in urinary volume, sodium excretion, or extracellular fluid have not been seen acutely (even in acute heart failure), and if present, these changes have not necessarily been sustained after 1 to 2 weeks (2,3,10,13,16,26-28). SGLT2 inhibitors do not have an immediate effect to reduce circulating natriuretic peptides or to alter the dose of diuretic agents used for the treatment of heart failure in most patients (24,28-31). In the current study, treatment with empagliflozin did not change serum sodium values and produced very small increases in serum albumin.

FIGURE 2 Effect of Empagliflozin on the Time to First Visit Reporting Intensification of Diuretic Agents in Patients With or Without Recent Volume Overload at Baseline

Cumulative function plots, with hazard ratios (HR), 95% confidence intervals (CIs), and p values for the comparison of empagliflozin and placebo. The interaction p value for the difference in the effect of empagliflozin on the **left and right** is 0.88. HR = hazard ratio.

The latter effect has been previously reported with the use of SGLT2 inhibitors in type 2 diabetes (32), and it is likely related to reactive changes in the nonerythrocyte component of blood volume that follow any drug-induced increases in red blood cell mass (32,33).

Despite these observations, it is possible that diuretic effects could have occurred before our week 4 assessments, and even if transient, they could conceivably have contributed to the short-term benefits of these drugs. In our trial, the effects of empagliflozin to improve NYHA functional class and to reduce the risk of hospitalizations for heart failure were statistically significant within 12 to 28 days and were accompanied by a decrease in body weight (34). Theoretically, a diuretic effect could explain these early benefits, even if non-diuretic mechanisms are responsible for the favorable effects seen during longer-term treatment. However, in the current study, these early effects on NYHA functional class, body weight, and heart failure events were not more apparent in patients with recent volume overload. Furthermore, neither patients with nor without recent volume overload had early effects on symptoms and heart failure hospitalizations accompanied by an important decrease in circulating natriuretic peptides. These observations do not support a role for a short-term diuretic effect in mediating the early benefits of SGLT2 inhibitors on functional class or on heart failure outcomes.

Our observations also raise questions about the role of diuresis in mediating changes in body weight, hematocrit, and natriuretic peptides during treatment with SGLT2 inhibitors. The time course of changes in body weight did not closely parallel changes in natriuretic peptides or hematocrit. When treatment continued beyond 4 weeks, body weight did not decline further, even though hematocrit continued to increase and NT-proBNP continued to decrease. Changes in body weight were poorly correlated with changes in NT-proBNP or with changes in hematocrit in individual patients treated with empagliflozin, both after 4 weeks and after 52 weeks. It therefore seems likely that the effects of SGLT2 inhibitors on these physiological measures are explicable by nondiuretic actions of these drugs. The decline in body weight appears to be related to the loss of calories in the urine as a result of renal glycosuria (16,17,35). The increase in hematocrit is preceded by an increase in erythropoietin and reticulocytosis (36,37), presumably related to enhanced signaling of upstream regulators of erythropoietin synthesis (14,38,39). Finally, the effect of SGLT2 inhibitors to decrease natriuretic peptides is primarily seen after many months of treatment, a finding suggesting that it reflects the favorable effects of SGLT2 inhibitor on left ventricular remodeling rather than the consequence of a diuretic action (40).

STUDY STRENGTHS AND LIMITATIONS. The findings of the current study should be viewed in light of its

TABLE 3 Changes in Vital Signs and Biomarkers in Patients Randomized to Placebo and Empagliflozin, According to Recent History of Volume Overload at Baseline

