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ORIGINAL RESEARCH PAPER

Recency of Heart Failure Hospitalization, Outcomes, and the Effect of Empagliflozin

An EMPEROR-Pooled Analysis

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ABSTRACT

BACKGROUND Patients with a recent heart failure (HF) hospitalization have a high risk of rehospitalization and mortality. Early treatment may have a substantial impact on patient outcomes.

OBJECTIVES The study sought to study the outcomes and effect of empagliflozin according to timing of prior HF hospitalization.

METHODS EMPEROR-Pooled (EMPEROR-Reduced (EMPagliflozin outcome tRial in Patients With chrOnic hearT Failure With Reduced Ejection Fraction) and EMPEROR-Preserved (EMPagliflozin outcome tRial in Patients With chrOnic hearT Failure With Preserved Ejection Fraction) combined) included 9,718 HF patients who were grouped according to the recency of HF hospitalization (none, <3 months, 3-6 months, 6-12 months, >12 months). The primary outcome was a composite of time to first of HF hospitalization or cardiovascular death, over a median follow-up of 21 months.

RESULTS The primary outcome event rates (per 100 person-years) in the placebo group were 26.7, 18.1, 13.7, and 2.8 for patients hospitalized within 3 months, 3-6 months, 6-12 months, and >12 months, respectively. The relative risk reduction of primary outcome events with empagliflozin was similar across HF hospitalization categories (P interaction = 0.67). The primary outcome absolute risk reduction was more pronounced among patients with a recent HF hospitalization but without statistical heterogeneity of treatment effect: -6.9, -5.5, -0.8, and -0.6 events prevented per 100 person-years for patients hospitalized within <3 months, 3-6 months, 6-12 months, and >12 months, respectively, and -2.4 events prevented per 100 person-years of follow-up in those without a prior HF hospitalization (P interaction = 0.64). Empagliflozin was safe irrespective of HF hospitalization recency.

CONCLUSIONS Patients with a recent HF hospitalization have a high risk of events. Empagliflozin reduced HF events regardless of HF hospitalization recency. (J Am Coll Cardiol HF 2023;■:■-■) © 2023 by the American College of Cardiology Foundation. Published by Elsevier. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

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**ABBREVIATIONS
AND ACRONYMS****aARR** = annualized absolute risk reduction**eGFR** = estimated glomerular filtration rate**HF** = heart failure**LVEF** = left ventricular ejection fraction**NT-proBNP** = N-terminal pro-B-type natriuretic peptide**SGLT2** = sodium-glucose cotransporter 2

Patients with a recent heart failure (HF) hospitalization have a high risk of rehospitalization and mortality.^{1,2} The early postdischarge period (~3 months) after an HF hospitalization is often referred to as the “vulnerable phase” in which the risk of event recurrence is highest.³ Interventions within the vulnerable phase may have a substantial impact on a patient’s outcomes.^{4,5}

Sodium-glucose cotransporter 2 (SGLT2) inhibitors improve outcomes of patients with chronic HF irrespective of ejection fraction or diabetes status.⁶⁻⁸ Thus, these are candidate therapies to be initiated during hospital stay or early in postdischarge period,⁹ as the potential to improve outcomes with SGLT2 inhibitors may be more pronounced among such high-risk patients. Recent studies supported the in-hospital or early postdischarge initiation of SGLT2 inhibitors.⁹⁻¹¹

In this post hoc analysis of the EMPEROR-Pooled (EMPEROR-Reduced and EMPEROR-Preserved combined),¹² we aim to study the prognostic associations and the effect of empagliflozin (vs placebo) according to the timing since prior HF hospitalization.

METHODS

STUDY DESIGN AND PATIENT POPULATION. The design and primary results of EMPEROR-Pooled have been previously published.^{12,13} In brief, the EMPEROR-Pooled combined individual patient data from EMPEROR-Reduced (EMPagliflozin outcome tRial in Patients With chrOnic heaRt Failure With Reduced Ejection Fraction; NCT03057977) and EMPEROR-Preserved (EMPagliflozin outcome tRial in Patients With chrOnic heaRt Failure With Preserved Ejection Fraction; NCT03057951), the 2 phase 3 international, multicenter, randomized, double-blind, parallel-group, placebo-controlled trials that enrolled adult patients with chronic HF with New York Heart Association functional class II to IV symptoms for at least 3 months and elevated natriuretic peptide levels across a wide range of left ventricular ejection fraction (LVEF) ($\leq 40\%$ in EMPEROR-Reduced and $>40\%$ with no prior measurement $\leq 40\%$ in EMPEROR-Preserved).^{6,8}

In EMPEROR-Reduced, patients without a history of HF hospitalization within the 12 months before randomization and an ejection fraction $\geq 30\%$ required higher N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels to enter the trial. Specifically, NT-proBNP levels of at least 1,000 pg/mL were required in patients with an ejection fraction of 31% to 35% and at least 2,500 pg/mL for patients with an ejection fraction between 36% and 40%, as compared with a level of at least 600 pg/mL in those with an ejection fraction $\leq 30\%$ or those hospitalized for HF within 12 months prior to inclusion. These NT-proBNP thresholds were doubled in patients with atrial fibrillation.⁶

In EMPEROR-Preserved, patients without history of HF hospitalization within 12 months before randomization could enter the trial only if they had structural heart disease (left atrial enlargement and/or left ventricular hypertrophy).⁸

The median follow-up time was 16 months in EMPEROR-Reduced, 26 months in EMPEROR-Preserved, and 21 months in EMPEROR-Pooled.

