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Baseline characteristics of patients with heart failure with preserved ejection fraction in the EMPEROR-Preserved trial

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Aims

EMPEROR-Preserved is an ongoing trial evaluating the effect of empagliflozin in patients with heart failure with preserved ejection fraction (HFpEF). This report describes the baseline characteristics of the EMPEROR-Preserved cohort and compares them with patients enrolled in prior HFpEF trials.

Methods and results

EMPEROR-Preserved is a phase III randomized, international, double-blind, parallel-group, placebo-controlled trial in which 5988 symptomatic HFpEF patients [left ventricular ejection fraction (LVEF) >40%] with and without type 2 diabetes mellitus (T2DM) have been enrolled. Patients were required to have elevated N-terminal pro B-type

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natriuretic peptide (NT-proBNP) concentrations (i.e. >300 pg/mL in patients without and >900 pg/mL in patients with atrial fibrillation) along with evidence of structural changes in the heart or documented history of heart failure hospitalization. Among patients enrolled from various regions (45% Europe, 11% Asia, 25% Latin America, 12% North America), the mean age was 72 ± 9 years, 45% were women. Almost all patients had New York Heart Association class II or III symptoms (99.6%), and 23% had prior heart failure hospitalization within 12 months. Thirty-three percent of the patients had baseline LVEF of 41–50%. The mean LVEF ($54 \pm 9\%$) was slightly lower while the median NT-proBNP [974 (499–1731) pg/mL] was higher compared with previous HFpEF trials. Presence of comorbidities such as diabetes (49%) and chronic kidney disease (50%) were common. The majority of the patients were on angiotensin-converting enzyme inhibitors/angiotensin receptor blockers/angiotensin receptor–neprilysin inhibitors (80%) and beta-blockers (86%), and 37% of patients were on mineralocorticoid receptor antagonists.

Conclusion

When compared with prior trials in HFpEF, the EMPEROR-Preserved cohort has a somewhat higher burden of comorbidities, lower LVEF, higher median NT-proBNP and greater use of mineralocorticoid receptor antagonists at baseline. Results of the EMPEROR-Preserved trial will be available in 2021.

Keywords

Heart failure with preserved ejection fraction • Sodium–glucose co-transporter 2 inhibitors • Empagliflozin

Introduction

Heart failure (HF) with preserved ejection fraction (HFpEF) affects many million patients globally and is associated with substantial morbidity and mortality for patients and cost to society.¹ There are no therapies that are approved to reduce HF hospitalizations or mortality in HFpEF patients.^{2–4} In addition to being at high risk of mortality and morbidity, HFpEF patients also often have impaired quality of life and functional capacity, which is comparable to patients living with end-stage renal disease.⁵ The mechanistic pathways to develop successful novel therapeutics in HFpEF are still being explored. In the recent PARAGON-HF [Prospective Comparison of ARNI (angiotensin receptor–neprilysin inhibitor) with ARB (angiotensin receptor blockers) Global Outcomes in HF with Preserved Ejection Fraction], sacubitril/valsartan narrowly missed the primary endpoint ($P = 0.058$) of total hospitalizations for HF and death from cardiovascular causes among patients with HF and an ejection fraction of 45% or higher.⁶

Sodium–glucose co-transporter 2 (SGLT2) inhibitors have emerged as novel anti-hyperglycaemic agents which have shown consistent benefit for HF hospitalizations in patients with type 2 diabetes mellitus (T2DM), who are especially prone to develop HFpEF.^{7–10} Furthermore, results from the DAPA HF trial (Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction) and EMPEROR-Reduced (Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction) showed that the risk of worsening HF or cardiovascular mortality was significantly lower with SGLT2 inhibitors compared with placebo by 25%, regardless of the presence or absence of T2DM, indicating that the therapeutic role of SGLT2 inhibitors in HF with reduced ejection fraction (HFrEF) extends to patients beyond T2DM.^{10–12} Independent of their glucose-lowering action, SGLT2 inhibitors exert broader multi-system metabolic benefits, including reduction in cardiac inflammation and fibrosis, weight loss, reduction in blood pressure and improvement in kidney

function.^{13,14} These effects may contribute to improving HFpEF outcomes.

The EMPEROR program is evaluating the effects of empagliflozin on HF in two large randomized controlled trials with one focusing on patients with a reduced ejection fraction (EMPEROR-Reduced, NCT03057977) and the other focusing on patients with a preserved ejection fraction (EMPEROR-Preserved, NCT03057951). This report describes the baseline characteristics of the EMPEROR-Preserved cohort and compares them with the patients enrolled in prior HFpEF trials.^{6,15–18}

Methods

Study design

The EMPEROR-Preserved trial is a phase III multicentre, randomized, double-blind, parallel-group, placebo-controlled trial evaluating the effects of empagliflozin on morbidity and mortality in patients with established HFpEF, with or without T2DM (Figure 1). The trial is registered as ClinicalTrials.gov Identifier: NCT03057951. The design paper has been published in full previously and is summarized below briefly.¹⁹

