Recency of Heart Failure Hospitalization, Outcomes, and the Effect of Empagliflozin: An EMPEROR-Pooled Analysis

EMPEROR Heart failure studies

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BACKGROUND

- Patients with a recent heart failure (HF) hospitalization have a high-risk of re-hospitalization and mortality.
- Sodium-glucose co-transporter-2 inhibitors improve outcomes of patients with chronic HF and clinical studies support their initiation either during hospital stay for HF or early post-discharge.

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OBJECTIVE

- To evaluate the outcomes and effect of empagliflozin according to time of prior hospitalization for HF (HHF).

METHODS

- This *post hoc* analysis of EMPEROR-Pooled (EMPEROR-Reduced[1] and EMPEROR-Preserved[2] combined) included 9718 patients with HF across the entire spectrum of ejection fraction, randomized to either empagliflozin 10 mg daily or placebo, in addition to their usual therapy.
- Participants were categorized according to the time since prior HHF as <3, 3 to 6, 6 to 12, >12 months, and no prior HHF.
- The primary outcome was a composite of cardiovascular (CV) death or HHF. The effect of empagliflozin versus placebo was assessed using Cox proportional hazards models including prespecified baseline covariates.
- Additional endpoints included components of the primary outcome, HHF, an extended endpoint including outpatient HF worsening episodes, all-cause death, composite renal endpoints, estimated glomerular filtration rate (eGFR), and adverse events (AEs) leading to treatment discontinuation.

RESULTS

- 6270 (64.5%) of randomized participants did not have a prior HHF. The median follow-up time in EMPEROR-Pooled was 21 months.
- Key baseline characteristics are detailed in **Table 1**.

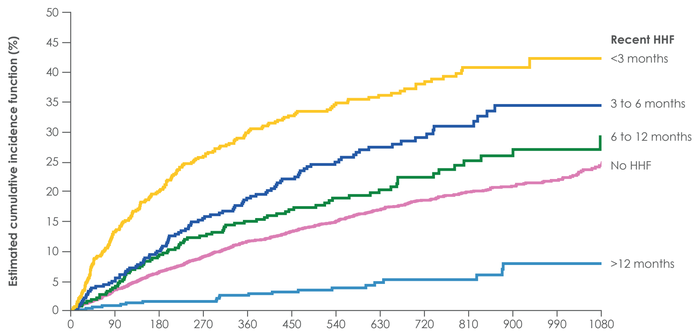
Table 1. Baseline characteristics of the EMPEROR-Pooled population by recency of HHF

Baseline characteristics	Time since most recent HHF, months					*p*-value
	No prior HHF (n=6270)	>12 (n=928)	6 to 12* (n=736)	3 to 6 (n=734)	<3 (n=1050)	
EMPEROR-Reduced	2155 (34.4)	424 (45.7)	308 (41.8)	341 (46.5)	502 (47.8)	-
EMPEROR-Preserved	4115 (65.6)	504 (54.3)	428 (58.2)	393 (53.5)	548 (52.2)	-
Age, years	70.4±10.2	69.9±9.9	69.7±10.8	68.2±10.3	68.6±11.2	<0.01
Men	3880 (61.9)	577 (62.2)	485 (65.9)	507 (69.1)	700 (66.7)	<0.01
BMI, kg/m²	29.2±5.7	29.0±5.6	28.9±6.2	29.0±6.1	29.0±5.8	0.67
Race						
White	4736 (75.5)	712 (76.7)	490 (66.6)	485 (66.1)	748 (71.2)	<0.01
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)	
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)						
<20	195 (9.0)	26 (6.1)	23 (7.5)	28 (8.2)	49 (9.8)	<0.01
20 to 30	1412 (65.5)	294 (69.3)	183 (59.4)	208 (61.0)	311 (62.0)	
>30 to 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)						
<50	1308 (31.8)	188 (37.3)	137 (32.0)	158 (40.2)	192 (35.0)	<0.01
50 to <60	1383 (33.6)	182 (36.1)	169 (39.5)	142 (36.1)	182 (33.2)	
≥60	1424 (34.6)	134 (26.6)	122 (28.5)	93 (23.7)	174 (31.8)	
NT-proBNP, pg/ml	1195 (621-2146)	1122 (588-2088)	1540 (787-2785)	1461 (771-2580)	1716 (967-3290)	<0.01**
eGFR, ml/min/1.73 m²	61.3±20.3	61.8±19.8	59.7±20.7	61.9±21.9	60.0±21.7	0.05
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**
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	1221(19.5)	148 (15.9)	186 (25.3)	155 (21.1)	321 (30.6)	<0.01
Time since HF diagnosis, years	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	2598 (41.4)	445 (48.0)	307 (41.7)	295 (40.2)	401 (38.2)	<0.01
History of AF	2828 (45.1)	459 (49.5)	389 (52.9)	348 (47.4)	552 (52.6)	<0.01
History of hypertension	5260 (83.9)	762 (82.1)	608 (82.6)	611 (83.2)	881 (83.9)	0.64
History of T2D	3007 (48.0)	413 (44.5)	395 (53.7)	378 (51.5)	601 (57.2)	<0.01
ACEI/ARB	4807 (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	5563 (88.7)	862 (92.9)	654 (88.9)	674 (91.8)	947 (90.2)	<0.01
Thiazide diuretic	1118 (17.8)	131 (14.1)	78 (10.6)	71 (9.7)	126 (12.0)	<0.01
Loop diuretic	4264 (68.0)	730 (78.7)	633 (86.0)	639 (87.1)	938 (89.3)	<0.01
MRA	2881 (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 -P)	261 (4.2)	83 (8.9)	42 (5.7)	35 (4.8)	45 (4.3)	<0.01
Randomization to empagliflozin	3090 (49.3)	494 (53.2)	376 (51.1)	372 (50.7)	528 (50.3)	-