The protocol of each trial complied with the Declaration of Helsinki and was approved by the Ethical Committee of the participating sites, and all patients gave written informed consent to participate in the study.

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

Patients with acute decompensated HF requiring intravenous diuretics, vasodilators, inotropic agents, or mechanical support within 1 week of screening and during the screening period prior to randomization were excluded from the EMPEROR trials.

Patients with a prior HF hospitalization were categorized according to the timing since hospitalization of <3 months, timing since hospitalization of 3-6 months, timing since hospitalization of 6-12 months, timing since hospitalization of >12 months, and no prior HF hospitalization. There were tick boxes in the case report forms to collect

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whether the patient had been hospitalized for HF within the last 12 months. If the patient had been hospitalized for HF, then the date was also to be recorded. There were some cases with missing dates that we categorized as prior HF hospitalization within 6-12 months ($n = 29$).

ENDPOINTS. The primary outcome in the EMPEROR trials was a composite of cardiovascular death or HF hospitalization. Additionally, we studied first and recurrent HF hospitalizations, an extended endpoint including outpatient HF-worsening episodes, cardiovascular (including HF-related) and all-cause death, 2 composite renal endpoints (consisting of sustained decline in estimated glomerular filtration rate [eGFR] $\geq 40\%$ or $\geq 50\%$ from baseline and sustained eGFR < 15 or < 10 mL/min/1.73 m² [for patients with baseline eGFR ≥ 30 or < 30 mL/min/1.73 m², respectively], chronic dialysis or renal transplantation, or renal death if eGFR decline was $\geq 50\%$ from baseline), changes in annualized eGFR slope (chronic slope), and adverse events leading to drug discontinuation.

STATISTICAL ANALYSIS. Baseline characteristics were compared across categories of timing since prior HF hospitalization (< 3 months, 3-6 months, 6-12 months, > 12 months, and no prior HF hospitalization) using analysis of variance for continuous variables and the chi-square test for categorical variables. Associations between baseline timing since prior HF hospitalization categories and subsequent outcomes were studied by comparing the placebo events rates across categories. The effect of treatment (empagliflozin vs placebo) on the study outcomes was assessed using Cox proportional hazards models (and a joint frailty model for recurrent HF hospitalizations and a random intercept-random slope model for between-group differences in eGFR slope using on-treatment data) including the prespecified baseline covariates of age, sex, geographical region, diabetes, study (EMPEROR-Reduced or EMPEROR-Preserved), LVEF, eGFR, timing since prior HF hospitalization category, and a treatment-by-timing since prior HF hospitalization category interaction term, according to the intention-to-treat principle. Annualized absolute risk reductions (aARRs) were calculated from the treatment difference in annualized event rates and were compared across timing since prior HF hospitalization category using a Poisson regression model adjusted by the same covariates used in the Cox model. P values and 95% CIs presented in this report have not been adjusted for multiplicity. All analyses were performed using SAS version 9.4 (SAS Institute).

RESULTS

PATIENT CHARACTERISTICS BY TIMING SINCE PRIOR HF HOSPITALIZATION.

A total of 9,718 patients were included in this analysis. Of these, 6,270 patients did not have a prior HF hospitalization, 928 had been hospitalized more than 12 months prior to enrollment, 736 had been hospitalized within the previous 6-12 months (including 29 patients with missing values), 734 had been hospitalized within the previous 3-6 months, and 1,050 had been hospitalized within the previous 3 months prior to enrollment. Only 275 (2.8%) patients had a hospitalization within 30 days of inclusion. Patients with a more recent HF hospitalization were younger, more frequently were men, more frequently were Asian, had a lower LVEF, had a higher NT-pro BNP, had a higher heart rate, had lower blood pressure, presented more frequently with New York Heart Association functional class III or IV, had a more frequent history of atrial fibrillation and type 2 diabetes mellitus, and were more frequently treated with loop diuretics, mineralocorticoid receptor antagonists, and angiotensin receptor-neprilysin inhibitors. Patients hospitalized > 12 months before enrollment had the highest proportion of angiotensin-converting enzyme inhibitor/angiotensin receptor blocker and beta-blocker treatment (Table 1).

EVENT RATES BY TIMING SINCE PRIOR HF HOSPITALIZATION.

The more recent the prior HF hospitalization was, the higher the event rates were. For example, the primary outcome event rates (per 100 person-years) in the placebo group were 26.7 in patients hospitalized within the previous 3 months, 18.1 in patients hospitalized in the previous 3-6 months, 13.7 in patients hospitalized in the previous 6-12 months, and 2.8 for those hospitalized more than 12 months prior to enrollment. Patients without a prior HF hospitalization had a higher risk of primary outcome events than patients hospitalized more than 12 months prior to enrollment (10.6 vs 2.8). A similar pattern was found for the individual components of the primary outcome, all-cause mortality, and composite renal events. Adverse events leading to drug discontinuation were also more frequent among patients with a more recent HF hospitalization (Figure 1).