Study patients

Adults ≥ 18 years with chronic HF [New York Heart Association (NYHA) class II–IV] for at least 3 months and in whom left ventricular ejection fraction (LVEF) was $>40\%$ at its most recent assessment and in whom no prior measurement of ejection fraction of $\leq 40\%$ was noted were enrolled. Eligible patients were required to have elevated N-terminal pro B-type natriuretic peptide (NT-proBNP) concentrations (i.e. >300 pg/mL in patients without atrial fibrillation and >900 pg/mL in patients with atrial fibrillation) and structural heart changes (increased left atrial size or left ventricular mass) or a documented hospitalization for HF within 12 months of screening. After a screening period of 4–28 days, patients were randomized 1:1 to placebo or empagliflozin 10 mg/day, in addition to standard of care

EMPEROR-Preserved

Phase III randomised double-blind placebo-controlled event driven trial

Key Inclusion Criteria: T2D and non-T2D, aged ≥ 18 years, chronic HF (NYHA class II–IV) with LVEF $>40\%$, elevated NT-proBNP concentrations and structural heart changes or documented HHF within 12 months.

Key Exclusion Criteria: Symptomatic hypotension and eGFR <20 mL/min/1.73m².

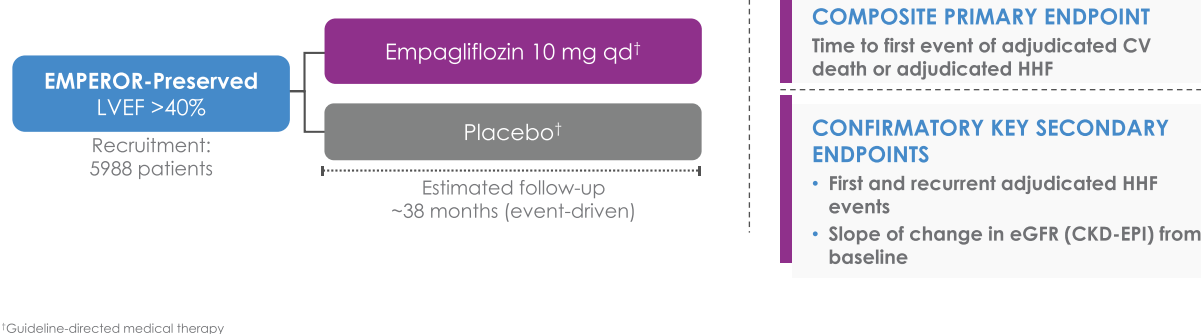


Figure 1 The design of the EMPEROR-Preserved trial. CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HF, heart failure; HHF, hospitalization for heart failure; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association; T2D, type 2 diabetes.

that is mostly driven by the management of comorbidities (e.g. coronary artery disease and hypertension) and as per the discretion of the treating physician. Randomization was done using permuted block design with a computer pseudo-random number generator and was stratified based on geographical region, estimated glomerular filtration rate (eGFR) and status of T2DM. The primary endpoint was the time-to-first-event analysis of the combined risk for adjudicated cardiovascular death and adjudicated hospitalization for HF. The trial is event-driven and will end when 841 adjudicated primary events have occurred.

Baseline data

All patients underwent a detailed baseline visit which included medical and social history based on patient self-report and chart review. The following variables were collected at the baseline visit: prior hospitalization for HF, myocardial infarction, stroke, chronic obstructive pulmonary disease, asthma, hypertension, dyslipidaemia, defibrillator, pacemaker, atrial fibrillation, T2DM, chronic kidney disease, smoking history and alcohol intake. All medications were also noted at the time of baseline visit. Physical examination and laboratory data included heart rate, systolic and diastolic blood pressure, height, weight, complete blood count, and urine microalbumin. Twelve-lead electrocardiogram (ECG) and health status assessment using the 23-question Kansas City Cardiomyopathy Questionnaire were also performed.

Comparisons with other relevant trials

Baseline characteristics from EMPEROR-Preserved were compared with those of other large-scale HFpEF trials, including patients enrolled

in PARAGON-HF, TOPCAT (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist), I-PRESERVE (Irbesartan in Heart Failure With Preserved Ejection Fraction), CHARM-Preserved (Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity) and PEP-CHF (Perindopril in Elderly People With Chronic Heart Failure).^{6,15–18} Baseline characteristics comparing patients by region of enrolment at baseline are also reported.

Results

Enrolment of study participants

Between March 2017 and April 2020, 11 585 patients were screened in 23 countries, and 5988 patients were ultimately enrolled in EMPEROR-Preserved. Six percent of the patients were enrolled in the trial based only on HF hospitalization within the past 12 months, 77% were enrolled based on evidence for presence of structural heart disease, while 16% had both.