Values are mean ± SD, median (IQR) or n (%). *Category includes missing values (29 patients), **Based on log-transformed results.
ACEI, angiotensin converting enzyme inhibitor; AF, atrial fibrillation or flutter; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; BMI, body mass index; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CRT, cardiac resynchronization therapy in the presence (-D) or absence of a defibrillator (-P); DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate with CKD-EPI formula; Hb, hemoglobin; HF, heart failure; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-pro BNP, N-terminal pro-B type natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure; T2D, type diabetes mellitus; UACR, urine albumin-to-creatinine ratio.

- The more recent the prior HHF, the greater the incidence of primary outcome events is observed (**Figure 1**).

Figure 1. Placebo group cumulative incidence of primary outcome events by recency of HHF subgroups



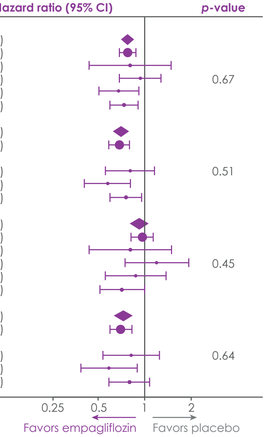
Participants at risk, n													
No HHF	3180	3043	2928	2746	2541	2233	1844	1546	1224	979	690	466	275
>12 months	434	426	420	387	364	317	249	199	157	124	88	65	40
6 to 12 months	360	346	325	293	271	237	185	157	121	90	65	44	29
3 to 6 months	362	338	314	275	252	225	181	151	111	85	60	47	24
<3 months	522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

- Relative risk reduction of the first HHF or CV death with empagliflozin versus placebo was similar across timing of HHF categories (interaction p-value=0.67). However, the annual absolute risk reduction was more pronounced among participants with a recent HHF, particularly in those hospitalized <3 months prior to enrolment (**Figure 2A**).
- A similar pattern was found for HHF (**Figure 2A**), and for extended outcome including outpatient worsening HF events (**Figure 2B**).
- Treatment differences in eGFR slope and AEs leading to drug discontinuation were similar across timing of HHF categories (**Figure 2C**).