TREATMENT EFFECT BY TIMING SINCE PRIOR HF HOSPITALIZATION.

The relative risk reduction of primary outcome events with empagliflozin was similar across the timing of HF hospitalization

TABLE 1 Characteristics of the EMPEROR-Pooled Population by Recency of HF Hospitalization

	Time Since Most Recent HF Hospitalization					P Value
	No Prior HF Hospitalization (n = 6,270)	>12 mo (n = 928)	6-12 mo (n = 736) ^a	3-6 mo (n = 734)	<3 mo (n = 1,050)	
EMPEROR-Reduced	2,155 (34.4)	424 (45.7)	308 (41.8)	341 (46.5)	502 (47.8)	—
EMPEROR-Preserved	4,115 (65.6)	504 (54.3)	428 (58.2)	393 (53.5)	548 (52.2)	—
Age, y	70.4 ± 10.2	69.9 ± 9.9	69.7 ± 10.8	68.2 ± 10.3	68.6 ± 11.2	<0.01
Male	3,880 (61.9)	577 (62.2)	485 (65.9)	507 (69.1)	700 (66.7)	<0.01
BMI, kg/m ²	29.2 ± 5.7	29.0 ± 5.6	28.9 ± 6.2	29.0 ± 6.1	29.0 ± 5.8	0.67
Race						<0.01
White	4,736 (75.5)	712 (76.7)	490 (66.6)	485 (66.1)	748 (71.2)	
Asian	776 (12.4)	165 (17.8)	178 (24.2)	179 (24.4)	198 (18.9)	
Black	366 (5.8)	26 (2.8)	34 (4.6)	37 (5.0)	52 (5.0)	
Other or missing	392 (6.3)	25 (2.7)	34 (4.6)	33 (4.5)	52 (5.0)	
Region						<0.01
North America	736 (11.7)	88 (9.5)	84 (11.4)	126 (17.2)	110 (10.5)	
Latin America	2,133 (34.0)	140 (15.1)	165 (22.4)	138 (18.8)	225 (21.4)	
Europe	2,477 (39.5)	525 (56.6)	278 (37.8)	267 (36.4)	495 (47.1)	
Asia	574 (9.2)	133 (14.3)	157 (21.3)	143 (19.5)	172 (16.4)	
Other	350 (5.6)	42 (4.5)	52 (7.1)	60 (8.2)	48 (4.6)	
LVEF, %	45.3 ± 15.2	41.6 ± 14.6	43.4 ± 15.1	41.2 ± 14.7	41.0 ± 15.3	<0.01
LVEF (EMPEROR-Reduced)						<0.01
<20%	195 (9.0)	26 (6.1)	23 (7.5)	28 (8.2)	49 (9.8)	
20%-30%	1,412 (65.5)	294 (69.3)	183 (59.4)	208 (61.0)	311 (62.0)	
>30%-35%	453 (21.0)	89 (21.0)	64 (20.8)	74 (21.7)	79 (15.7)	
≥35%	95 (4.4)	15 (3.5)	38 (12.3)	31 (9.1)	63 (12.5)	
LVEF (EMPEROR-Preserved)						<0.01
<50%	1,308 (31.8)	188 (37.3)	137 (32.0)	158 (40.2)	192 (35.0)	
50% to <60%	1,383 (33.6)	182 (36.1)	169 (39.5)	142 (36.1)	182 (33.2)	
≥60%	1,424 (34.6)	134 (26.6)	122 (28.5)	93 (23.7)	174 (31.8)	
NT-proBNP, pg/mL	1,195 (621-2,146)	1,122 (588-2,088)	1,540 (787-2,785)	1,461 (771-2,580)	1,716 (967-3,290)	<0.01 ^b
Heart rate, beats/min	70.7 ± 11.8	70.7 ± 11.3	70.8 ± 11.7	71.2 ± 12.4	72.6 ± 12.0	<0.01
SBP, mm Hg	128.7 ± 16.2	128.3 ± 15.3	127.3 ± 17.1	126.9 ± 16.7	125.4 ± 17.0	<0.01
DBP, mm Hg	75.3 ± 10.6	75.3 ± 10.2	73.9 ± 10.7	74.3 ± 11.4	74.7 ± 11.2	<0.01
eGFR, mL/min/1.73 m ²	61.3 ± 20.3	61.8 ± 19.8	59.7 ± 20.7	61.9 ± 21.9	60.0 ± 21.7	0.05
eGFR <60 mL/min/1.73 m ²	3,047 (48.6)	445 (48.0)	391 (53.1)	353 (48.1)	551 (52.5)	0.03
UACR, mg/g	21.2 (8.0-75.1)	14.1 (6.2-48.6)	25.3 (8.0-97.0)	20.0 (8.0-69.8)	28.3 (9.7-105)	<0.01 ^b
Hb, g/dL	13.5 ± 1.6	13.7 ± 1.6	13.3 ± 1.6	13.3 ± 1.7	13.4 ± 1.6	<0.01
NYHA functional class III/IV	1,221 (19.5)	148 (15.9)	186 (25.3)	155 (21.1)	321 (30.6)	<0.01
Lung rales	452 (7.2)	124 (13.4)	66 (9.0)	58 (7.9)	92 (8.8)	<0.01
Peripheral edema	1,655 (26.4)	209 (22.5)	227 (30.8)	212 (28.9)	297 (28.3)	<0.01
Jugular venous distension	422 (6.7)	62 (6.7)	59 (8.0)	56 (7.6)	95 (9.0)	0.07
Time since HF diagnosis, y	5.2 ± 5.6	6.3 ± 5.7	4.5 ± 6.1	3.5 ± 5.3	4.6 ± 5.4	<0.01
Ischemic cause of HF	2,598 (41.4)	445 (48.0)	307 (41.7)	295 (40.2)	401 (38.2)	<0.01