Baseline demographic and clinical characteristics

Among patients enrolled from various regions (45% Europe, 11% Asia, 25% Latin America, 12% North America and 6% other), the mean age was 72 ± 9 years, and 45% were women. Overall, 76% of the patients were white (Table 1). The median duration of HF prior to randomization was 2.6 [interquartile range (IQR) 1.0–5.8] years. The majority of the patients had a history of hypertension (90%), but blood pressure was 132/76 mmHg at time

Table 1 Comparison of baseline demographic and clinical characteristics of patients enrolled in EMPEROR-Preserved and previous heart failure with preserved ejection fraction trials

	EMPEROR-Preserved (n = 5988)	PARAGON-HF (n = 4822)	TOPCAT (n = 3445)	I-PRESERVE (n = 4128)	CHARM-Preserved (n = 3023)	PEP-CHF (n = 850)
Age (years) ^a	72 ± 9	73 ± 8	69 ± 10	72 ± 7	67 ± 11	75 (72–79)
Women (%)	45	52	52	60	40	56
Obese (%)	45	49	55	41	38	NR
Race (%)						
White	76	82	89	93	92	N/A
Black	4	2	9	2	4	N/A
Asian	14	13	1	1	2	N/A
Native American/other	6	1	<1	NR	0	N/A
NYHA class (%)						
II	82	72	63	22	61	NR
III	18	27	33	77	38	NR
IV	0.3	0.6	<1	3	2	NR
Hypertension (%)	90	96	91	89	64	79
Diabetes (%)	49	43	32	27	28	21
Chronic kidney disease (%)	50	47	39	31	35	NR
Obstructive/central sleep apnoea (%)	7 / 1	NR	NR	NR	NR	NR
COPD (%)	13	14	12	NR	NR	NR
Current smoker (%)	7	7	10	NR	14	NR
Anaemia (%)	14	NR	NR	15	27	NR
History of CAD (%)	35	43	59	13	33	NR
History of myocardial infarction (%)	29	23	26	24	44	27
History of atrial fibrillation/flutter (%)	52	52	35	29	29	NR
History of malignancy	10	NR	NR	NR	NR	NR
Stroke (%)	10	10	8	10	9	NR
Prior HF hospitalization within 12 months before visit 1 (%)	23	48	72	23	69	NR
ICD (%)	4	0.4	1	NR	0.8	NR
MAGGIC risk score	19.1 ± 5.6	20 ± 6	NR	NR	NR	NR
Medications (%)						
Diuretics	86	96	82	Loop = 83; thiazide = 52	75	Loop = 46; thiazide = 55
ACE inhibitors	40	40	65	26	19 ^a	–
ARBs	39	45	20	N/A	N/A	–
ARNI	2	–	NR	NR	NR	NR
MRA	37	24	–	15	12	NR
Beta-blockers	86	75	78	59	56	55
CCB	30	36	38	40	31	33
Nitrates	12	17	15	27	33	51
Aspirin	42	40	65	NR	58	66
Antiplatelet (except aspirin)	16	13	NR	59	5	NR
Anticoagulants	48	27	23	19	10	16
Statins	69	62	53	NR	NR	NR
Cardiac glycosides	9	9	NR	14	28	12

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; CAD, coronary artery disease; CCB, calcium channel blocker; COPD, chronic obstructive pulmonary disease; HF, heart failure; ICD, implantable cardioverter defibrillator; MAGGIC, Meta-Analysis Global Group in Chronic Heart Failure; MRA, mineralocorticoid receptor antagonist; N/A, not applicable; NR, not recorded; NYHA, New York Heart Association.

^aMean ± standard deviation (except for median and interquartile range for PEP-CHF).

of study enrolment. At baseline, 2163 patients (36%) had a systolic blood pressure ≥140 mmHg or a diastolic blood pressure ≥90 mmHg. Most patients had NYHA functional class II symptoms (82%) at baseline. Almost half of the patients had T2DM (49%),

chronic kidney disease defined as an eGFR <60 mL/min/1.73 m² (50%), or a history of atrial fibrillation or atrial flutter (52%); a large percentage were overweight or obese with a body mass index (BMI) >30.0 kg/m² (45%). The proportion of patients with

anaemia was 14%. Most of the patients were on a diuretic (86%), on renin–angiotensin–aldosterone system inhibitor therapy with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (78%) or sacubitril/valsartan (2%) and beta-blockers (86%). Thirty-seven percent of the patients were on a mineralocorticoid receptor antagonist (MRA) and 67% were on a loop or high ceiling diuretic, while 21% were on thiazides or low-ceiling diuretics. Twenty-three percent of patients had a prior HF hospitalization within the past 12 months. The mean MAGGIC (Meta-Analysis Global Group in Chronic Heart Failure) risk score for mortality at baseline was 19.1 ± 5.6 . Many patients had peripheral oedema (29%), abnormal jugular venous distention (7%) and pulmonary rales (8%) at baseline. S3 gallop was not frequently present (1%).

Comparison of baseline demographic and clinical characteristics to prior heart failure with preserved ejection fraction trials

Overall, the characteristics of patients enrolled in EMPEROR-Preserved were similar to the patients enrolled in the PARAGON-HF trial. A larger percentage of patients were on MRA (37% vs. 24%) and beta-blocker (86% vs. 75%) therapy in EMPEROR-Preserved compared with PARAGON-HF. The use of any diuretic (86% vs. 96%), history of coronary artery disease (35% vs. 43%) and presence of NYHA class III symptoms (18% vs. 27%) was higher in the PARAGON-HF cohort. T2DM (49% vs. 43%) was more common in the patients enrolled in EMPEROR-Preserved. Compared with TOPCAT, I-PRESERVE, CHARM-Preserved and PEP-CHF, EMPEROR-Preserved study participants had higher burden of comorbidities (particularly regarding presence of chronic kidney disease and T2DM), but had similar age and sex distribution. EMPEROR-Preserved (14%) and PARAGON-HF (13%) had significantly higher enrolment of Asian individuals than other prior HFpEF trials (Table 1). The overall mean MAGGIC risk score at baseline in EMPEROR-Preserved (19.1 ± 5.6) and PARAGON-HF (20 ± 6) was similar. HF signs such as peripheral oedema, abnormal jugular venous distention and pulmonary rales were more frequently present in PARAGON-HF (45%, 17% and 11%, respectively) and TOPCAT (60%, 18% and 15%, respectively) compared with EMPEROR-Preserved.