Figure 2. Event rates and treatment effect by recency of HHF

2A

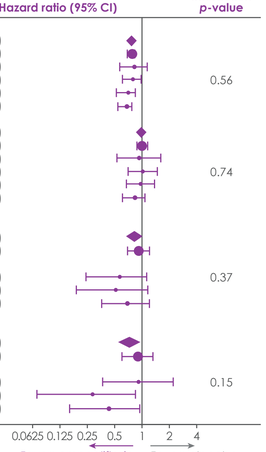
Outcome	Empagliflozin Events, n (%)	Empagliflozin Events/ 100 py	Placebo Events, n (%)	Placebo Events/ 100 py	aARR	Hazard ratio (95% CI)	Interaction *p*-value
CV death or first HHF							
Overall	776 (16.0)	9.3	973 (20.0)	12.0	−2.7	0.77 (0.70, 0.84)	
No prior HHF	447 (14.5)	8.2	583 (18.3)	10.6	−2.4	0.77 (0.68, 0.87)	
>12 months	19 (3.8)	2.2	21 (4.8)	2.8	−0.6	0.80 (0.43, 1.48)	
6 to 12 months*	77 (20.5)	12.9	79 (21.9)	13.7	−0.8	0.93 (0.68, 1.27)	0.67
3 to 6 months	77 (20.7)	12.6	100 (27.6)	18.1	−5.5	0.67 (0.50, 0.91)	
<3 months	156 (29.5)	19.9	190 (36.4)	26.7	−6.9	0.73 (0.59, 0.90)	
First HHF							
Overall	505 (10.4)	6.1	694 (14.3)	8.6	−2.5	0.70 (0.62, 0.78)	
No prior HHF	270 (8.7)	4.9	399 (12.5)	7.3	−2.3	0.68 (0.58, 0.79)	
>12 months	1 (0.2)	0.1	0	0	0.1	NC	
6 to 12 months*	52 (13.8)	8.7	62 (17.2)	10.7	−2.0	0.80 (0.55, 1.15)	0.51
3 to 6 months	53 (14.2)	8.7	82 (22.7)	14.8	−6.2	0.57 (0.40, 0.80)	
<3 months	129 (24.4)	16.4	151 (28.9)	21.2	−4.8	0.75 (0.59, 0.95)	
CV death							
Overall	406 (8.4)	4.6	446 (9.2)	5.0	−0.4	0.91 (0.80, 1.05)	
No prior HHF	255 (8.3)	4.4	279 (8.8)	4.7	−0.3	0.96 (0.81, 1.13)	
>12 months	19 (3.8)	2.2	21 (4.8)	2.8	−0.6	0.80 (0.43, 1.49)	
6 to 12 months*	37 (9.8)	5.6	30 (8.3)	4.6	1.0	1.19 (0.74, 1.93)	0.45
3 to 6 months	36 (9.7)	5.5	39 (10.8)	6.0	−0.5	0.87 (0.55, 1.37)	
<3 months	59 (11.2)	6.4	77 (14.8)	8.8	−2.5	0.71 (0.51, 1.00)	
Total HHF							
Overall	795	–	1094	–	–	0.72 (0.63, 0.82)	
No prior HHF	397	–	580	–	–	0.69 (0.59, 0.82)	
>12 months	1	–	0	–	–	NC	
6 to 12 months*	82	–	103	–	–	0.81 (0.53, 1.24)	0.64
3 to 6 months	79	–	125	–	–	0.58 (0.38, 0.89)	
<3 months	236	–	286	–	–	0.79 (0.58, 1.07)	



aARR is expressed as events prevented per 100 py of follow-up.
*Category includes missing values (29 patients).
aARR, annualized absolute risk reduction; CI, confidence interval; CV, cardiovascular; HHF, hospitalization for heart failure; NC, not calculated; py, patient-years.

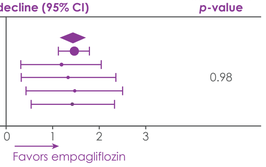
2B

Outcome	Empagliflozin Events, n (%)	Empagliflozin Events/ 100 py	Placebo Events, n (%)	Placebo Events/ 100 py	aARR	Hazard ratio (95% CI)	Interaction *p*-value
Extended endpoint*							
Overall	1286 (26.5)	16.8	1634 (33.6)	22.6	−5.8	0.74 (0.68, 0.79)	
No prior HHF	786 (25.4)	15.6	1026 (32.3)	20.8	−5.2	0.75 (0.69, 0.83)	
>12 months	61 (12.3)	7.4	66 (15.2)	9.3	−1.9	0.80 (0.57, 1.14)	
6 to 12 months†	128 (34.0)	24.1	146 (40.6)	30.2	−6.1	0.77 (0.61, 0.97)	0.56
3 to 6 months	113 (30.4)	20.3	147 (40.6)	30.1	−9.7	0.67 (0.52, 0.85)	
<3 months	198 (37.5)	27.5	249 (47.7)	40.5	−13.1	0.65 (0.54, 0.78)	
All-cause death							
Overall	671 (13.8)	7.6	693 (14.3)	7.8	−0.2	0.97 (0.87, 1.08)	
No prior HHF	439 (14.2)	7.6	455 (14.3)	7.7	−0.03	1.00 (0.88, 1.15)	
>12 months	25 (5.1)	2.9	24 (5.5)	3.1	−0.3	0.92 (0.53, 1.61)	
6 to 12 months†	57 (15.2)	8.6	54 (15.0)	8.3	0.4	1.02 (0.70, 1.48)	0.74
3 to 6 months	61 (16.4)	9.3	59 (16.3)	9.1	0.3	0.96 (0.67, 1.38)	
<3 months	89 (16.9)	9.6	101 (19.3)	11.5	−2.0	0.81 (0.61, 1.07)	
Renal endpoint of time to first event of sustained eGFR reduction ≥40% from baseline or end-stage renal disease							
Overall	138 (2.8)	2.0	170 (3.5)	2.5	−0.5	0.80 (0.64, 1.00)	
No prior HHF	96 (3.1)	2.1	106 (3.3)	2.3	−0.2	0.91 (0.69, 1.20)	
>12 months	7 (1.4)	1.0	5 (1.2)	0.8	0.2	NC	
6 to 12 months†	10 (2.7)	2.0	19 (5.3)	3.8	−1.8	0.53 (0.24, 1.13)	0.37
3 to 6 months	7 (1.9)	1.4	15 (4.1)	3.0	−1.6	0.47 (0.19, 1.15)	
<3 months	18 (3.4)	2.6	25 (4.8)	3.9	−1.3	0.66 (0.36, 1.21)	
Renal endpoint of time to first event of sustained eGFR reduction ≥50% from baseline or end-stage renal disease or renal death							
Overall	68 (1.4)	1.0	95 (2.0)	1.4	−0.4	0.70 (0.51, 0.95)	
No prior HHF	48 (1.6)	1.0	53 (1.7)	1.1	−0.1	0.89 (0.60, 1.32)	
>12 months	1 (0.2)	0.1	3 (0.7)	0.5	−0.4	NC	
6 to 12 months†	9 (2.4)	1.8	11 (3.1)	2.2	−0.4	0.90 (0.37, 2.19)	0.15
3 to 6 months	3 (0.8)	0.6	12 (3.3)	2.4	−1.8	0.24 (0.07, 0.84)	
<3 months	7 (1.3)	1.0	16 (3.1)	2.5	−1.5	0.39 (0.16, 0.95)	