Continued on the next page

categories (P interaction = 0.67). However, the primary outcome aARRs (expressed as events prevented per 100 person-years of follow-up) were more pronounced among patients with a recent HF hospitalization, particularly among those hospitalized <3 months prior to enrollment (−6.9 in <3 months, −5.5 in 3-6 months, −0.8 in 6-12 months, −0.6 in >12 months, and −2.4 in those without a prior HF hospitalization), but without statistical heterogeneity of treatment

effect (P interaction = 0.64). A similar pattern was found for HF hospitalizations and for the expanded outcome including outpatient worsening HF events (**Central Illustration**).

The effect of empagliflozin on cardiovascular mortality was overall neutral regardless of HF hospitalization recency (in <3 months, HR: 0.71 [95% CI: 0.51-1.00]; in 3-6 months, HR: 0.87 [95% CI: 0.55-1.37]; in 6-12 months, HR: 1.19 [95% CI: 0.74-1.93]; in

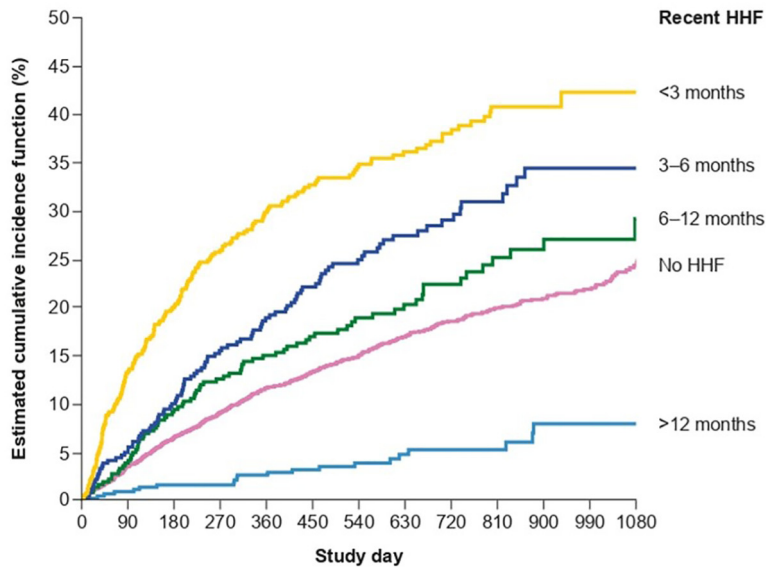
TABLE 1 Continued

	Time Since Most Recent HF Hospitalization					P Value
	No Prior HF Hospitalization (n = 6,270)	>12 mo (n = 928)	6-12 mo (n = 736) ^a	3-6 mo (n = 734)	<3 mo (n = 1,050)	
History of AF	2,828 (45.1)	459 (49.5)	389 (52.9)	348 (47.4)	552 (52.6)	<0.01
History of hypertension	5,260 (83.9)	762 (82.1)	608 (82.6)	611 (83.2)	881 (83.9)	0.64
History of T2D	3,007 (48.0)	413 (44.5)	395 (53.7)	378 (51.5)	601 (57.2)	<0.01
ACE inhibitor/ARB	4,807 (76.7)	727 (78.3)	506 (68.8)	516 (70.3)	749 (71.3)	<0.01
ARNI	494 (7.9)	80 (8.6)	76 (10.3)	73 (9.9)	138 (13.1)	<0.01
Beta-blocker	5,563 (88.7)	862 (92.9)	654 (88.9)	674 (91.8)	947 (90.2)	<0.01
Thiazide diuretic	1,118 (17.8)	131 (14.1)	78 (10.6)	71 (9.7)	126 (12.0)	<0.01
Loop diuretic	4,264 (68.0)	730 (78.7)	633 (86.0)	639 (87.1)	938 (89.3)	<0.01
MRA	2,881 (45.9)	496 (53.4)	433 (58.8)	435 (59.3)	660 (62.9)	<0.01
ICD	629 (10.0)	147 (15.8)	97 (13.2)	86 (11.7)	113 (10.8)	<0.01
CRT (CRT-D or CRT-P)	261 (4.2)	83 (8.9)	42 (5.7)	35 (4.8)	45 (4.3)	<0.01
Randomization to empagliflozin	3,090 (49.3)	494 (53.2)	376 (51.1)	372 (50.7)	528 (50.3)	–

Values are n (%), mean ± SD, or median (IQR). ^aCategory includes missing values (29 patients). ^bBased on log-transformed results.