Baseline laboratory, echocardiographic and electrocardiographic characteristics

The LVEF of patients enrolled in EMPEROR-Preserved is $54 \pm 9\%$ (mean \pm standard deviation) – 33% of patients had a baseline LVEF 41–50%, and 782 patients (13.1%) had a baseline LVEF 41–45%. The majority (82%) of the patients had left atrial enlargement at baseline. The median (IQR) NT-proBNP concentration was 974 (499–1730) pg/mL (Table 2). In the 5216 patients with baseline LVEF >45%, median NT-proBNP concentration was 963 (494–1705) pg/mL. Overall, the median (IQR) eGFR was 60 (46–75) mL/min/1.73 m². Twenty-four percent of the patients had eGFR <45 mL/min/1.73 m². The mean haemoglobin A1c in patients

with diabetes at baseline was $7.3 \pm 1.5\%$ [median: 6.8% (6.3–7.8%)]. Based on ECG recording at the time of screening, atrial fibrillation or atrial flutter was present in 35% of the patients.

Comparison of baseline laboratory and electrocardiographic characteristics to prior heart failure with preserved ejection fraction trials

The median NT-proBNP concentration was slightly higher while the mean LVEF was lower in the EMPEROR-Preserved cohort compared with prior HFpEF trials including PARAGON-HF (Table 2). Presence of atrial fibrillation at screening was largely similar in all trials except PEP-CHF (21%), in which it was markedly lower. A higher number of patients in the EMPEROR-Preserved cohort had eGFR <45 mL/min/1.73 m² compared with the previous trials (24% vs. 18%).

Baseline characteristics by region of enrolment

Table 3 shows the baseline characteristics according to region of enrolment. Patients enrolled in Asia had lower average BMI and were less likely to be in NYHA class III, to have chronic obstructive pulmonary disease or to be on angiotensin-converting enzyme inhibitors. Patients enrolled in North America were more likely to be obese, have obstructive sleep apnoea, anaemia, history of coronary artery disease and malignancy. Baseline blood pressure, heart rate, mean eGFR and LVEF were similar across the patients enrolled in different regions.

Discussion

EMPEROR-Preserved is the first randomized controlled trial of treatment with an SGLT2 inhibitor in HFpEF patients with and without T2DM aiming to show the impact of this therapeutic approach on hard outcome events. It represents the most contemporary cohort and largest outcomes trial for HFpEF conducted to date with approximately 1000 more patients enrolled than in the PARAGON-HF trial (Graphical Abstract). The baseline characteristics of HFpEF patients enrolled in EMPEROR-Preserved were generally similar to the broader population of HFpEF and prior trials with some differences including higher burden of comorbidities, lower ejection fraction, slightly higher NT-proBNP and greater use of MRA at baseline. Similar to previous trials,^{6,15–18} more than 30% of the patients had atrial fibrillation or atrial flutter at screening and more than half had atrial fibrillation/flutter at screening or prior history of atrial fibrillation/flutter suggesting the close relationship between HFpEF and atrial fibrillation.

There are several interesting differences between the baseline characteristics of EMPEROR-Preserved and recent prior studies in HFpEF. The majority of the patients were enrolled based on evidence of presence of structural changes in the heart (i.e. increases in left atrial size or left ventricular mass on echocardiography within 6 months of enrolment). Only

Table 2 Comparison of baseline physical examination, laboratory, echocardiographic and electrocardiographic characteristics of patients enrolled in EMPEROR-Preserved and previous heart failure with preserved ejection fraction trials

