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RESEARCH ARTICLE

Health status across major subgroups of patients with heart failure and preserved ejection fraction

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Aims There are limited data on health status and changes in it over time across major subgroups of patients with heart failure and preserved ejection fraction (HFpEF), including ejection fraction spectrum, age, sex, region, body mass index (BMI), and comorbidities including diabetes, chronic kidney disease (CKD), anaemia, and atrial fibrillation/flutter.

Methods and results In the EMPEROR-Preserved trial, the Kansas City Cardiomyopathy Questionnaire (KCCQ) was assessed at baseline, 12, 32 and 52 weeks. Determinants of baseline KCCQ score and change over time, and the impact of empagliflozin on KCCQ scores were studied in specified subgroups. A Cox model was used to assess the association between 5- and 10-point increase and 5-point decrease in KCCQ score from baseline to week 12 and later outcomes. Among 2979 participants in the placebo arm, mean KCCQ clinical summary score (CSS) was 70.7 (20.8). Older age, female sex, BMI, anaemia, and a history of diabetes, and CKD were associated with worse scores. KCCQ-CSS score improved during follow-up; patients with atrial fibrillation/flutter at enrollment (p trend = 0.014) and CKD (p trend < 0.001) had less improvement. A 5-point increase in KCCQ-CSS at week 12 was associated with lower risk of cardiovascular death or heart failure hospitalization (5%), cardiovascular death (8%), and first heart failure hospitalization (4%) subsequently. A similar trend was seen with KCCQ total symptom score (TSS) and overall summary score (OSS). Empagliflozin improved KCCQ-CSS, -TSS and -OSS scores similarly across subgroups studied except for greater improvement in patients with the highest BMI (p trend = 0.153, 0.08 and 0.078, respectively).

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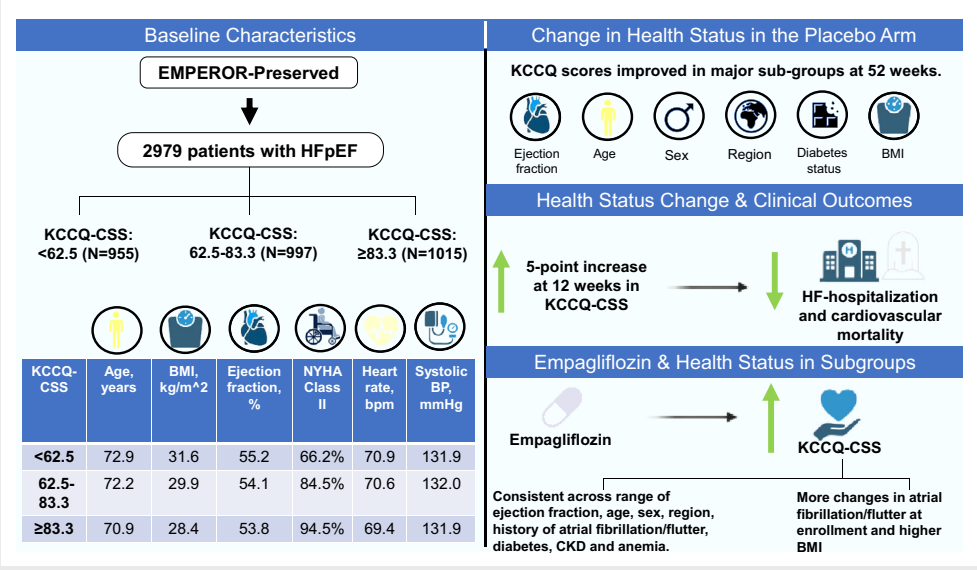
Conclusion Health status in patients with HFpEF is impaired, especially in elderly, women, and those with obesity and comorbidities. Empagliflozin improved health status among all key subgroups studied with a greater effect in obese patients.

Graphical Abstract



Health status change in patients with heart failure and preserved ejection fraction (HFpEF). BMI, body mass index; BP, blood pressure; CSS, clinical summary score; CKD, chronic kidney disease; HF, heart failure; KCCQ, Kansas City Cardiomyopathy Questionnaire; NYHA, New York Heart Association.

Keywords Empagliflozin • Heart failure with preserved ejection fraction • Kansas City Cardiomyopathy Questionnaire

Patients with heart failure (HF) are at an increased risk of hospitalization and mortality, as well as for a significant burden of symptoms that impacts physical function and health status.[1,2] Although it is known that patients with HF with preserved ejection fraction (HFpEF) have markedly impaired health status, little is known about the factors that govern health status and its progression in this population. It is important to identify these factors given that the HFpEF population is heterogeneous in terms of aetiology, clinical characteristics, and comorbidities.[3,4] The EMPEROR-Preserved (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction) trial provides a unique opportunity to study the determinants, natural history and clinical correlates of health status in patients with HFpEF.[5] Furthermore, in EMPEROR-Preserved, empagliflozin improved health status, as assessed by the Kansas City Cardiomyopathy Questionnaire (KCCQ), across domains. We also sought to assess whether this benefit extends to key subgroups.