2C

Outcome	Mean (SE) ml/min/1.73 m² Empagliflozin	Mean (SE) ml/min/1.73 m² Placebo	Difference in rate of decline (95% CI)	Interaction *p*-value
eGFR slope				
Overall	−1.1 (0.1)	−2.6 (0.1)	1.46 (1.18, 1.73)	
No prior HHF	−1.2 (0.1)	−2.7 (0.1)	1.48 (1.14, 1.81)	
>12 months	−0.5 (0.3)	−1.7 (0.3)	1.20 (0.33, 2.07)	
6 to 12 months†	−1.4 (0.4)	−2.7 (0.4)	1.35 (0.34, 2.37)	0.98
3 to 6 months	−1.1 (0.5)	−2.6 (0.4)	1.49 (0.45, 2.53)	
<3 months	−0.9 (0.3)	−2.3 (0.3)	1.45 (0.55, 2.35)	



Outcome	Empagliflozin Events, n (%)	Empagliflozin Events/ 100 py	Placebo Events, n (%)	Placebo Events/ 100 py	aARR	Odds ratio (95% CI)	Interaction *p*-value
AE leading to treatment discontinuation							
Overall	893 (18.4)	11.4	879 (18.1)	11.2	0.1	1.02 (0.92, 1.13)	
No prior HHF	599 (19.4)	11.8	590 (18.6)	11.3	0.6	1.06 (0.94, 1.21)	
>12 months	40 (8.1)	4.8	41 (9.5)	5.8	−1.0	0.86 (0.54, 1.36)	
6 to 12 months†	71 (18.9)	12.3	67 (18.6)	11.6	0.7	1.02 (0.70, 1.49)	0.51
3 to 6 months	73 (19.6)	12.5	76 (21.1)	13.8	−1.2	0.86 (0.60, 1.25)	
<3 months	110 (20.8)	13.8	105 (20.2)	14.0	−0.1	1.01 (0.74, 1.37)	

aARR is expressed as events prevented per 100 py of follow-up.
*Time to first of CV death, HHF or equivalent event or visit reporting intensification of diuretic therapy.
†Category includes missing values (29 patients).
aARR, annualized absolute risk reduction; AE, adverse event; CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HHF, hospitalization for heart failure; NC, not calculated; py, patient-years.

CONCLUSIONS

- Patients with a recent HHF have a higher risk of HF rehospitalization or mortality.
- Empagliflozin reduced the composite endpoint of HHF or CV mortality, extended endpoint including outpatient worsening HF events as well as HHF regardless of the timing of prior HHF.
- Patients with recent HHF may experience larger absolute benefit from the treatment with empagliflozin.
- These findings emphasize the importance of initiating empagliflozin as early as possible during or early after HHF.

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Presenter: TBC

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1. Packer M *et al. N Engl J Med* 2020;383:1413–1424.
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Disclosures
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