Effects of Empagliflozin in Men and Women with Heart Failure and Preserved Ejection Fraction: Results from the EMPEROR-Preserved Trial

EMPEROR Heart failure studies

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BACKGROUND

- Heart failure and preserved ejection fraction (HFpEF) is more common among women than men, and HFpEF pathophysiology and phenotype vary by sex.[1–5]
- Men and women with HFpEF may differ in their clinical characteristics and their response to therapy.[6]
- Empagliflozin was shown to significantly reduce the risk of a composite of cardiovascular (CV) death or hospitalization for heart failure (HHF) in patients with HFpEF in the EMPEROR-Preserved trial.[7]

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OBJECTIVE

- To examine the sex-based differences in the effects of empagliflozin on pre-specified clinical outcomes and health status.

METHODS

- In the EMPEROR-Preserved trial, patients with New York Heart Association (NYHA) functional class II–IV symptoms and a left ventricular ejection fraction (LVEF) >40% were randomized to receive empagliflozin 10 mg once daily or placebo in addition to standard of care.
- The primary outcome was time to first event of the composite of CV death or HHF.
- The secondary outcomes included first HHF, total (first and recurrent) HHF, CV death, all-cause death, and health status measured by Kansas City Cardiomyopathy Questionnaire (KCCQ).
- Time-to-first-event outcomes were analyzed using Cox regression models. Total (first and recurrent) HHF events were evaluated using a joint frailty model with CV death as competing risk.
- Changes in health status over time were assessed using a mixed model for repeated measurements.

RESULTS

- Among 5988 participants, women (n=2676; 44.7%) were older, had higher body mass index, higher LVEF, lower estimated glomerular filtration rate (eGFR), were more likely to have nonischemic etiology, and were less likely to have diabetes compared with men (**Table 1**).
- Women had worse baseline health status based on NYHA class and KCCQ Clinical Summary Score estimates compared with men (**Table 1**).

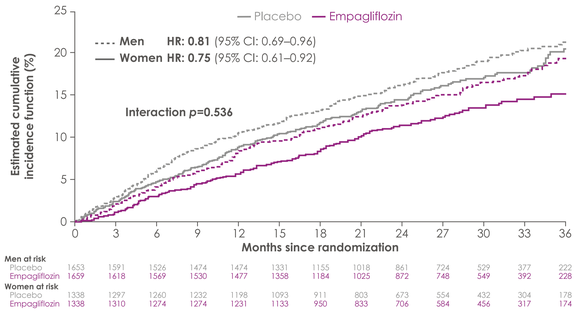
Table 1. Baseline characteristics of participants according to sex

