SUPPLEMENTAL MATERIAL

Effect of Empagliflozin on the Clinical Stability of Patients with Heart Failure and a Reduced Ejection Fraction: the EMPEROR-Reduced Trial

Figure I

Time to first event analysis of all-cause mortality or all-cause hospitalization in the placebo and empagliflozin groups

Figure II

Effect of empagliflozin on total (first and recurrent) adjudicated hospitalizations for heart failure in 12 prespecified subgroups

Figure III

Time to first event analysis of all-cause mortality, heart failure hospitalization or emergent/urgent care visit for worsening heart failure in the placebo and empagliflozin groups during first 40 days following randomization

Figure IV

Total study visits reporting interval intensification of diuretics for worsening heart failure in the placebo and empagliflozin groups

Figure V

Changes in hematocrit during double-blind treatment in the placebo and empagliflozin groups

Figure VI

Changes in uric acid during double-blind treatment in the placebo and empagliflozin groups

Figure VII

Changes in body weight during double-blind treatment in the placebo and empagliflozin groups

Figure VIII

Changes in N-terminal proBNP during double-blind treatment in the placebo and empagliflozin groups

Figure IX

Changes in systolic blood pressure during double-blind treatment in the placebo and empagliflozin groups

<u>Table I</u>

Frequencies of major outcomes and worsening heart failure events

Figure I Time to first event of all-cause mortality or all-cause hospitalization



Abbreviations: HR=hazard ratio; CI = confidence interval

Figure II Effect of empagliflozin on total (first and recurrent) adjudicated hospitalizations for heart failure in 12 prespecified subgroups

	Empagliflozin Total / N analyzed	Placebo Total / N analyzed	Hazard ratio (95% CI)		Interaction p-value
Overall	388/1863	553/1867	0.70 (0.58, 0.85)	⊢● −	
Baseline diabetes status					0.4428
Diabetic	221/927	337/929	0.65 (0.50, 0.85)	⊢	
Non-diabetic	167/936	216/938	0.76 (0.57, 1.01)	⊢	
Age, years					0.2804
<65 years	137/675	251/740	0.62 (0.45, 0.84)	⊢	
≥65 years	251/1188	302/1127	0.77 (0.60, 0.98)	⊢	
Sex					0.3679
Male	299/1426	433/1411	0.74 (0.59, 0.92)	⊢	
Female	89/437	120/456	0.60 (0.40, 0.89)	⊢	
Race					0.0049
White	287/1325	297/1304	0.90 (0.71, 1.13)	⊢● 	
Black/African-American	23/123	65/134	0.40 (0.20, 0.80)		
Asian	70/337	160/335	0.45 (0.29, 0.70)	⊢−−− +	
Other	1/51	15/63	NC		
Body mass index, kg/m ²					0.4681
<30	232/1263	371/1300	0.66 (0.52, 0.83)	⊢ ●−−1	
≥30	156/600	182/567	0.76 (0.55, 1.06)	⊢	
Baseline eGFR (CKD-EPI), ml/min/1.73 m ²					0.1233
≥60	157/969	267/960	0.60 (0.45, 0.79)	⊢	
<60	231/893	286/906	0.81 (0.62, 1.06)	⊢	
History of HHF (in last 12 months)					0.5561
No	198/1286	309/1293	0.65 (0.51, 0.82)	⊢ ●−−1	
Yes	190/577	244/574	0.73 (0.53, 0.99)	⊢	
Etiology of heart failure					0.6195
Ischemic	221/983	281/946	0.73 (0.56, 0.95)	⊢	
Non-ischemic	167/880	272/921	0.66 (0.50, 0.88)	⊢ ●	
Baseline NYHA class					0.4006
II	226/1399	353/1401	0.65 (0.51, 0.81)	⊢ −●−−1	
	162/464	200/466	0.77 (0.55, 1.09)	⊢	
Heart failure physiology					0.3812
LVEF ≤30% and NTproBNP <median< td=""><td>69/699</td><td>122/724</td><td>0.59 (0.41, 0.85)</td><td></td><td></td></median<>	69/699	122/724	0.59 (0.41, 0.85)		
LVEF ≤30% and NTproBNP ≥median	206/631	309/661	0.66 (0.50, 0.88)	⊢	
LVEF >30%	112/526	118/475	0.84 (0.59, 1.22)	⊢	
Baseline use of mineralocorticoid receptor anta	igonist				0.8782
No	126/557	165/512	0.69 (0.48, 0.97)	••	
Yes	262/1306	388/1355	0.71 (0.56, 0.89)	└ ──● ──┤	
Baseline use of neprilysin inhibitor					0.7159
No	318/1523	432/1480	0.71 (0.58, 0.88)	⊢ ●−−1	
Yes	70/340	121/387	0.65 (0.42, 1.00)		_
				0.25 0.5 1	$\xrightarrow{2}$