Methods

Study design and patient population

The EMPEROR-Preserved trial was a randomized, double-blind, parallel-group, placebo-controlled trial that enrolled HFpEF patients ≥18 years of age with New York Heart Association (NYHA) functional class II to IV for at least 3 months and a left ventricular ejection fraction (LVEF) of >40% with no prior measurement of ≤40%.[6] Patients were also required to have elevated N-terminal pro-B-type natriuretic peptide levels (>900 or >300 pg/ml in patients with or without atrial fibrillation, respectively) and have a documented hospitalization for HF or evidence of structural heart disease (increased left ventricular mass or left atrial size) within the last 12 months. The protocol was approved by the Ethics Committee of each of the 520 participating sites in 23 countries, and all patients gave written informed consent.

Quality of life outcome assessment

The KCCQ is a self-administered instrument that has been validated in patients with HFpEF. It maps seven domains (symptom frequency, symptom burden, symptom stability, physical limitations, social limitations, quality of life, self-efficacy) and contains three summary scores: clinical summary score (CSS), total symptom score (TSS) and overall summary score (OSS). The scores range from 0 to 100 with 100 being the best possible score. The KCCQ was completed by patients at baseline, 12, 32, and 52 weeks post randomization; this study focused on 12- (early) and 52-week (sustained) changes as results were similar at 32 weeks.

Subgroups of interest

Several subgroups of interest were studied including: (a) LVEF <50%, 50–<60%, and ≥60%; (b) age <65, 65–74, and ≥75 years; (c) men or women; (d) region (North America, Latin America, Europe, Asia Pacific, or other); (e) body mass index (BMI) <25, 25–<30, 30–<35 or ≥35 kg/m^2; and (f) comorbidities including diabetes, chronic kidney disease, history of atrial fibrillation/flutter, atrial fibrillation/flutter at enrolment and anaemia defined using sex-specific baseline haemoglobin thresholds (men <13 g/dl and women <12 g/dl).

Statistical analysis

Patients in the placebo arm were categorized according to tertiles of baseline KCCQ-CSS. Baseline characteristics were summarized as frequencies and percentages or means with standard deviations (SD). KCCQ scores at baseline and changes from baseline to 52 weeks were studied in the overall placebo arm as well as subgroups of interest. To evaluate the association between 5-, 10-point increase and 5-point decrease in KCCQ scores at 12 weeks and subsequent outcome events (primary composite of cardiovascular death and hospitalization for HF and its individual components) occurring after 12 weeks, a landmark analysis was performed using a Cox model adjusted for the same covariates listed below and KCCQ score response at 12 weeks. To assess the effect of empagliflozin on health-related quality of life (HRQoL) in each subgroup, differences between treatment groups in mean KCCQ-CSS, -TSS, and -OSS at 52 weeks were calculated with a mixed model for repeated measures, and the least-squares mean difference between treatment groups was estimated. All models were adjusted for baseline KCCQ score, estimated glomerular filtration rate, age, region, sex, diabetes status and LVEF. All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

Patient population

Among the 2979 participants in the placebo arm with baseline KCCQ assessment, the mean KCCQ-CSS, -TSS and -OSS scores were 70.7 (20.8), 74.0 (21.7) and 69.3 (20.7), respectively. For the seven KCCQ individual domains, the mean scores were symptom frequency 73.0 (23.0), symptom burden 74.9 (22.2), symptom stability 53.8 (17.2), physical limitations 67.2 (23.9), social limitations 69.6 (27.6), quality of life 66.0 (23.1), and self-efficacy 73.7 (24.0). Baseline characteristics of patients in the placebo arm according to KCCQ-CSS tertiles are shown in *Table 1*. In the placebo arm, there were some differences noted in the baseline KCCQ scores among key subgroups including lower scores in older participants, women, those enrolled in North America, and those with a history of diabetes and chronic kidney disease. A linear relationship was also noted with lower scores with increasing BMI (*Table 2*).