	EMPEROR-Preserved (n = 5988)	PARAGON-HF (n = 4822)	TOPCAT (n = 3445)	I-PRESERVE (n = 4128)	CHARM-Preserved (n = 3023)	PEP-CHF (n = 850)
BMI (kg/m ²) ^a	30 ± 6	30 ± 5	32 ± 7	30 ± 5	29 ± 6	28 (25–30)
Atrial fibrillation/flutter (% at screening) ^b	35	32	28	29	29	21
LBBB (%)	9	7	8	8	NR	NR
RBBB (%)	9	NR	11	NR	NR	NR
LV hypertrophy (%)	10	NR	29	31	15	NR
Paced rhythm (%)	8	NR	7	NR	NR	NR
E/e' ≥13 (%)	13	NR	NR	NR	NR	NR
Any LA size/volume increase at baseline (%)	82	92 ^c	NR	NR	NR	NR
LA width ≥4 cm (%)	59	NR	NR	NR	NR	NR
LA length ≥5 cm (%)	21	NR	NR	NR	NR	NR
LA area ≥20 cm ² (%)	23	NR	NR	NR	NR	NR
LA volume ≥55 mL (%)	15	NR	NR	NR	NR	NR
LA volume index ≥34 mL/m ² (%)	20	NR	NR	NR	NR	NR
Baseline weight (kg)	82 ± 19	NR	90 ± 22	NR	NR	NR
Baseline heart rate ^a	70 ± 12	70 ± 12	69 ± 10	71 ± 10	71 ± 12	73 (66–82)
Baseline SBP (mmHg) ^a	132 ± 16	136 ± 15	129 ± 14	136 ± 15	136 ± 18	139 (129–150)
Baseline DBP (mmHg) ^a	76 ± 11	77 ± 11	76 ± 11	79 ± 9	78 ± 11	80 (74–86)
Baseline NT-proBNP (pg/mL)	974 (499–1730)	885 (863–908)	950 (588–1920)	–	–	–
LVEF (%) ^a	54 ± 9	58 ± 8	57 ± 7	59 ± 9	54 ± 9	64 (56–66)
eGFR (mL/min) ^a	60.6 ± 19.8	63 ± 19	68 ± 20	73 ± 23	NR	NR
<45	23.8	18	NR	NR	NR	NR
45 to <60	26.1	30	NR	31	NR	NR
≥60	50.1	53	NR	NR	NR	NR
Baseline haemoglobin (g/dL) ^a	13 ± 2	NR	13 ± 2	14	13	NR
Baseline troponin (ng/mL) ^a	23.7 ± 30	NR	NR	NR	NR	NR
Haemoglobin A1c (%) ^a	7.3 ± 1.5	NR	NR	NR	NR	NR

BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; LBBB, left bundle branch block; LA, left atrial; LVEF, left ventricular ejection fraction; NR, not recorded; NT-proBNP, N-terminal pro B-type natriuretic peptide; RBBB, right bundle branch block; SBP, systolic blood pressure.

^aMean ± standard deviation where available (except for median and interquartile range for PEP-CHF).

^bBased on electrocardiogram.

^cSite reported.

23% of the patients in the EMPEROR-Preserved cohort had a recent HF hospitalization. This low rate was only similar to that in I-PRESERVE.¹⁶ In comparison, in TOPCAT overall and in CHARM-Preserved, 70% of the patients had hospitalization for HF within the 12 months prior to enrolment.^{15,17} This was somewhat lower with 50% in sites of the Americas in TOPCAT as well as in PARAGON-HF.^{20,21} The relatively low rates of recent HF hospitalization in EMPEROR-Preserved should have no major effect on generalizability of the trial results, if not increase the generalizability slightly, as patients were enrolled based on structural changes in the heart or elevated NT-proBNP which may be more commonly consistent with real-world HFpEF patients.

The differences in baseline characteristics may, to some degree, also be related to the somewhat differential requirements for natriuretic peptide elevation in these studies, and notably different requirements based on whether or not the patient had previously been admitted to hospital for HF. For example, in TOPCAT only

patients without a prior hospitalization with HF had to have elevated natriuretic peptides (B-type natriuretic peptide ≥100 pg/mL or NT-proBNP ≥360 pg/mL).¹⁵ In PARAGON-HF, patients without compared to those with a prior HF hospitalization had to meet a higher NT-proBNP threshold level for inclusion [e.g. those without prior HF hospitalization had to meet a >300 pg/mL limit (>600 pg/mL if AF was present at screening), while those with a prior HF hospitalization had to meet >200 pg/mL (>600 pg/mL, if in AF at screening)]. In EMPEROR-Preserved, however, all patients had to have raised NT-proBNP levels to be eligible with NT-proBNP >300 pg/mL (or >900 pg/mL, if in AF at screening).¹⁹ The inclusion of patients with LVEF of 41–44% did not impact the median NT-proBNP observed in the EMPEROR-Preserved cohort (974 pg/mL for all patients vs. 963 pg/mL without the 782 patients with LVEF <45%).

Other relevant differences in baseline characteristics are worthy of discussion. I-PRESERVE, PARAGON-HF and TOPCAT

Table 3 Baseline characteristics of patients enrolled in EMPEROR-Preserved stratified by region of enrolment