Favors empagliflozin Favors placebo

Abbreviations: HHF= heart failure hospitalization; LVEF = left ventricular ejection fraction; NYHA= New York Heart Association

Figure III

Time to first event analysis of all-cause mortality, heart failure hospitalization or emergent/urgent care visit for worsening heart failure in the placebo and empagliflozin groups during first 40 days following randomization



Abbreviations: HR=hazard ratio; CI = confidence interval

Figure IV Total study visits reporting interval intensification of diuretics for worsening heart failure



Abbreviations: HR=hazard ratio; CI = confidence interval

Figure V Changes in hematocrit in the placebo and empagliflozin groups



Figure VI Changes in uric acid in the placebo and empagliflozin group



Figure VII Changes in body weight in the placebo and empagliflozin groups



Figure VIII Changes in N-terminal proBNP in the placebo and empagliflozin groups



Abbreviations: NT-proBNP = N-terminal prohormone B-type natriuretic peptide

Figure IX Changes in systolic blood pressure in the placebo and empagliflozin groups



Table I. Frequencies of Major Outcomes and Worsening Heart Failure Events

	Placebo	Empagliflozin			
Adjudicated hospitalizations for heart failure					
Patients hospitalized once	231	160			
Patients hospitalized twice	61	50			
Patients hospitalized \ge 3 times	50	36			
Total (first and recurrent) adjudicated hospitalizations for heart failure					
Number of hospitalizations requiring only oral diuretics	27	15			
Number of hospitalizations requiring only intravenous diuretics	266	204			
Number of hospitalizations requiring IV vasodilators	54	36			
Number of hospitalizations requiring IV vasopressors or positive inotropic drugs	152	92			
Number of hospitalizations with mechanical or surgical intervention	34	24			
Total (first and recurrent) emergent or urgent care visits for heart failure requiring intravenous therapy					
Patients who required emergent or urgent care once	141	87			
Patients who required emergent or urgent care twice	22	27			
Patients who required emergent or urgent care \geq 3 times	22	12			
Changes in diuretic dose since prior study visit					
Number of patients who had diuretics were intensified since prior study visit	414 (22.2%)	297 (15.9%)			
Total number of study visits that reported that the dose of diuretics had been intensified since prior study visit	564	380			
Number of patients who had reduction in the dose of diuretics since prior study visit	246 (13.2)	281 (15.1%)			
Total number of study visits that reported that the dose of diuretics had been reduced since prior study visit	293	334			
Adjudicated cardiovascular events other than heart failure					
Adjudicated myocardial infarction	20 (1.1%)	19 (1.0%)			
Adjudicated stroke	35 (1.9%)	40 (2.1%)			
Adjudicated transient ischemic attack	7 (0.4%)	7 (0.4%)			

Categories are ordered according to severity of intervention, with each category including less intensive but excluding more intensive interventions, i.e., use of intravenous vasopressors or positive inotropic drugs includes the use of diuretics or intravenous vasodilators, but exclude mechanical or surgical intervention). A total of 20 patients in the placebo group and 16 in empagliflozin group did not have complete information on the utilization or drug or non-drug interventions during hospitalization.