Change in health status in the placebo arm

The KCCQ-CSS improved (3.66, 1.57 and 2.92) for patients with baseline KCCQ-CSS <62.6, 62.5–83.3 and ≥83.3, respectively (p trend = 0.898). Similar results were observed for KCCQ-TSS and KCCQ-OSS. *Table 3* shows subgroup analyses of change in KCCQ scores at 52 weeks in the placebo arm. Improvements in KCCQ-CSS were less likely to have occurred in patients with atrial fibrillation or atrial flutter at enrolment (p = 0.014) and chronic kidney disease (p < 0.001). Similar trends were seen with KCCQ-TSS and KCCQ-OSS.

Association between health status change and clinical outcomes

A 5-point increase at 12 weeks in KCCQ-CSS was associated with a subsequent reduced risk of the composite of cardiovascular death and hospitalization for HF (hazard ratio [HR], 0.95 [95% confidence interval 0.91, 0.99]), cardiovascular death (HR 0.92 [0.98, 0.96]), and HF hospitalization (HR 0.96 [0.92, 1.00]) (*Figure 1*). Improvements for 10-point increase at 12 weeks were cardiovascular death and HF hospitalization HR 0.89 (0.84, 0.96), cardiovascular death 0.84 (0.77, 0.92), and HF hospitalization 0.92 (0.84, 1.00). A 5-point decrease at 12 weeks in KCCQ-CSS was associated with an increased risk of subsequent cardiovascular death and HF hospitalization (HR 1.06 [1.02, 1.09]), cardiovascular death (1.09 [1.04, 1.14]), and HF hospitalization (1.04 [1.00, 1.09]. Similar results were seen for KCCQ-TSS and KCCQ-OSS.

Effect of empagliflozin on health status in subgroups

The median (interquartile range) duration of follow-up was 26.2 (18.1, 33.1) months. At 52 weeks, empagliflozin improved KCCQ-CSS similarly across the range of LVEF (p trend = 0.390), age (p trend = 0.483), sex (p interaction = 0.777), regions (p interaction = 0.239), diabetes (p interaction = 0.511), chronic kidney disease (p interaction = 0.704), and anaemia (p interaction = 0.782). Empagliflozin improved KCCQ scores more in patients with atrial fibrillation or atrial flutter at enrolment (p interaction = 0.009), but this pattern was not seen in patients with a history of atrial fibrillation/flutter (p interaction = 0.263). Empagliflozin improved KCCQ-CSS, -TSS and -OSS scores similarly across subgroups studied except for greater improvement in patients with the highest BMI, that is, >25 kg/m^2 (p trend = 0.153, 0.08 and 0.078, respectively) (*Figure 2*, online supplementary *Figures Appendix S1* and *S2*.

Table 1 Baseline characteristics according to Kansas City Cardiomyopathy Questionnaire clinical summary score at baseline in the placebo arm

	KCCQ-CSS			
	Tertile <62.5 (*n* = 955)	Tertile 62.5–83.3 (*n* = 997)	Tertile ≥83.3 (*n* = 1015)	*p*-value
Age (years)	72.9 ± 9.6	72.2 ± 9.6	70.9 ± 9.4	<0.001
Women	555 (58.1)	445 (44.6)	324 (31.9)	<0.001
Race[a]				<0.001
Asian	42 (4.4)	109 (10.9)	243 (23.9)	
Black or African American	58 (6.1)	34 (3.4)	32 (3.2)	
White	795 (83.2)	797 (79.9)	658 (64.8)	
Other including mixed race	59 (6.2)	57 (5.7)	82 (8.1)	
Missing	1 (0.1)	0	0	
Geographic region				<0.001
Asia	30 (3.1)	88 (8.8)	222 (21.9)	
Europe	436 (45.7)	499 (50.1)	404 (39.8)	
North America	152 (15.9)	110 (11.0)	95 (9.4)	
Latin America	270 (28.3)	245 (24.6)	241 (23.7)	
Other	67 (7.0)	55 (5.5)	53 (5.2)	
HF hospitalization within 1 year	222 (23.2)	209 (21.0)	203 (20.0)	0.199
BMI (kg/m^2)	31.6 ± 6.1	29.9 ± 5.7	28.4 ± 5.5	<0.001
Ejection fraction at screening (%)	55.2 ± 8.6	54.1 ± 8.8	53.8 ± 8.9	<0.001
New York Heart Association class II	632 (66.2)	842 (84.5)	959 (94.5)	<0.001
Systolic blood pressure (mmHg)	131.9 ± 16.8	132.0 ± 15.0	131.9 ± 15.3	0.996
Heart rate (bpm)	70.9 ± 12.0	70.6 ± 11.9	69.4 ± 11.4	0.009
Hypertension	878 (91.9)	906 (90.9)	900 (88.7)	0.041
Diabetes mellitus	507 (53.1)	487 (48.8)	464 (45.7)	0.005
History of atrial fibrillation	503 (52.7)	510 (51.2)	494 (48.7)	0.180
Coronary artery disease	300 (31.4)	339 (34.0)	387 (38.1)	0.007
ACE-I, ARB[b], or ARNI	734 (76.9)	816 (81.8)	837 (82.5)	0.003
Diuretic[c]	836 (87.5)	819 (82.1)	725 (71.4)	<0.001
Beta-blocker	812 (85.0)	874 (87.7)	872 (85.9)	0.226
Mineralocorticoid receptor antagonist	369 (38.6)	364 (36.5)	381 (37.5)	0.624
Statin	667 (69.8)	678 (68.0)	726 (71.5)	0.227
Haemoglobin (g/dl)	130.3 ± 15.4	133.7 ± 15.9	136.1 ± 15.5	<0.001
eGFR (ml/min/1.73 m^2)				<0.001
<60	561 (58.7)	499 (50.1)	411 (40.5)	
≥60	394 (41.3)	497 (49.8)	603 (59.4)	
NT-proBNP (pg/ml)	1063 [510–1881]	981 [508–1764]	851 [485–1516]	<0.001*