	North America (n = 719)	Latin America (n = 1515)	Europe (n = 2689)	Asia (n = 686)	Other (n = 379)
Age (years) ^a	73 ± 10	70 ± 10	73 ± 8	72 ± 9	69 ± 11
Women (%)	44	47	46	36	46
Obese (%)	59	44	50	9	48
Race (%)					
White	86	71	99	0	48
Black	11	10	0.2	0	8
Asian	2	2	0.1	100	27
Native American/other (%)	1	17	0.7	0	17
NYHA class (%)					
II	76	85	81	89	70
III	23	15	19	10	30
IV	0.7	0.3	0.2	0.4	0
Hypertension (%)	95	91	92	81	86
Diabetes (%)	51	54	47	44	52
Obstructive sleep apnoea (%)	32	2	4	5	13
COPD (%)	24	10	13	5	16
Current smoker (%)	7	5	8	10	6
Anaemia (%)	34	8	12	19	15
History of CAD (%)	46	31	34	38	29
History of myocardial infarction (%)	31	37	27	25	23
History of atrial fibrillation/flutter (%)	57	30	63	60	45
History of malignancy	23	4	11	8	12
Stroke (%)	10	9	9	16	8
Prior HF hospitalization within 12 months before visit 1 (%)	26	14	23	34	29
ICD (%)	8	2	4	2	3
Medications (%)					
Non-MRA diuretics	84	74	85	67	83
ACE inhibitors	32	33	52	22	33
ARBs	34	52	31	46	34
ARNI	4	3	1	4	3
MRA	24	40	38	43	40
Beta-blockers	85	86	88	83	75
CCB	36	26	30	40	27
Nitrates	26	11	9	12	19
Aspirin	50	56	32	36	46
Anticoagulants	50	25	61	53	42
Statins	74	68	70	60	74
Digoxin	7	6	12	11	8
Baseline NT-proBNP (pg/mL) ^b	1043 (528–1860)	835 (449–1624)	956 (482–1639)	1213 (686–2036)	1073 (536–1945)
LVEF (%) ^a	56 ± 8	54 ± 9	53 ± 8	57 ± 9	55 ± 9
Baseline SBP (mmHg) ^a	131 ± 17	130 ± 16	134 ± 15	129 ± 16	133 ± 17
Baseline DBP (mmHg) ^a	73 ± 11	76 ± 10	76 ± 10	75 ± 12	76 ± 11
Baseline heart rate (bpm) ^a	69 ± 12	69 ± 11	71 ± 12	72 ± 13	71 ± 12
BMI (kg/m ²) ^a	32 ± 6	30 ± 6	30 ± 5	25 ± 4	31 ± 6
eGFR (mL/min) ^a	56.3 ± 19.8	62.1 ± 21.4	60 ± 18	64 ± 19	62.5 ± 22.9
<45	31	23	23	18	27
45 to <60	28	23	28	27	21
≥60	41	54	49	55	52
Baseline haemoglobin (g/dL) ^a	13 ± 2	13 ± 2	14 ± 1	13 ± 2	13 ± 2
Baseline troponin (ng/mL) ^a	29.1 ± 37	22.5 ± 27.9	22.1 ± 27	26.3 ± 38	25.5 ± 24.1
Haemoglobin A1c (%) ^a	7.4 ± 1.6	7.6 ± 1.7	7.0 ± 1.2	6.9 ± 1.1	7.6 ± 1.8

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; CAD, coronary artery disease; CCB, calcium channel blocker; BMI, body mass index; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; 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.

^aMean ± standard deviation.

^bMedian and interquartile range.

included only those patients with HF and LVEF ≥45%, while EMPEROR-Preserved enrolled patients with HF and LVEF >40%. The use of an LVEF threshold of 40% explains why the ejection fractions were lower in EMPEROR-Preserved. The use of an LVEF threshold of 40% might allow for treatment of potentially more therapy-responsive patients and avoid ambiguity of the ‘mid-range’

between prior standards for reduced and preserved LVEF. Furthermore, the burden of comorbidities (particularly with chronic kidney disease and T2DM) was somewhat higher in patients enrolled in EMPEROR-Preserved and a higher number of patients had eGFR <45 mL/min/1.73 m². This could have been due to the exclusion criteria cut-off set at 20 mL/min/1.73 m² instead of

30 mL/min/1.73 m² compared with other trials such as TOPCAT and PARAGON-HF. In EMPEROR-Preserved, 310 patients had an eGFR <30 mL/min/1.73 m², and 1113 patients had an eGFR of 30.0 to <45 mL/min/1.73 m². Interestingly, mean BMI was rather similar in the trials compared here, despite noticeable differences in BMI inclusion criteria. EMPEROR-Preserved included patients with a BMI <45 kg/m² at screening, whereas it was for instance ≤40 kg/m² in PARAGON-HF.

Lastly, background therapy with MRAs and beta-blockers was considerably higher while the use of diuretics (any) was somewhat lower in EMPEROR-Preserved compared with PARAGON-HF (86% vs. 96%). In comparison, use of any diuretic at baseline in TOPCAT was 82%. Regarding MRA use, this may in part be due to the results of the TOPCAT trial, which suggested possible benefit in reducing first and recurrent HF hospitalizations with spironolactone in HFpEF patients.¹⁵ This is important because studies have suggested that MRAs can exert systemic effects on collagen metabolism and may help to reduce pre- and afterload that may specifically hinder or reverse myocardial, vascular and renal fibrosis, which may have an important component in HFpEF.^{22,23} Consequently, EMPEROR-Preserved will be able to test the potential efficacy of empagliflozin in addition to the use of MRAs (mostly spironolactone). Higher use of diuretics in PARAGON-HF may be related to the protocol which mandated diuretic therapy for at least 30 days before screening.

Some limitations should be considered while interpreting baseline data of EMPEROR-Preserved. The comparison of the severity and overall burden of comorbidities between EMPEROR-Preserved and prior HFpEF trials could not be done for some variables (in part due to lack of such information from other trials).

In summary, the EMPEROR-Preserved trial is the largest clinical trial ever conducted in patients with HFpEF to date. Compared to other contemporary HFpEF trials, the EMPEROR-Preserved cohort has some notable differences. These include a higher burden of comorbidities, many patients with low eGFR and T2DM, and overall these patients have a somewhat lower ejection fraction, slightly higher NT-proBNP concentration and high use of MRAs at baseline. EMPEROR-Preserved will determine whether the SGLT2 inhibitor empagliflozin – which has previously been shown to improve outcomes in HFpEF patients independent of T2DM status¹¹ – will also reduce morbidity and mortality in patients with HFpEF. As several biomarkers of cardiac and renal injury (including NT-proBNP, troponin T and eGFR), metabolic markers (including uric acid, haemoglobin A1c and haemoglobin), a large array of omics biomarkers, as well as adiposity and body weight change will also be evaluated, the EMPEROR-Preserved trial is also well poised to further our mechanistic understanding of the disease and of the pathophysiologic effects of empagliflozin. Results of the EMPEROR-Preserved trial will be available in 2021.

