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► To cite this version:

Andrew J.S. Coats, Javed Butler, Hiroyuki Tsutsui, Wolfram Doehner, Gerasimos Filippatos, et al.. Efficacy of empagliflozin in heart failure with preserved ejection fraction according to frailty status in **EMPEROR-Preserved**. *Journal of Cachexia, Sarcopenia and Muscle*, 2024, 15 (1), pp.412-424. 10.1002/jcsm.13393 . hal-04383248

HAL Id: hal-04383248

<https://hal.univ-lorraine.fr/hal-04383248v1>

Submitted on 9 Jan 2024

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Efficacy of empagliflozin in heart failure with preserved ejection fraction according to frailty status in EMPEROR-Preserved

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Abstract

Background Frailty is a severe, common co-morbidity associated with heart failure (HF) with preserved ejection fraction (HFpEF). The impact of frailty on HFpEF outcomes may affect treatment choices in HFpEF. The impact of frailty on HFpEF patients and any impact on the clinical benefits of sodium glucose co-transporter 2 (SGLT2) inhibition in HFpEF have been described in only a limited number of trials. Whether the SGLT2 inhibitor empagliflozin would improve or worsen frailty status when given to HFpEF patients is also not known. The aims of this study were, therefore, to evaluate, in HFpEF patients enrolled in the EMPEROR-Preserved trial (Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction), the impact of frailty on clinical outcomes, and on the effects of empagliflozin, as well as the effect of empagliflozin on frailty status during treatment period.

Methods We calculated a cumulative deficit-derived frailty index (FI) using 44 variables including clinical, laboratory and quality of life parameters recorded in EMPEROR-Preserved. Patients were classified into four groups: non-frail (FI < 0.21), mild frailty (0.21 to <0.30), moderate frailty (0.30 to <0.40) and severe frailty (\geq 0.40). Clinical outcomes and health-related quality of life were evaluated according to baseline FI along with the effect of empagliflozin on chronological changes in FI (at 12, 32 and 52 weeks).

Results The patient distribution was 1514 (25.3%), 2100 (35.1%), 1501 (25.1%) and 873 (14.6%) in non-frail, mild frailty, moderate frailty and severe frailty, respectively. Severe frailty patients tended to be female and have low Kansas City Cardiomyopathy Questionnaire (KCCQ) scores, more co-morbidities and more polypharmacy. Incidence rates of the primary outcome of cardiovascular death or HF hospitalization increased as frailty worsened (hazard ratio [HR] of each FI category compared with the non-frail group: 1.10 [95% confidence interval, CI, 0.89–1.35], 2.00 [1.63–2.47] and 2.61 [2.08–3.27] in the mild frailty, moderate frailty and severe frailty groups, respectively; P trend < 0.001). Compared with placebo, empagliflozin reduced the risk for the primary outcome across the four FI categories, HR: 0.59 [95% CI 0.42–0.83], 0.79 [0.61–1.01], 0.77 [0.61–0.96] and 0.90 [0.69–1.16] in non-frail to

severe frailty categories, respectively (P value for trend = 0.097). Empagliflozin also improved other clinical outcomes and KCCQ score across frailty categories. Compared with placebo, empagliflozin-treated patients had a higher likelihood of being in a lower FI category at Weeks 12, 32 and 52 ($P < 0.05$), odds ratio: 1.12 [95% CI 1.01–1.24] at Week 12, 1.21 [1.09–1.34] at Week 32 and 1.20 [1.09–1.33] at Week 52.

Conclusions Empagliflozin improved key efficacy outcomes with a possible diminution of effect in very frail patients. Empagliflozin also improved frailty status during follow-up.

Keywords empagliflozin; frailty; heart failure with preserved ejection fraction; randomized clinical trial; SGLT2 inhibitors

Received: 5 September 2023; Revised: 22 October 2023; Accepted: 6 November 2023

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Registration: <https://www.clinicaltrials.gov>; unique identifier: NCT03057951.