Data are given as mean ± standard deviation, *n* (%), or median [interquartile range].
ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; BMI, body mass index; eGFR, estimated glomerular filtration rate; HF, heart failure; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire clinical summary score; NT-proBNP, N-terminal pro–B-type natriuretic peptide.
[a]Race was reported by the patients. Those who identified with more than one race or with no race were classified as 'other'.
[b]ARB is excluding valsartan when taken with sacubitril because sacubitril/valsartan is shown as ARNI.
[c]Excluding mineralocorticoid receptor antagonists.
* *P*-value for NT-proBNP was done on log-transformed data.

Discussion

This secondary analysis of the EMPEROR-Preserved trial yields several key findings (*Graphical Abstract*). First, patients with HFpEF had impaired health status, as indicated by decreased scores across all domains and summary scores of the KCCQ. Several factors were associated with worse health status, including older age, female sex, higher BMI and a history of diabetes or chronic kidney disease. Second, a 5-point increase in KCCQ-CSS at 12 weeks was associated with the reduced risk of subsequent primary composite of cardiovascular death and HF hospitalization, and its components cardiovascular death and first HF hospitalization by

Table 2 Baseline Kansas City Cardiomyopathy Questionnaire scores among subgroups in the placebo arm

Subgroups	Baseline mean (standard deviation)					
	KCCQ-CSS	*p* trend	KCCQ-TSS	*p* trend	KCCQ-OSS	*p* trend
LVEF (%)						
<50 (*n* = 988)	73.5 (19.7)	<0.001*	76.7 (20.3)	<0.001*	71.4 (19.9)	0.003*
50–<60 (*n* = 1030)	69.1 (21.5)		72.7 (22.6)		67.8 (21.2)	
≥60 (*n* = 973)	69. 4 (20.9)		72.6 (21.8)		68.6 (20.8)	
Age (years)						
<65 (*n* = 605)	71.7 (21.6)	<0.001*	73.7 (22.9)	0.046*	68.6 (21.6)	0.049*
65–≤75 (*n* = 1092)	72.7 (20.6)		75.7 (21.7)		71.3 (20.7)	
≥75 (*n* = 1294)	68.4 (20.4)		72.7 (20.9)		67.9 (20.2)	
Gender						
Men (*n* = 1653)	74.8 (19.9)	<0.001	77.5 (20.9)	<0.001	73.1 (19.8)	<0.001
Women (*n* = 1338)	65.5 (20.7)		69.6 (21.8)		64.6 (20.8)	
Region						
North America (*n* = 359)	65.2 (22.0)	<0.001	68.7 (23.2)	<0.001	65.5 (21.9)	<0.001
Latin America (*n* = 757)	68.9 (22.3)		72.0 (23.7)		66.4 (22.6)	
Europe (*n* = 1343)	69.9 (19.4)		73.9 (20.3)		69.4 (19.3)	
Asia Pacific (*n* = 343)	84.8 (15.2)		85.2 (16.9)		80. 4 (16.4)	
Other (*n* = 189)	67.6 (20.1)		72.2 (20.7)		66.9 (20.2)	
Diabetes mellitus						
Yes (*n* = 1472)	69.0 (21.6)	<0.001	72.5 (22.7)	<0.001	67.5 (21.4)	<0.001
No (*n* = 1519)	72.2 (19.9)		75.4 (20.5)		71.0 (19.8)	
History of atrial fibrillation or atrial flutter						
Yes (*n* = 1427)	70.4 (20.3)	0.394	73.7 (21.1)	0.511	69.2 (20.1)	0.768
No (*n* = 1559)	71.0 (21.3)		74.3 (22.3)		69.4 (21.3)	
Atrial fibrillation or atrial flutter at enrolment						
Yes (*n* = 1016)	69.8 (19.8)	0.086	73.1 (20.8)	0.086	68.6 (19.8)	0.180
No (*n* = 1966)	71.1 (21.2)		74.5 (22.0)		69.7 (21.1)	
Chronic kidney disease						
Yes (*n* = 1583)	67.3 (21.4)	<0.001	71.2 (22.4)	<0.001	66.3 (21.4)	<0.001
No (*n* = 1400)	74.5 (19.4)		77.2 (20.3)		72.7 (19.4)	
Anaemia[a]						
Yes (*n* = 852)	67.7 (21.5)	<0.001	71.2 (22.6)	<0.001	66.6 (21.5)	<0.001
No (*n* = 2137)	71.8 (20.4)		75.0 (21.2)		70.3 (20.3)	
Body mass index (kg/m^2)						
<25 (*n* = 638)	76.5 (19.2)	<0.001*	79.8 (19.1)	<0.001*	74.1 (19.3)	<0.001*
25–<30 (*n* = 1004)	73.2 (19.5)		76.6 (20.3)		71.1 (19.9)	
30–<35 (*n* = 760)	69.2 (20.3)		72.7 (21.3)		68.6 (20.3)	
≥35 (*n* = 589)	61.9 (22.0)		65.0 (23.8)		61.9 (21.9)	