	Patients Without Recent Volume Overload (n = 2,249)		Patients With Recent Volume Overload (n = 1,477)		Interaction p Value
	Placebo (n = 1,110)	Empagliflozin (n = 1,139)	Placebo (n = 754)	Empagliflozin (n = 723)	
NT-proBNP, ratio of adjusted geometric means					
At 4 weeks	0.93 (0.90-0.97)	0.90 (0.87-0.93)	0.90 (0.86-0.94)	0.84 (0.80-0.88)	0.38
		0.96 (0.92-1.01), p = 0.14		0.93 (0.88-0.99), p = 0.02	
At 52 weeks	0.91 (0.86-0.97)	0.79 (0.74-0.83)	0.78 (0.72-0.83)	0.69 (0.64-0.74)	0.67
		0.86 (0.79-0.94), p = 0.0004		0.89 (0.80-0.98), p = 0.017	
Systolic blood pressure, mm Hg					
At 4 weeks	-2.1 ± 0.4	-3.1 ± 0.4	-0.8 ± 0.5	-2.9 ± 0.5	0.17
		-1.0 ± 0.6 (p = 0.086)		-2.2 ± 0.7 (p = 0.0017)	
At 52 weeks	-2.3 ± 0.5	-2.7 ± 0.5	-0.5 ± 0.6	-1.7 ± 0.6	0.51
		-0.4 ± 0.7 (p = 0.61)		-1.1 ± 0.9 (p = 0.20)	
Body weight, kg					
At 4 weeks	+0.16 ± 0.09	-0.59 ± 0.09	+0.02 ± 0.11	-0.61 ± 0.11	0.53
		-0.75 ± 0.12 (p < 0.0001)		-0.63 ± 0.15 (p < 0.0001)	
At 52 weeks	-0.08 ± 0.17	-0.76 ± 0.17	+0.32 ± 0.21	-0.69 ± 0.21	0.39
		-0.68 ± 0.24 (p = 0.0045)		-1.00 ± 0.29 (p = 0.0006)	
Hematocrit, %					
At 4 weeks	-0.57 ± 0.08	+0.49 ± 0.08	-0.68 ± 0.10	+0.67 ± 0.10	0.11
		+1.06 ± 0.11 (p < 0.0001)		+1.34 ± 0.14 (p < 0.0001)	
At 52 weeks	-0.46 ± 0.13	+1.89 ± 0.13	-0.27 ± 0.16	+2.11 ± 0.16	0.92
		+2.35 ± 0.18 (p < 0.0001)		+2.80 ± 0.22 (p < 0.0001)	
Serum sodium, mEq/l					
At 4 weeks	0.0 ± 0.1	-0.1 ± 0.1	0.0 ± 0.1	-0.3 ± 0.1	0.39
		-0.1 ± 0.1 (p = 0.45)		-0.2 ± 0.1 (p = 0.084)	
At 52 weeks	-0.2 ± 0.1	-0.1 ± 0.1	-0.1 ± 0.1	0.0 ± 0.1	0.94
		+0.1 ± 0.1 (p = 0.30)		+0.1 ± 0.2 (p = 0.46)	
Serum albumin, g/dl					
At 4 weeks	-0.03 ± 0.01	+0.01 ± 0.01	-0.04 ± 0.01	+0.03 ± 0.01	0.13
		+0.04 ± 0.01 (p = 0.0002)		+0.07 ± 0.01 (p < 0.0001)	
At 52 weeks	-0.03 ± 0.01	0.00 ± 0.01	+0.01 ± 0.01	+0.04 ± 0.01	0.79
		+0.04 ± 0.01 (p = 0.016)		+0.03 ± 0.02 (p = 0.10)	

Values are hazard ratio (95% confidence interval) or mean ± SD. Because of the exceptional non-normal distribution, changes in NT-proBNP are shown as the ratio of adjusted geometric means and 95% confidence intervals.
NT-proBNP = N-terminal pro-B-type natriuretic peptide.

strengths and limitations. Because there are no accepted criteria for defining euvoemia in the clinical setting, site investigators relied on their judgment to identify patients with volume overload. Despite the subjective nature of this assessment, these physicians correctly identified a group of patients who were more likely to have had fluid retention and clinical instability in the previous year and who were likely to require diuretic therapy intensification and experience worsening heart failure events following randomization. However, we did not perform baseline or sequential measurements of plasma or extracellular volume or assess changes in urinary sodium or water excretion in our patients. Such measurements are typically carried out in small, short-term, mechanistic studies conducted under highly controlled conditions where dietary salt and water

can be closely monitored and standardized. Yet small mechanistic studies cannot ascertain long-term effects or determine whether physiological changes produced by a drug are related to changes in the risk of subsequent heart failure events.