Introduction

Frailty is becoming more common as the populations of the world age and as previously fatal conditions are being managed better, thereby allowing patients to survive longer whilst accumulating an increased burden of co-morbidities.¹ There is no precise definition of frailty as it is a combination of multiple physiological and pathological deficiencies that lead to a reduction in the reserve capacity of the body to cope with physiological or physical stressors, as recently reviewed.² Frailty is of increasing interest for healthcare systems worldwide, and the impact of frailty on how best to manage other illnesses is of great importance. Frailty frequently accompanies a diagnosis of heart failure (HF),³ and as heart failure with preserved ejection fraction (HFpEF) is typically a condition of the elderly, it may be even more likely to be associated with frailty.^{4,5} Frailty in patients with HF is up to six times more common than in the general population,^{6,7} and this is more likely in HFpEF compared with heart failure with reduced ejection fraction (HFrEF) because of the average older age and the greater frequency of co-morbidities in HFpEF. HF predisposes to frailty through multiple mechanisms including its impact on skeletal muscle volume and function,⁸ as well as on other systems including cognition.⁹

Previous studies have demonstrated that sodium glucose co-transporter 2 (SGLT2) inhibitors effectively reduce cardiovascular (CV) events and hospitalization for heart failure (HHF), not only in at-risk type 2 diabetic patients¹⁰ but also in HFrEF patients¹¹ and HFpEF patients¹² with or without diabetes. SGLT2 inhibitors have been shown to cause weight loss of around 2–3 kg in trials in diabetes,^{13–15} so concern has been expressed that frail patients with frequent low skeletal muscle mass may be made worse by SGLT2 inhibitors.

Several reports have identified treatments of HFrEF and the differential response to these therapies in patients with or without frailty,¹⁶ but the number of reports of this potential interaction within HFpEF is limited. The SGLT2 inhibitors empagliflozin and dapagliflozin are the only two agents that

have been proven in prospective outcome trials to be of benefit for HFpEF patients, and it is thus of interest to evaluate the impact of one of these successful treatments for HFpEF, empagliflozin, by analysing the impact of frailty in the EMPEROR-Preserved trial (Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction). This may be of particular importance given that the SGLT2 inhibitors can lead to calorie loss in patients with diabetes and overall lead to a small but consistent reduction in body weight, which some physicians feel may be a risk to already frail patients. Thus, it is important to analyse the relationship between frailty and prognosis in a trial that recruited significant number of severely frail and frail high-risk patients among HFpEF subjects, as did EMPEROR-Preserved.

Frail patients may receive guideline-directed medical therapy less frequently compared with non-frail patients, possibly because of the perception that they may have a lower tolerance of drug interventions.¹⁷ The number of reports that have specifically evaluated the impact of frailty on the ability to tolerate HF therapies and the relative effectiveness of these therapies in frail HF patients is very limited. A recent paper reported the impact of frailty in the DELIVER trial of dapagliflozin in HFpEF patients.¹⁸ It reported a high frequency of frailty in the recruited HFpEF patients with only 37.6% being non-frail. It reported that higher grades of frailty were associated with higher rates of the primary endpoint (CV mortality or HF hospitalization). There was no significant interaction between the severity of frailty and the effect of dapagliflozin on the primary endpoint of the trial or on the risk of side effects, although the authors reported a slightly greater improvement in Kansas City Cardiomyopathy Questionnaire (KCCQ) with dapagliflozin in the more frail patients, albeit with them starting from a lower baseline. In addition, this manuscript did not report the impact of dapagliflozin on frailty status during follow-up. The objective of this study was to evaluate the impact of frailty on clinical outcomes, the influence of frailty on the clinical effects of empagliflozin and the effect of empagliflozin on frailty status over time in the EMPEROR-Preserved trial.

Methods

Trial design and study participants

This is a post hoc analysis of the phase 3 randomized clinical trial EMPEROR-Preserved (ClinicalTrials.gov: NCT03057951). The design of EMPEROR-Preserved has been described previously.¹⁹ In brief, symptomatic HFpEF patients (left ventricular ejection fraction [LVEF] > 40% and no previous LVEF ≤ 40%) in New York Heart Association (NYHA) class II–IV with an elevated N-terminal pro-B-type natriuretic peptide (NT-proBNP) (>900 or >300 pg/mL in patients with and without atrial fibrillation, respectively) and documented evidence of structural heart disease, or an HHF within 12 months before enrolment, were randomized to once daily empagliflozin 10 mg or matching placebo for a median of 26 months. Exclusion criteria included symptomatic hypotension, systolic blood pressure (SBP) of <100 or ≥180 mmHg or an estimated glomerular filtration rate (eGFR) < 20 mL/min/1.73 m². The trial was approved by each local ethics committees, and all patients provided written informed consent.