CSS, clinical summary score; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; OSS, overall summary score; TSS, total symptom score.

[a]Anaemia is defined using sex-specific baseline haemoglobin thresholds (men <13 g/dl and women <12 g/dl).

**P*-value from trend test assuming a linear trend for LVEF, age and body mass index subgroups.

5%, 8% and 4%, respectively. A 5- or 10-point increase or a 5-point decrease in KCCQ score at week 12 was associated with better and worse outcomes, respectively. Lastly, empagliflozin generally improved health status across major subgroups studied, except obese patients showed the largest benefit.

Few studies have comprehensively profiled health status in patients with HFpEF using validated instruments; moreover, even fewer have reported the natural history of health status in this population. Patients in the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist) trial had a lower mean score of 54.8 ± 19.6 at randomization.[7] Given the association between NYHA functional class and KCCQ scores, part of these differences could be explained by the higher enrolment of patients with NYHA functional class III and IV in the TOPCAT trial compared with EMPEROR-Preserved (33.4% vs. 18.4%). In contrast, the PARAGON-HF (Prospective Comparison of ARNI with ARB Global Outcomes in HFpEF) trial enrolled patients with a baseline health status similar to that in EMPEROR-Preserved (mean KCCQ-CSS, 74.2).[8] SOCRATES-PRESERVED (Soluble Guanylate Cyclase Stimulator in Heart Failure Patients with Preserved Ejection Fraction) enrolled 477 HFpEF patients with a baseline mean KCCQ-CSS of 55.2 ± 23 and NEAT-HFpEF (Nitrate's Effect on

Table 3 Change in Kansas City Cardiomyopathy Questionnaire scores at 52 weeks among subgroups in the placebo arm