ACE = angiotensin-converting enzyme; AF = atrial fibrillation or flutter; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; BMI = body mass index; CRT = cardiac resynchronization therapy; CRT-D = cardiac resynchronization therapy with defibrillator; CRT-P = cardiac resynchronization therapy with pacemaker; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate with Chronic Kidney Disease Epidemiology Collaboration formula; EMPEROR-Pooled = EMPEROR-Reduced and EMPEROR-Preserved together; EMPEROR-Preserved = EMPagliflozin outcomE tRial in Patients With chrOnic hearT Failure With Preserved Ejection Fraction; EMPEROR-Reduced = EMPagliflozin outcomE tRial in Patients With chrOnic hearT Failure With Reduced Ejection Fraction; Hb, hemoglobin; HF = heart failure; ICD = implantable cardioverter-defibrillator; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; SBP = systolic blood pressure; T2D = type 2 diabetes mellitus, UACR = urinary albumin-to-creatinine ratio.

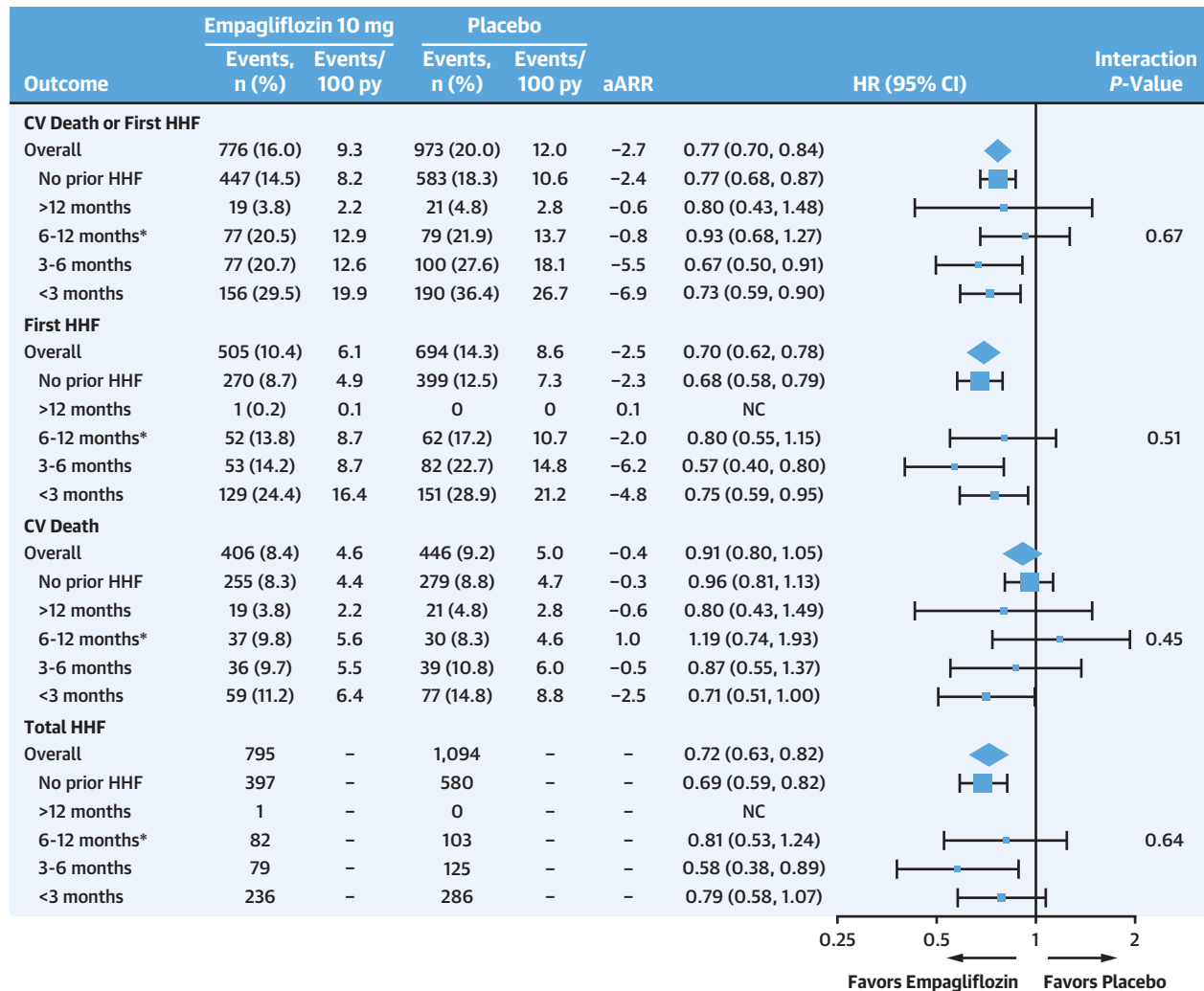
FIGURE 1 Placebo Group Cumulative Incidence of Primary Outcome Events by Recency of Hospitalization for HF Subgroups



Patients at risk

No HHF	3180	3043	2928	2746	2541	2233	1844	1546	1224	979	690	466	275
>12 months	434	426	420	387	364	317	249	199	157	124	88	65	40
6-12 months	360	346	325	293	271	237	185	157	121	90	65	44	29
3-6 months	362	338	314	275	252	225	181	151	111	85	60	47	24
<3 months	522	450	411	350	307	266	218	178	145	109	79	61	32

HF = heart failure.