Patients were randomized double-blind (in a 1:1 ratio) to receive placebo or empagliflozin 10 mg daily, in addition to their usual therapy for HF. Following entry into the trial, all appropriate treatments for HF or other medical conditions could be initiated or altered at the clinical discretion of the investigator. Patients were periodically assessed at study visits for major outcomes, symptoms and functional capacity related to HF, vital signs and biomarkers reflecting changes in the course of HF, and adverse events (AEs). All randomized patients were followed for the occurrence of prespecified outcomes for the entire duration of the trial, regardless of whether the study participants were taking their study medications.

Trial endpoints

The primary endpoint of the main EMPEROR-Preserved trial was the time-to-first-event analysis of the combined risk of CV death or HHF. Key secondary endpoints were (1) the total number of adjudicated HHF (including first and recurrent events) and (2) the slope of the change in eGFR during double-blind treatment.

In this analysis, we assessed the impact of empagliflozin on the primary outcome across four frailty categories, based on a cumulative deficit-derived frailty index (FI). We also assessed the effect of empagliflozin on other clinical outcomes and KCCQ score.

Previous reports have noted that AE rates increase as frailty worsens.¹⁸ We therefore assessed safety signals across frailty groups by investigating any AE and serious adverse events (SAEs) and looked in particular at acute renal failure, urinary tract infections (UTI), genital infections, lower limb

amputations, bone fractures, hypoglycaemia, symptomatic hypotension and any hypotension. Assessments were based on AEs reported by the investigators (coded according to the Medical Dictionary for Regulatory Activities [MedDRA] Version 23.1) and laboratory tests.

Frailty index

In our analysis, we developed an FI score using an adaptation of the Rockwood cumulative deficit approach, as has been used previously, calculating the sum of scores over all non-missing variables per subject, divided by sum of all non-missing variables assessed per subject. Rockwood described an index derived from at least 40 items related to ill-health (but not normal ageing) covering a range of body systems to construct a cumulative deficits score.²⁰ Measures can be categorical, ordinal or interval variables and should be defined as ranging from 0 = absence of a deficit to 1 = full expression of the deficit. Individual deficit scores are combined into an index, which thus varies between 0 and 1. Such an FI has been shown to be a reliable predictor of mortality.²¹ Previous studies in HFpEF, such as an analysis of PARADIGM-HF and ATMOSPHERE,²² used a 42-item FI, derived from patient data from a clinical trial with the final score being sub-divided into three groups, using a threshold of ≤0.21 as non-frail and then two extra groups in increments of 0.1, that is, 0.21–0.31 and ≥0.31. For this analysis of EMPEROR-Preserved in HFpEF, where patients were older and had more co-morbidities, we chose to sub-divide the patients into four frailty classes: non-frail (FI < 0.21), mild frailty (0.21 to <0.30), moderate frailty (0.30 to <0.40) and severe frailty (≥0.40), allowing for a more even distribution between severity classes, and to inform more about the impact of increasing frailty severity.

To construct our 44-parameter FI, we used a mixture of co-morbidities, clinical, laboratory and quality of life (QoL) observations and data on physical limitations and symptomatic status derived from 15 questions (of 23) from the KCCQ as proxy measures of disability. For full list, see *Table S1*. Categorical variables were scored 0/1 (absent/present); ordinal variables were scored between 0 and 1, with 1 the worst and 0 the best.

Statistical analysis

Baseline characteristics were summarized using descriptive statistics and compared across baseline status of these four frailty categories constructed from the 44 clinical variables, using ordinal regression likelihood ratio tests. Associations between baseline status of frailty categories and subsequent outcomes for the main trial endpoints and safety endpoints were analysed by comparing between empagliflozin and the

placebo groups and by comparing across frailty categories with the treatment arms combined.