	Mean change in KCCQ-CSS	*p* trend	Mean change in KCCQ-TSS	*p* trend	Mean change in KCCQ-OSS	*p* trend
LVEF (%)						
<50 (*n* = 988)	3.55 (2.46–4.64)	0.345*	4.61 (3.42–5.80)	0.086*	3.85 (2.78–4.92)	0.398*
50–<60 (*n* = 1030)	1.81 (0.76–2.86)		2.42 (1.27–3.57)		2.29 (1.26–3.32)	
≥60 (*n* = 973)	2.78 (1.72–3.85)		3.11 (1.95–4.28)		3.18 (2.14–4.23)	
Age (years)						
<65 (*n* = 605)	3.49 (2.08–4.90)	0.003*	4.08 (2.54–5.62)	0.049*	3.75 (2.36–5.13)	0.005*
65–<75 (*n* = 1092)	3.85 (2.84–4.87)		4.01 (2.91–5.12)		4.25 (3.26–5.24)	
≥75 (*n* = 1294)	1.35 (0.39–2.30)		2.47 (1.43–3.51)		1.80 (0.87–2.74)	
Gender						
Men (*n* = 1653)	3.06 (2.23–3.90)	0.208	3.95 (3.04–4.87)	0.060	3.22 (2.40–4.04)	0.655
Women (*n* = 1338)	2.24 (1.30–3.18)		2.62 (1.60–3.64)		2.93 (2.01–3.85)	
Region						
North America (*n* = 359)	0.81 (−1.03–2.64)	Ref	1.72 (−0.28–3.73)	Ref	2.37 (0.58–4.17)	Ref
Latin America (*n* = 757)	5.41 (4.17–6.66)	<0.001	6.37(5.01–7.73)	<0.001	5.84 (4.62–7.06)	0.002
Europe (*n* = 1343)	0.96 (0.05–1.86)	0.887	1.58 (0.59–2.57)	0.900	1.52 (0.63–2.41)	0.402
Asia Pacific (*n* = 343)	5.72 (3.88–7.56)	<0.001	5.82 (3.84–7.81)	0.005	4.46 (2.68–6.25)	0.108
Other (*n* = 189)	2.32 (−0.20–4.85)	0.340	2.77 (0.02–5.52)	0.548	2.40 (−0.07–4.87)	0.986
Diabetes mellitus						
Yes (*n* = 1472)	2.19 (1.31–3.07)	0.112	2.88 (1.92–3.84)	0.170	2.40 (1.54–3.27)	0.030
No (*n* = 1519)	3.19 (2.33–4.05)		3.82 (2.89–4.76)		3.75 (2.91–4.59)	
History of atrial fibrillation or atrial flutter						
Yes (*n* = 1427)	2.18 (1.32–3.03)	0.087	2.77 (1.84–3.71)	0.075	2.90 (2.07–3.74)	0.522
No (*n* = 1519)	3.28 (2.37–4.18)		4.02 (3.03–5.01)		3.31 (2.42–4.19)	
Atrial fibrillation or atrial flutter at enrolment						
Yes (*n* = 1016)	1.64 (0.59–2.69)	0.014	2.22 (1.08–3.37)	0.016	2.60 (1.56–3.63)	0.240
No (*n* = 1966)	3.27 (2.51–4.03)		3.97 (3.14–4.81)		3.36 (2.62–4.11)	
Chronic kidney disease						
Yes (*n* = 1583)	1.55 (0.69–2.42)	<0.001	2.23 (1.28–3.17)	<0.001	2.04 (1.19–2.88)	<0.001
No (*n* = 1400)	3.94 (3.04–4.85)		4.62 (3.63–5.60)		4.26 (3.37–5.14)	
Body mass index (kg/m^2)						
<25 (*n* = 638)	4.58 (3.17–5.99)	<0.001*	5.11 (3.57–6.64)	<0.001*	4.53 (3.15–5.91)	0.003*
25–<30 (*n* = 1004)	3.13 (2.07–4.19)		4.14 (2.99–5.30)		3.54 (2.50–4.58)	
30–<35 (*n* = 760)	2.04 (0.83–3.25)		2.73 (1.40–4.05)		2.48 (1.29–3.67)	
≥35 (*n* = 589)	0.91 (−0.52–2.33)		1.08 (−0.47–2.64)		1.67 (0.28–3.06)	

CSS, clinical summary score; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; OSS, overall summary score; TSS, total symptom score.
**P*-value from trend test assuming a linear trend for LVEF, age and body mass index subgroups.

Activity Tolerance in Heart Failure with Preserved Ejection Fraction) trial enrolled 110 HFpEF patients with a baseline mean KCCQ-CSS of 57.6 ± 23.9[9,10] Although some of the studies reported the factors that may influence baseline HRQoL, none of these reported natural history of HRQoL in patients with HFpEF.

EMPEROR-Preserved is one of the most diverse trials in terms of regional diversity for patients with HFpEF with almost a third of the patients from Latin America and Asia. We show that region was an important determinant of KCCQ scores with participants from North America having the poorest reported health status. The global variation in reported health status may have implications as study design and regulatory concerns related to health status as an outcome in clinical trials.[11]

Understanding factors that influence future health status can be important for medical decision so that therapies and more specific goals of care can be directed towards high-risk groups, especially as patients value health status comparably or more important than other outcome.[12] We observed that patients with atrial fibrillation or flutter at enrolment, and those with chronic kidney disease had poorer health status at baseline and lesser improvement in KCCQ score at 52 weeks, and may represent in general worse HF status. Similarly, female sex was associated with worse KCCQ scores at baseline. Previous studies have also suggested sex to be one of the strongest correlates of health status, independent of signs or symptoms of HF, and other clinical comorbidities.[13] This sex disparity for health status is not just unique for HF but also