CENTRAL ILLUSTRATION Effect of Empagliflozin According to Recency of Hospitalization for HF in EMPEROR

Ferreira JP, et al. J Am Coll Cardiol HF. 2023;■(■):■-■.

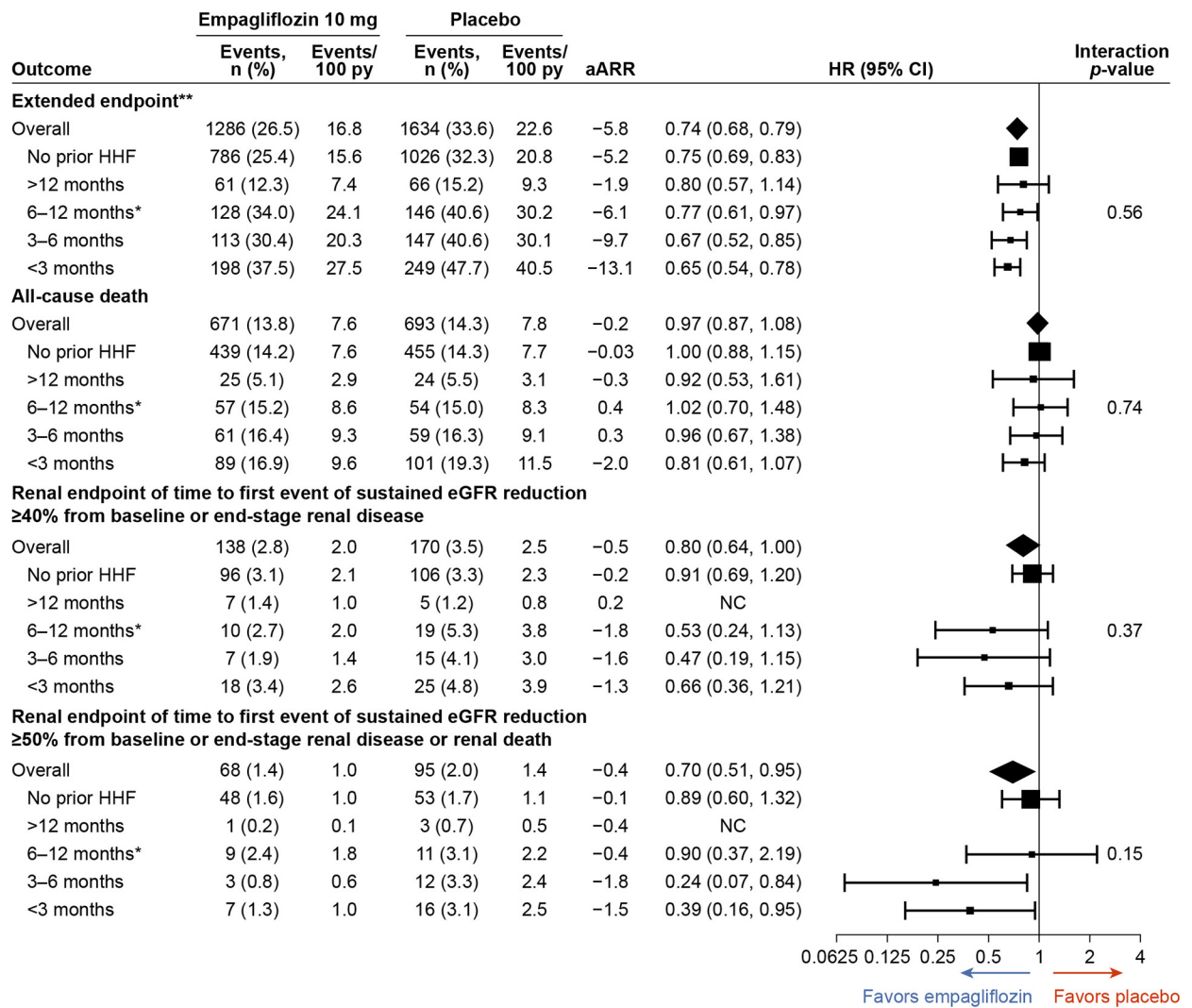
*Indicates including 29 patients with missing values. aARR = annualized absolute risk reduction; CV = cardiovascular; EMPEROR = EMPagliflozin outcome tRIal in Patients With chrOnic heaRt Failure; HF = heart failure; NC = not computed.

>12 months, HR: 0.80 [95% CI: 0.43-1.49]; and in those without a prior HF hospitalization, HR: 0.96 [95% CI: 0.81-1.13]; *P* interaction = 0.45) and aARR (expressed as events prevented per 100 person-years of follow-up; -2.5 in <3 months, -0.5 in 3-6 months, 1.0 in 6-12 months, -0.6 in >12 months, and -0.3 in those without a prior HF hospitalization; *P* interaction = 0.46). A similar pattern was found for all-cause mortality (Central Illustration).