Time-to-first-event outcomes were analysed using the Cox regression model with covariates of sex, age, region, diabetes status at baseline, LVEF, baseline eGFR, baseline status of frailty categories and treatment-by-baseline status of frailty categories interaction. The interaction between baseline status of frailty categories and treatment was tested using a trend test assuming ordered frailty categories. Total (first and recurrent) HHFs were evaluated using the joint frailty model with CV death as competing risk, adjusted for the same covariates as the Cox model. The change in eGFR slope was analysed based on on-treatment data, using a random intercept random slope model allowing intercept and slope to vary randomly between patients. The analysis model included age, baseline eGFR, baseline LVEF, sex, region, diabetes status at baseline, baseline eGFR-by-time interaction, treatment-by-baseline status of frailty categories interaction and time-by-treatment-by-baseline status of frailty categories interaction as covariates. In addition, as sensitivity analyses, the effect of treatment (empagliflozin vs. placebo) on the primary endpoint of the composite of adjudicated CV death or HHF and the two key secondary endpoints of total (first and recurrent) hospitalizations for HF and the slope of the change in eGFR were repeated using frailty categories using only the 41 clinical variables that were used for the analysis of chronological changes in the FI.

Changes in KCCQ score were analysed using a mixed model for repeated measurements including age, baseline eGFR and baseline LVEF as linear covariates and region, diabetes status, sex, last projected visit based on dates of randomization and trial closure, visit-by-treatment-by-baseline status of frailty categories interaction and baseline KCCQ score-by-visit interaction as fixed effects.

The frequencies of the prespecified safety outcomes were investigated using logistic regression modelling adjusted with the same covariates as the Cox model based on patients who have taken at least one dose of investigational treatment.

For analysis of FI score chronological change, neither fasting glucose nor percutaneous coronary intervention or coronary artery bypass grafting (PCI/CABG) was available during follow-up and nor was the total number of medications used at each trial visit reliably ascertained. These three parameters were therefore excluded from the calculation of frailty over time, and hence, a 41-parameter was used to assess FI change over time. FI at Weeks 12, 32 and 52 was analysed using partial proportional odds regression model adjusted for the same variables used in the Cox model and baseline FI, assuming proportionality for all covariates except region. In addition, responder analysis was performed to study the proportion of patients with an improvement or deterioration in FI category ≥ 1 from baseline to Weeks 12, 32 and 52 using a logistic regression model adjusted for the same variables used in the Cox model.

Analyses were done according to the intention-to-treat principle. No adjustments for multiple testing were made. All analyses were performed using SAS, Version 9.4 (SAS Institute).

Results

Patient characteristics

All 5988 patients randomized in EMPEROR-Preserved were included in this study, and the individual FI was calculated. The distribution of the FI using the 44-parameter is shown in *Figures 1* and *S1*. Baseline demographic and clinical characteristics according to FI categories are shown in *Table 1*. Patient distribution was 1514 (25.3%), 2100 (35.1%), 1501 (25.1%) and 873 (14.6%) in non-frail, mild frailty, moderate frailty and severe frailty, respectively. Compared with non-frail patients, those with higher grade frailty were more often female, more likely to be White or Black/African Americans and less likely to be Asian. Patients with higher body mass index (BMI) and higher SBP and pulse pressure more frequently had a higher grade FI. Those with lower eGFR, higher NT-proBNP or in NYHA class III–IV were more likely to exhibit a higher grade FI, whereas LVEF was similar across the different FI categories. Higher fasting glucose was associated with higher frailty grades. Patients with an ischaemic aetiology and other co-morbidities were, as expected, more often seen in the higher frailty severity categories. The patients with higher grades of frailty had worse QoL as assessed by KCCQ. The KCCQ Clinical Summary Score (CSS) was progressively lower in increasing FI categories, being 87.8 ± 10.4 in non-frail, 77.3 ± 13.9 in mild frailty, 61.4 ± 16.2 in moderate frailty and 39.1 ± 14.0 in severe frailty (P value for trend < 0.001). Similar results were seen for KCCQ Total Symptom Score (TSS) and Overall Summary Score (OSS). More severely frail patients were more likely to be treated with beta-blockers, diuretics and lipid-lowering drugs, but there was no significant difference in the use renin angiotensin system inhibitor (RASi) drugs (angiotensin-converting enzyme inhibitor/angiotensin receptor blocker/angiotensin receptor neprilysin inhibitor [ACEI/ARB/ARNI]) although there was a shift in the type of agent used in this class to more patients being treated with ARBs and fewer with an ARNI in more severely frail groups. Frail patients were on higher numbers of different drugs.