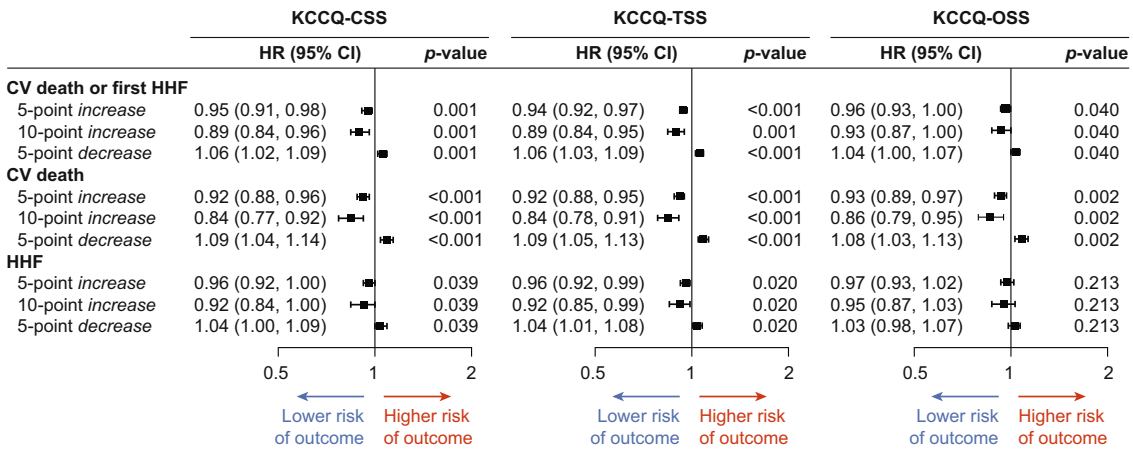


Figure 1 Multivariable adjusted association of change in the Kansas City Cardiomyopathy Questionnaire (KCCQ) score at 12 weeks with subsequent outcomes in the placebo arm. CI, confidence interval; CSS, clinical summary score; CV, cardiovascular; HHF, hospitalization for heart failure; OSS, overall summary score; TSS, total symptom score.