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EMPEROR-Reduced trial and served as a national lead investigator of the DAPA-HF and EMPEROR-Reduced trials; he is the President of the Canadian Medical and Surgical Knowledge Translation Research Group, a federally incorporated not-for-profit physician organization. D.V. reports grants and personal fees from Boehringer Ingelheim, during the conduct of the study; grants and personal fees from Novartis and Amgen, outside the submitted work. J.Z. reports personal fees from Boehringer Ingelheim, during the conduct of the study. W.J., S.S., J.M.S., and M.Br. are employees of Boehringer Ingelheim. S.J.P. reports that he is a consultant for Boehringer Ingelheim. F.Z. reports personal fees from Boehringer Ingelheim during the conduct of the study; personal fees from Janssen, Novartis, Boston Scientific, Amgen, CVRx, AstraZeneca, Myokardia, Vifor Fresenius, Cardior, Cerenopharmaceutical, Applied Therapeutics, Merck, Bayer, Owkin, and Cellprothera, outside the submitted work; and other support from CVCT and Cardiorenal, outside the submitted work. M.P. reports personal fees from Boehringer Ingelheim, during the conduct of the study; personal fees from AbbVie, Akcea, Amarin, AstraZeneca, Amgen, Boehringer Ingelheim, Cardior, Daiichi Sankyo, Johnson & Johnson, Lilly, Novartis, Pfizer, Relypsa, Sanofi, Synthetic Biologics, Theravance, and NovoNordisk, outside the submitted work. All other authors have nothing to disclose.

References

1. GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the global burden of disease study 2017. *Lancet* 2018;**392**:1789–1858.
2. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJ, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WH, Tsai EJ, Wilkoff BL; American College of Cardiology Foundation and American Heart Association Task Force on Practice Guidelines. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2013;**62**:e147–e239.
3. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P; Authors/Task Force Members and Document Reviewers. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2016;**18**:891–975.
4. Ferrari R, Bohm M, Cleland JG, Paulus WJ, Pieske B, Rapezzi C, Tavazzi L. Heart failure with preserved ejection fraction: uncertainties and dilemmas. *Eur J Heart Fail* 2015;**17**:665–671.
5. Lewis EF, Lamas GA, O'Meara E, Granger CB, Dunlap ME, McKelvie RS, Probstfield JL, Young JB, Michelson EL, Halling K, Carlsson J, Olofsson B, McMurray JJ, Yusuf S, Swedberg K, Pfeffer MA. Characterization of health-related quality of life in heart failure patients with preserved versus low ejection fraction in CHARM. *Eur J Heart Fail* 2007;**9**:83–91.
6. Solomon SD, McMurray JJ, Anand IS, Ge J, Lam CS, Maggioni AP, Martinez F, Packer M, Pfeffer MA, Pieske B, Redfield MM, Rouleau JL, van Veldhuisen DJ, Zannad F, Zile MR, Desai AS, Claggett B, Jhund PS, Boytsov SA, Comin-Colet J, Cleland J, Dungen HD, Goncalvesova E, Katova T, Kerr Saraiva JF, Lelonek M, Merkely B, Senni M, Shah SJ, Zhou J, Rizkala AR, Gong J, Shi VC, Lefkowitz MP; PARAGON-HF Investigators and Committees. Angiotensin-neprilysin inhibition in heart failure with preserved ejection fraction. *N Engl J Med* 2019;**381**:1609–1620.
7. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen OE, Woerle HJ, Broedl UC, Inzucchi SE; EMPA-REG OUT-COME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015;**373**:2117–2128.

8. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, Shaw W, Law G, Desai M, Matthews DR; CANVAS Program Collaborative Group. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med* 2017;**377**:644–657.
9. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, Silverman MG, Zelniker TA, Kuder JF, Murphy SA, Bhatt DL, Leiter LA, McGuire D, Wilding JP, Ruff CT, Gause-Nilsson IA, Fredriksson M, Johansson PA, Langkilde AM, Sabatine MS; DECLARE–TIMI 58 Investigators. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2019;**380**:347–357.
10. McMurray JJ, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, Ponikowski P, Sabatine MS, Anand IS, Böhöhlávek J, Böhm M, Chiang CE, Chopra VK, de Boer RA, Desai AS, Díez M, Drozd J, Dukát A, Ge J, Howlett JG, Katova T, Kitakaze M, Ljungman CE, Merkely B, Nicolau JC, O'Meara E, Petrie MC, Vinh PN, Schou M, Tereshchenko S, Verma S, Held C, DeMets DL, Docherty KF, Jhund PS, Bengtsson O, Sjöstrand M, Langkilde AM; DAPA-HF Trial Committees and Investigators. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med* 2019;**381**:1995–2008.
11. Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, Januzzi J, Verma S, Tsutsui H, Brueckmann M, Jamal W, Kimura K, Schnee J, Zeller C, Cotton D, Bocchi E, Böhm M, Choi DJ, Chopra V, Chuquiure E, Giannetti N, Janssens S, Zhang J, Gonzalez Juanatey JR, Kaul S, Brunner-La Rocca HP, Merkely B, Nicholls SJ, Perrone S, Pina I, Ponikowski P, Sattar N, Senni M, Seronde MF, Spinar J, Squire I, Taddei S, Wanner C, Zannad F; EMPEROR-Reduced Trial Investigators. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med* 2020;**383**:1413–1424.
12. Zannad F, Ferreira JP, Pocock SJ, Anker SD, Butler J, Filippatos G, Brueckmann M, Ofstad AP, Pfarr E, Jamal W, Packer M. SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: a meta-analysis of the EMPEROR-Reduced and DAPA-HF trials. *Lancet* 2020;**396**:819–829.
13. Honigberg MC, Vardeny O, Vaduganathan M. Practical considerations for the use of sodium-glucose co-transporter 2 inhibitors in heart failure. *Circ Heart Fail* 2020;**13**:e006623.
14. Butler J, Handelsman Y, Bakris G, Verma S. Use of sodium-glucose co-transporter-2 inhibitors in patients with and without type 2 diabetes: implications for incident and prevalent heart failure. *Eur J Heart Fail* 2020;**22**:604–617.
15. Pitt B, Pfeffer MA, Assmann SF, Boineau R, Anand IS, Claggett B, Clausell N, Desai AS, Diaz R, Fleg JL, Gordeev I, Harty B, Heitner JF, Kenwood CT, Lewis EF, O'Meara E, Probstfield JL, Shaburishvili T, Shah SJ, Solomon SD, Sweitzer NK, Yang S, McKinlay SM; TOPCAT Investigators. Spironolactone for heart failure with preserved ejection fraction. *N Engl J Med* 2014;**370**:1383–1392.
16. Massie BM, Carson PE, McMurray JJ, Komajda M, McKelvie R, Zile MR, Anderson S, Donovan M, Iverson E, Staiger C, Ptaszynska A; I-PRESERVE Investigators. Irbesartan in patients with heart failure and preserved ejection fraction. *N Engl J Med* 2008;**359**:2456–2467.
17. Yusuf S, Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJ, Michelon EL, Olofsson B, Ostergren J; CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved trial. *Lancet* 2003;**362**:777–781.
18. Cleland JG, Tendera M, Adamus J, Freemantle N, Polonski L, Taylor J; PEP-CHF Investigators. The perindopril in elderly people with chronic heart failure (PEP-CHF) study. *Eur Heart J* 2006;**27**:2338–2345.
19. Anker SD, Butler J, Filippatos GS, Jamal W, Salsali A, Schnee J, Kimura K, Zeller C, George J, Brueckmann M, Zannad F, Packer M; EMPEROR-Preserved Trial Committees and Investigators. Evaluation of the effects of sodium-glucose co-transporter 2 inhibition with empagliflozin on morbidity and mortality in patients with chronic heart failure and a preserved ejection fraction: rationale for and design of the EMPEROR-preserved trial. *Eur J Heart Fail* 2019;**21**:1279–1287.
20. Pfeffer MA, Claggett B, Assmann SF, Boineau R, Anand IS, Clausell N, Desai AS, Diaz R, Fleg JL, Gordeev I, Heitner JF, Lewis EF, O'Meara E, Rouleau JL, Probstfield JL, Shaburishvili T, Shah SJ, Solomon SD, Sweitzer NK, McKinlay SM, Pitt B. Regional variation in patients and outcomes in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) trial. *Circulation* 2015;**131**:34–42.
21. Solomon SD, Rizkala AR, Gong J, Wang W, Anand IS, Ge J, Lam CS, Maggioni AP, Martinez F, Packer M, Pfeffer MA, Pieske B, Redfield MM, Rouleau JL, Van Veldhuisen DJ, Zannad F, Zile MR, Desai AS, Shi VC, Lefkowitz MP, McMurray JJ. Angiotensin receptor neprilysin inhibition in heart failure with preserved ejection fraction: rationale and design of the PARAGON-HF trial. *JACC Heart Fail* 2017;**5**:471–482.
22. Zannad F, Alla F, Dousset B, Perez A, Pitt B. Limitation of excessive extracellular matrix turnover may contribute to survival benefit of spironolactone therapy in patients with congestive heart failure: insights from the Randomized Aldactone Evaluation Study (RALES). *Circulation* 2000;**102**:2700–2706.
23. Pellicori P, Ferreira JP, Mariottoni B, Brunner-La Rocca HP, Ahmed FZ, Verdon-schoot J, Collier T, Cuthbert JJ, Petutschnigg J, Mujaj B, Girerd N, González A, Clark AL, Cosmi F, Staessen JA, Heymans S, Latini R, Rossignol P, Zannad F, Cleland JG. Effects of spironolactone on serum markers of fibrosis in people at high risk of developing heart failure: rationale, design and baseline characteristics of a proof-of-concept, randomised, precision-medicine, prevention trial. The Heart OMics in AGing (HOMAGE) trial. *Eur J Heart Fail* 2020;**22**:1711–1723.