Some investigators might suggest that patients with recent volume overload had heart disease that was too advanced to respond favorably to any drug intervention. However, as compared with euvoemic patients, patients with recent volume overload did not have lower ejection fractions or systolic blood pressure or worse renal function. Furthermore, patients with advanced symptoms of heart failure respond as favorably (if not more favorably) to angiotensin-converting enzyme inhibitors, beta-blockers, and mineralocorticoid receptor antagonists, as compared with patients with less functional disability (39).

Interestingly, in the EMPEROR-Reduced trial, patients with an ejection fraction of 30% or less were particularly responsive to treatment with empagliflozin with respect to the effects on the risk of cardiovascular death and hospitalizations for heart failure (6).

Finally, some investigators have hypothesized that SGLT2 inhibitors act preferentially to reduce the accumulation of fluid in the interstitial space (5), an action that would not be readily discerned by measurements of weight or blood constituents. However, this mechanism has been based on modeling analyses and not on direct measurements of interstitial fluid. Furthermore, it is not clear how an effect of SGLT2 inhibitors on the proximal renal tubule could achieve a selective effect to reduce the interstitial fluid volume, especially when changes in the urinary excretion of sodium or water are modest (2,3,10,13,16,26-28). In the current analysis, investigators judged the volume of interstitial fluid by the clinical assessment of circulatory overload, tissue congestion, and peripheral edema. Previous studies have suggested that patients with expanded extracellular volume are particularly responsive to the diuretic effect of SGLT2 inhibitors (18,19), and thus, we anticipated that patients with volume overload would show a particular benefit with these drugs; however, our findings did not confirm this hypothesis. Of course, it is possible that patients who are resistant to the actions of a loop diuretic agent are also resistant to the action of a SGLT2 inhibitor on the proximal tubule. However, the presence of diuretic resistance at multiple renal tubular sites is typically seen in patients with meaningful renal impairment; in contrast, our patients with and without recent volume overload did not differ with respect to baseline renal function or with respect to changes in renal function during follow-up.

CONCLUSIONS

Patients with heart failure whose clinical course is characterized by episodes of volume overload despite the use of loop diuretic agents are not more likely to respond favorably to empagliflozin with respect to symptoms, functional capacity, health status, or the risk of hospitalizations for heart failure. Such patients do not exhibit an exaggerated benefit with SGLT2 inhibitors, even during short-term treatment. Short- and long-term changes in body weight are poorly correlated with changes in natriuretic peptides or hematocrit. These observations do not negate the possibility that SGLT2 inhibitors may exert effects on urine volume or composition or on fluid

compartments in the body. However, taken together, our findings do not support a dominant role of diuresis in mediating the physiological changes or clinical benefits of SGLT2 inhibitors on the course of heart failure in patients with a reduced ejection fraction.

DATA SHARING STATEMENT

Data related to the specific manuscript will be made available on request in compliance with transparency conventions in medical research and through requests to the corresponding author. The executive committee of EMPEROR has developed a comprehensive analysis plan and numerous pre-specified analyses, which will be presented in future scientific presentations and publications. At a later time, the full database will be made available in compliance with the ratified transparency policy.

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ADDRESS FOR CORRESPONDENCE: Dr. Milton Packer, Baylor Heart and Vascular Institute, 621 North Hall Street, Dallas, Texas 75226, USA. E-mail: milton.packer@baylorhealth.edu. Twitter: [@bswhealth](https://twitter.com/bswhealth).

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In patients with reduced left ventricular ejection fraction, actions other than the diuretic effects of SGLT2 inhibitors are the predominant mediators of reduced hospitalizations for heart failure.

TRANSLATIONAL OUTLOOK: Future studies should focus on effects of SGLT2 inhibitors other than urinary sodium excretion and plasma volume, such as promotion of nutrient deprivation signaling.

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