Characteristics	Men (N=3312)	Women (N=2676)	*p*-value
Age, years, mean ± SD	71.0±9.4	73.0±9.4	<0.001
Race*, n (%)			
Asian	522 (15.8)	302 (11.3)	<0.001
Black/African American	121 (3.7)	137 (5.1)	
White	2504 (75.6)	2038 (76.2)	
Other including mixed race	163 (4.9)	199 (7.4)	
Missing	2 (0.1)	0	
Geographic region, n (%)			
Asia Pacific	439 (13.3)	247 (9.2)	<0.001
Europe	1466 (44.3)	1223 (45.7)	
North America	403 (12.2)	316 (11.8)	
Latin America	799 (24.1)	716 (26.8)	
Other	205 (6.2)	174 (6.5)	
KCCQ, mean ± SD			
CSS	74.8±19.9	65.0±21.4	<0.001
OSS	72.9±20.0	64.1±21.5	<0.001
TSS	77.3±20.6	68.7±22.7	<0.001
HHF within 1 year, n (%)	801 (24.2)	568 (21.2)	0.007
BMI, kg/m^2, mean ± SD	29.4±5.6	30.4±6.2	<0.001
LVEF at screening, %, mean ± SD	52.7±8.3	56.3±9.0	<0.001
NYHA class, n (%)			
II	2808 (84.8)	2075 (77.5)	<0.001
III	494 (14.9)	589 (22.0)	
Systolic blood pressure, mmHg, mean ± SD	131.6±15.4	132.1±15.9	0.251
Diastolic blood pressure, mmHg, mean ± SD	76.0±10.5	75.4±10.7	0.055
Heart rate, bpm, mean ± SD	69.9±11.6	71.0±12.1	<0.001
Hemoglobin, g/dl, mean ± SD	13.7±1.6	12.9±1.4	<0.001
eGFR, ml/min/1.73 m^2, mean ± SD	62.6±19.8	58.2±19.6	<0.001
NT-proBNP, pg/ml, median (IQR)	989 (516, 1758)	953 (480, 1711)	0.119
History of comorbidities, n (%)			
Hypertension	2962 (89.4)	2462 (92.0)	<0.001
Diabetes mellitus	1682 (50.8)	1256 (46.9)	0.003
Atrial fibrillation	1686 (50.9)	1371 (51.2)	0.770
Coronary artery disease	1427 (43.1)	667 (24.9)	<0.001
Ischemic etiology of heart failure	1411 (42.6)	706 (26.4)	<0.001
Medication use, n (%)			
ACEi, ARB†, ARNi	2668 (80.6)	2164 (80.9)	0.762
Diuretic	2788 (84.2)	2375 (88.8)	<0.001
Beta-blocker	2882 (87.0)	2285 (85.4)	0.069
Mineralocorticoid receptor antagonist	1231 (37.2)	1013 (37.9)	0.585
Statin	2404 (72.6)	1727 (64.5)	<0.001

Categorical variables were compared using the chi-squared test. Continuous variables were summarized using the t-test.
*Race was self-reported. Those who identified with more than 1 race or with no race were classified as 'other'.
†ARB excludes valsartan when taken with sacubitril because sacubitril/valsartan is shown as ARNi.
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor-neprilysin inhibitor; BMI, body mass index; bpm, beats per minute; CSS, Clinical Summary Score; eGFR, estimated glomerular filtration rate; HHF, hospitalization for heart failure; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; OSS, Overall Summary Score; SD, standard deviation; TSS, Total Summary Score.

- Empagliflozin treatment improved the primary outcome of time to first CV death or HHF (**Figure 1**), as well as the secondary outcomes of total HHF and first HHF, irrespective of sex (all interaction *p*-values >0.05; **Figure 2**).

Figure 1. Estimated cumulative incidence for time to first CV death or HHF according to sex



Cox regression model adjusted for age, eGFR, LVEF, region, diabetes, and sex-by-treatment interaction.
CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HHF, hospitalization for heart failure; HR, hazard ratio; LVEF, left ventricular ejection fraction.

Figure 2. Effect of empagliflozin on primary and secondary outcomes according to sex

	Placebo n/N	Placebo Events/100 patient-years	Empagliflozin 10 mg n/N	Empagliflozin 10 mg Events/100 patient-years	HR (95% CI)	Interaction *p*-value
CV death or HHF						0.536
Men	297/1653	9.15	253/1659	7.59	0.81 (0.69, 0.96)	
Women	214/1338	8.09	162/1338	5.97	0.75 (0.61, 0.92)	
Total (first and recurrent) HHF*						0.780
Men	308†		253†		0.75 (0.59, 0.95)	
Women	233†		154†		0.71 (0.53, 0.94)	
First HHF						0.836
Men	198/1653	6.10	151/1659	4.53	0.72 (0.58, 0.89)	
Women	154/1338	5.82	108/1338	3.98	0.70 (0.54, 0.89)	
CV death						0.673
Men	148/1653	4.17	138/1659	3.90	0.94 (0.74, 1.18)	
Women	96/1338	3.37	81/1338	2.83	0.86 (0.64, 1.16)	
All-cause death						0.778
Men	267/1653	7.53	269/1659	7.60	1.02 (0.86, 1.20)	
Women	160/1338	5.61	153/1338	5.35	0.98 (0.78, 1.22)	

Cox regression model adjusted for age, eGFR, LVEF, region, diabetes, and sex-by-treatment interaction.
*Joint frailty model with CV death as competing risk. Model was adjusted for age, eGFR, LVEF, region, diabetes, and sex-by-treatment interaction.
†Number of total (first plus recurrent) events.
CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HHF, hospitalization of heart failure; HR, hazard ratio; LVEF, left ventricular ejection fraction.