Relative and absolute reductions of composite renal outcomes were consistent regardless of HF

hospitalization recency. For the endpoint of $\geq 50\%$ sustained eGFR drop, the HR was 0.39 (95% CI: 0.16-0.95) in <3 months, was 0.24 (95% CI: 0.07-0.84) in 3-6 months, was 0.90 (95% CI: 0.37-2.19) in 6-12 months, was not calculated in >12 months because only 4 events occurred; and was 0.89 (95% CI: 0.60-1.32) in those without a prior HF hospitalization (*P* interaction = 0.15), and the aARR (expressed as events prevented per 100 person-years of follow-up) was -1.5 in <3 months, -1.8 in 3-6 months, -0.4 in 6-12 months, -0.4 in >12 months, and -0.1 in those

FIGURE 2 Event Rates and Treatment Effect by Recency of Hospitalization for HF



Annualized absolute risk reduction (aARR) is expressed as events prevented per 100 person-years of follow-up. Event rates are presented as per 100 person-years (py). The primary outcome was the composite of cardiovascular death or hospitalization for HF. *Category includes missing values (29 patients). **Time to first of cardiovascular death, heart failure hospitalization, or equivalent event or visit reporting intensification of diuretic therapy. AE = adverse event; eGFR = estimated glomerular filtration rate; other abbreviation as in Figure 1.

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without a prior HF hospitalization (P interaction = 0.08) (Figure 2A).

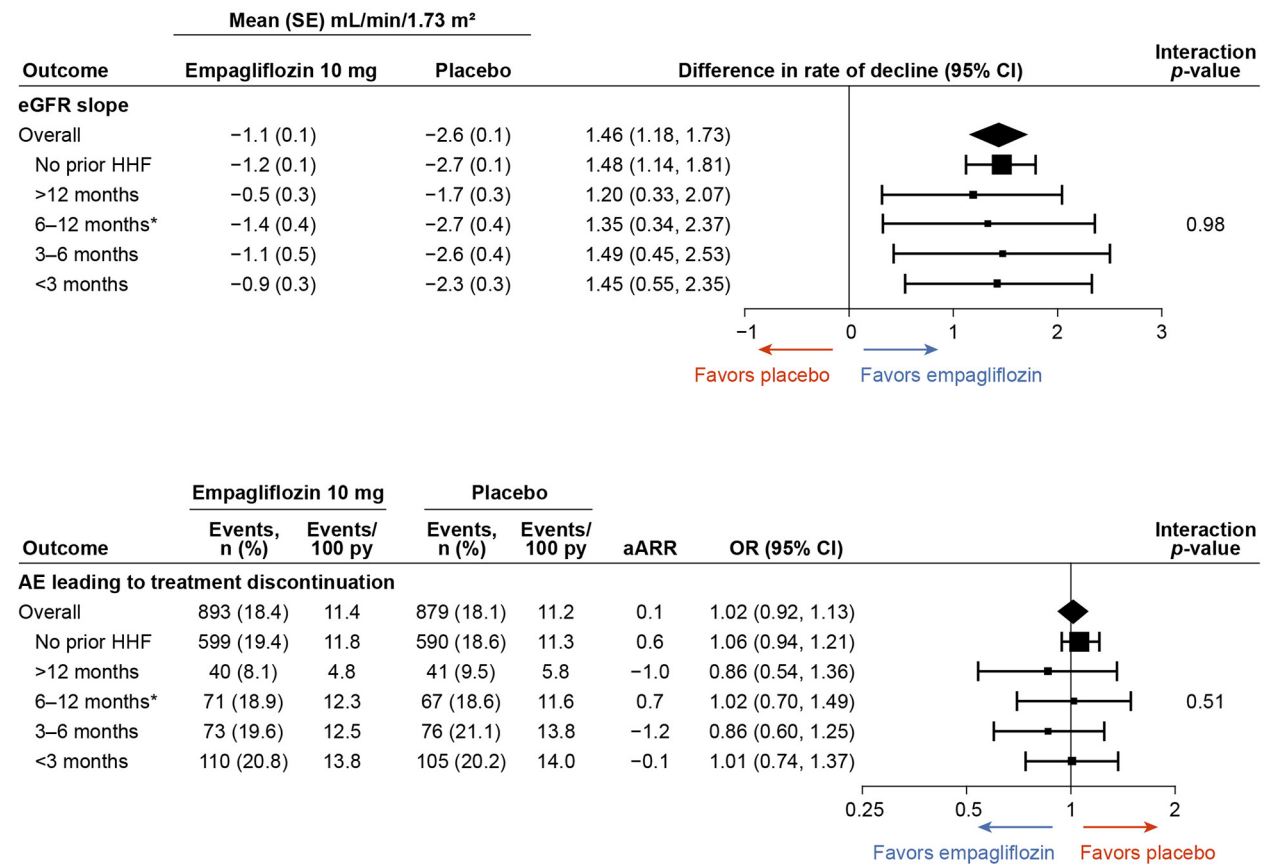
Treatment differences in eGFR slope and adverse events leading to drug discontinuation were similar across timing of HF hospitalization categories (Figure 2B).

Relative and absolute reductions of primary outcome events with empagliflozin were consistent

across timing of HF hospitalization categories in EMPEROR-Reduced and EMPEROR-Preserved (Supplemental Table 1).

A higher proportion of patients with <80% study drug compliance was observed among patients who had never been hospitalized for HF vs those hospitalized >12 months before inclusion (Supplemental Table 2).

FIGURE 2 Continued



DISCUSSION

Patients with a recent HF hospitalization had a higher risk of subsequent events, and our study shows that the effect of empagliflozin was consistent regardless of the timing of prior HF hospitalization. These findings underscore the importance of initiating empagliflozin as early as possible including within or early after an HF hospitalization if the patient was hospitalized.