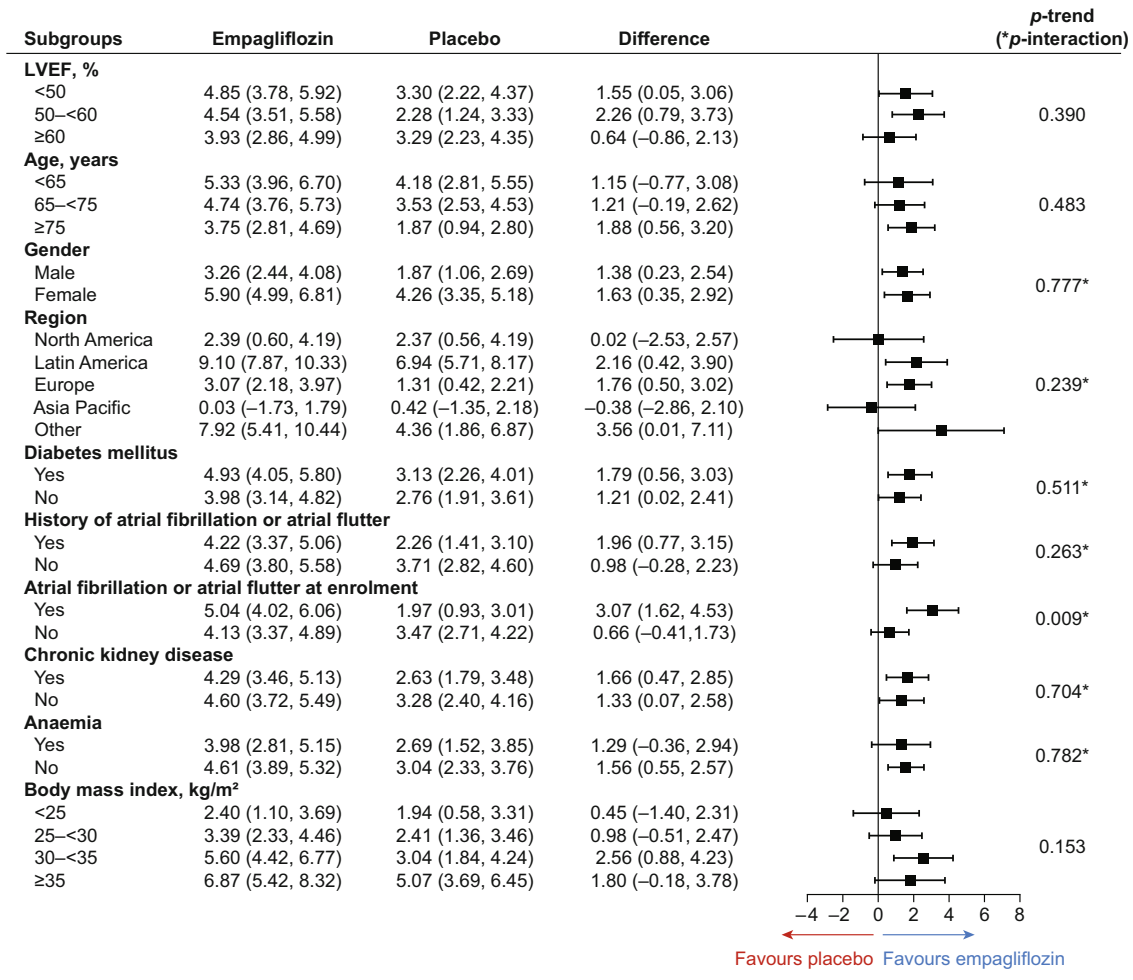


Figure 2 Effect of empagliflozin on Kansas City Cardiomyopathy Questionnaire changes in clinical summary score at 52 weeks by subgroup. LVEF, left ventricular ejection fraction.

seen with other chronic disease such as coronary artery disease and diabetes mellitus and may be partly due to more depression and less social support among women with these chronic diseases.[14]

It is well documented that change in KCCQ scores overtime are predictors for cardiovascular outcomes in patients with HF with reduced ejection fraction (HFrEF) with risk of cardiovascular death and HF hospitalization increasing by 6–11% for every 5-point decrease in KCCQ score.[15–17] However, less evidence is available in patients with HFpEF. Analysis of the Alberta HEART (Heart Failure Aetiology and Analysis Team) cohort showed that the composite outcomes of death and rehospitalization were more common in patients with HFpEF who had exhibited decreases in their KCCQ as compared with those with stable KCCQ.[18] However, this study was based on a small cohort ($n = 191$) of very homogeneous patients with HFpEF. To our knowledge, this is largest study to quantitatively confirm these findings.

The presence of some modifiable and non-modifiable risk factors may impact the degree to which a HF-specific intervention may improve HRQoL. We show that empagliflozin's benefit on health status also extends to HFpEF patients with these risk factors such those with history of diabetes, chronic kidney disease and atrial fibrillation/flutter. Empagliflozin also impacted health status similarly in women and men. These findings build up on our current understanding of the important benefit of empagliflozin which extends across broad range of HFpEF patients.

Few trials have assessed the effect of sodium–glucose cotransporter 2 (SGLT2) inhibition on health status in patients with HFpEF. In particular, the recent PRESERVED-HF (Dapagliflozin in Preserved Ejection Fraction Heart Failure) trial randomized 324 patients to receive dapagliflozin or placebo and showed that at 12 weeks dapagliflozin significantly improved KCCQ-CSS by 5.8 points. Compared to PRESERVED-HF, EMPEROR-Preserved showed an overall numerically less benefit on health stutus.[19] However, the patients recruited in PRESERVED-HF were more likely to be obese than the patients enrolled in EMPEROR-Preserved (mean BMI ~35 vs. ~30 kg/m^2). Analyses of the DELIVER trial also showed a greater effect of dapagliflozin on KCCQ in patients with higher BMI.[20] It is therefore noteworthy that patients who were obese showed a larger benefit from empagliflozin in the current analysis of the EMPEROR-Preserved trial. These observations from three different trials, considered together, indicate that obesity likely potentiates the beneficial effect of SGLT2 inhibitors on health status. This is particularly important since obese patients are least likely to show improvement in KCCQ during long-term follow-up if treated with placebo (*Table 3*).

In EMPEROR-Preserved, empagliflozin improved health status more in patients with atrial fibrillation or atrial flutter at enrolment. However, no influence of atrial fibrillation or flutter was seen when the rhythm was assessed by medical history. Therefore, the findings with respect to atrial arrhythmias are likely related to the play of chance.

The findings of this study should be considered considering certain limitations. The assessment of mean change in KCCQ scores within subgroups was done post hoc. Long-term health status data were not collected in this trial. Lastly, these results may not be generalizable to patients who did not fulfil the eligibility criteria for participation in the EMPEROR-Preserved trial.

In conclusion, health status is impaired in patients with HFpEF across most domains and summary scores, with greatest impairment in older patients, women and particularly those with obesity and comorbidities. Comorbidities were also important determinants for change in health status at 52 weeks, which is an important predictor of further clinical events in patients with HFpEF. The beneficial influence of empagliflozin on health status was seen across all subgroups studied, with obese patients showing a greater benefit.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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