- KCCQ improvement with empagliflozin treatment was similar in both sexes (**Figure 3**).

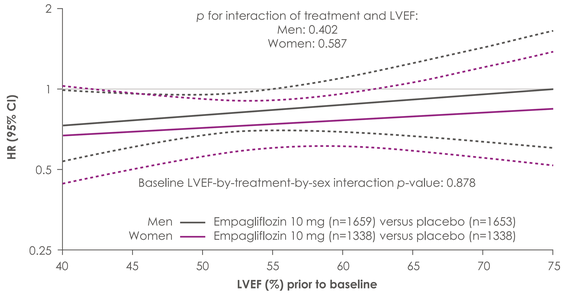
Figure 3. Effect of empagliflozin on health status at Weeks 12, 32, and 52 according to sex

Subgroup	Adjusted mean difference (95% CI), empagliflozin 10 mg versus placebo	Interaction *p*-value for treatment by sex
KCCQ-TSS		
Week 12		
Men	1.90 (0.84, 2.96)	0.717
Women	1.60 (0.42, 2.79)	
Week 32		
Men	2.05 (0.88, 3.23)	0.185
Women	0.86 (-0.45, 2.18)	
Week 52		
Men	1.98 (0.74, 3.21)	0.822
Women	2.19 (0.81, 3.57)	
KCCQ-CSS		
Week 12		
Men	1.03 (0.07, 1.98)	0.982
Women	1.04 (-0.02, 2.11)	
Week 32		
Men	1.43 (0.35, 2.52)	0.593
Women	0.99 (-0.21, 2.20)	
Week 52		
Men	1.38 (0.23, 2.54)	0.777
Women	1.63 (0.35, 2.92)	
KCCQ-OSS		
Week 12		
Men	1.35 (0.40, 2.29)	0.445
Women	0.79 (-0.26, 1.85)	
Week 32		
Men	1.83 (0.78, 2.89)	0.403
Women	1.16 (-0.03, 2.34)	
Week 52		
Men	1.78 (0.65, 2.91)	0.650
Women	1.39 (0.13, 2.65)	

Mixed model for repeated measurements.
CI, confidence interval; CSS, Clinical Summary Score; KCCQ, Kansas City Cardiomyopathy Questionnaire; OSS, Overall Summary Score; TSS, Total Summary Score.

- Empagliflozin reduced the risk of CV death or HHF comparably in both sexes, regardless of baseline LVEF (**Figure 4**).

Figure 4. The effect of empagliflozin on time to first CV death or HHF in women and men by baseline LVEF



Cox regression model adjusted for age, eGFR, LVEF, region, diabetes, and sex-by-treatment interaction.
CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; LVEF, left ventricular ejection fraction.

CONCLUSIONS

- Empagliflozin produced similar benefits on clinical outcomes and health status outcomes in men and women with HFpEF. The effect of empagliflozin on the risk of CV death and HHF was consistent, irrespective of baseline ejection fraction in both men and women.

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References
1. Borlaug BA *et al. Circulation* 2011;123:2006–2013.
2. Scantlebury DC *et al. Curr Opin Cardiol* 2011;26:562–568.
3. Gori M *et al. Eur J Heart Fail* 2014;16:535–542.
4. Stolfo D *et al. JACC Heart Fail* 2019;7:505–515.
5. Beale AL *et al. JACC Heart Fail* 2019;7:239–249.
6. Solomon SD *et al. N Engl J Med* 2019;381:1609–1620.
7. Anker S *et al. N Engl J Med* 2021;385:1451–1461.

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