Patients with a recent HF hospitalization usually present a high risk of subsequent events.^{3,14} In previous risk-based analyses of the EMPEROR trials, a recent HF hospitalization was one of the strongest event predictors only after NT-proBNP and high-sensitivity troponin T.^{1,2} High-risk patients (such as those with a recent HF hospitalization) may experience important absolute risk reductions with empagliflozin treatment.^{1,2} Therefore, if not initiated to prevent a first HF

hospitalization, early initiation of an SGLT2 inhibitor within or early after an HF hospitalization is important due to the capacity of these agents to rapidly modify prognosis within a few days of treatment initiation.¹⁵⁻¹⁷ This rapid benefit may be particularly marked in patients with a recent HF hospitalization and during the vulnerable phase due to the capacity of SGLT2 inhibitors to reduce congestion and improve the clinical stability of HF patients.^{15,16}

In SOLOIST-WHF (Effect of Sotagliflozin on Cardiovascular Events in Patients With Type 2 Diabetes Post Worsening Heart Failure), enrolling patients with type 2 diabetes mellitus and a recent HF hospitalization, the SGLT1/2 inhibitor sotagliflozin reduced the first occurrence of either cardiovascular death or HF hospitalization by 29% (HR: 0.71 [95% CI: 0.56-0.89]),¹¹ an event reduction that was similar to the 27% seen in patients with a recent HF hospitalization (<3 months) in EMPEROR-Pooled

(HR: 0.73 [95% CI: 0.59-0.90]). In EMPULSE (A Study to Test the Effect of Empagliflozin in Patients Who Are in Hospital for Acute Heart Failure), enrolling in-hospital 530 patients admitted for acute HF, empagliflozin provided greater clinical benefit than placebo at 90 days by improving health status along with a concordant reduction in HF events and mortality.⁹

An analysis from PARAGON-HF (Prospective Comparison of ARNI with ARB Global Outcomes in HFpEF) showed that the risk of HF rehospitalizations and mortality was highest among patients with a recent HF hospitalization (<3 months, in particular), who were the patients with the largest relative and absolute benefit from sacubitril/valsartan treatment compared with valsartan.⁵ In DELIVER (Dapagliflozin Evaluation to Improve the LIVES of Patients With PReserved Ejection Fraction Heart Failure), patients with a recent HF hospitalization also experienced a high risk of events, and the relative reduction of primary outcome events with dapagliflozin was similar in patients with and without a recent HF hospitalization, but the absolute reduction was higher among patients with a recent HF hospitalization.¹⁰

In EMPEROR-Pooled, the high risk of primary outcome events seen in patients with a recent HF hospitalization (26.7 events per 100 person-years in the placebo group in patients hospitalized within the previous 3 months) was markedly reduced with empagliflozin (to 19.9 events per 100 person-years), corresponding to an aARR of -6.9 events prevented per 100 person-years of follow-up and a number needed to treat to benefit of 19 patients. The event rate reduction with empagliflozin seen in patients hospitalized within the previous 3 months changed the risk of these patients (who were in the vulnerable phase) to a risk similar to placebo-treated patients hospitalized more than 3 months prior to enrollment (who were no longer in the vulnerable phase). Our findings confirm prior (previously referenced) studies supporting the SGLT2 inhibitor initiation within the hospital or early after discharge.

One should also note that patients hospitalized more than 12 months prior to enrollment had lower event rates than patients who had never been hospitalized. This may be partly due to a better background HF treatment of patients who had been hospitalized in the past, which is supported by the higher proportion of angiotensin-converting enzyme inhibitor/angiotensin receptor blocker and beta-

blocker use among patients hospitalized more than 12 months prior to enrollment. Furthermore, patients hospitalized more than 12 months before inclusion had better study drug compliance than those who had never been hospitalized; thus, the better compliance may also have occurred for other guideline-directed medical therapy, providing an additional explanation for the lower event rate observed among patients with an HF hospitalization occurring >12 months before inclusion compared with patients who had never been hospitalized.

STUDY LIMITATIONS. This is a nonprespecified post hoc analysis, and these results should be regarded as hypothesis-generating. Subgroups of timing since a prior HF hospitalization have limited power to assess within-group treatment effects. Less than 3% of patients were hospitalized in the 30 days prior to inclusion; thus, these results may not be generalizable to patients hospitalized in the previous month.

CONCLUSIONS

Patients with a recent HF hospitalization, particularly if occurring within the previous 3 months, have a high risk of HF rehospitalization and mortality and experience large absolute benefit from empagliflozin treatment. These findings underscore the importance of initiating empagliflozin as early as possible within or early after an HF hospitalization, if not possible to initiate treatment to prevent a first HF hospitalization.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Our findings suggest that empagliflozin benefits patients regardless of the timing of prior HF hospitalization.

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Empagliflozin should be initiated within the hospital or early after discharge, if not possible to use it for preventing a first HF hospitalization.

TRANSLATIONAL OUTLOOK: Patients with a recent HF hospitalization have a high risk of subsequent events, and future trials should aim reducing events in this high-risk population.

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KEY WORDS empagliflozin, heart failure hospitalization recency, risk

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