Effects of empagliflozin on heart failure outcomes and mortality by frailty index

Major adverse clinical outcomes of the EMPEROR-Preserved trial were more likely in more severely frail patients, and

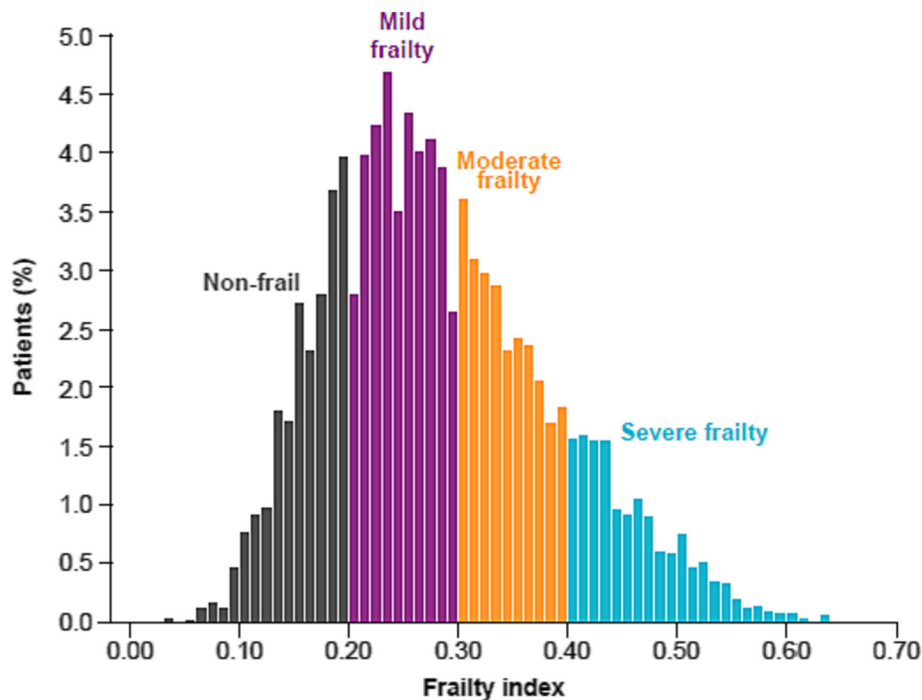


Figure 1 Distribution of frailty index in all randomized patients.

the hazard ratio of primary outcome (time to first event of CV death or HHF) by empagliflozin treatment was 0.59 (0.42, 0.83), 0.79 (0.61, 1.01), 0.77 (0.61, 0.96) and 0.90 (0.69, 1.16) in the non-frail, mild frailty, moderate frailty and severe frailty groups, respectively (P trend = 0.097) (Table 2, Figure S2). The hazard ratio of key secondary outcome (first and recurrent HHF) by empagliflozin treatment was 0.50 (0.33, 0.77), 0.66 (0.47, 0.92), 0.83 (0.61, 1.14) and 0.80 (0.54, 1.17) in the non-frail, mild frailty, moderate frailty and severe frailty groups, respectively (P trend = 0.077) (Table 2). There was no significant trend in another key secondary endpoint of slope of eGFR decline in relation to the severity of frailty, and the eGFR decline was consistently reduced by empagliflozin across the FI categories (P trend = 0.159) (Table 2).

There was similarly no significant trend on the impact of empagliflozin on protection from the other secondary endpoints of the EMPEROR-Preserved trial (time to first HHF, time to CV death and time to all-cause mortality), all of which were more likely in more severe grades of frailty (Table S2). Empagliflozin improved QoL as assessed by KCCQ-CSS consistently across FI categories (P trend = 0.778) from baseline to Week 52 (Figure S3).

Similar results were seen in the sensitivity analyses with FI categories using the 41 clinical variables that were used for the analysis of chronological changes in the FI.

The impact of frailty severity on changes on the composite renal endpoint

We saw no significant interaction (P trend = 1.000) between FI categories and the empagliflozin treatment effect on the composite renal endpoint (sustained reduction of $\geq 40\%$ eGFR or end-stage kidney disease [chronic dialysis/renal transplant] or sustained eGFR < 15 mL/min/1.73 m² for patients with baseline eGFR ≥ 30 mL/min/1.73 m² or sustained eGFR < 10 mL/min/1.73 m² for patients with baseline eGFR < 30 mL/min/1.73 m²). Increasing FI was associated with an increasing risk of the composite renal endpoint (Table S2).

The impact of frailty severity on major clinical events irrespective of treatment group

With both treatment groups combined, we performed an analysis of the impact of baseline FI categories on the primary and secondary endpoints of the EMPEROR-Preserved trial. Figure 2 shows the results for the primary outcome (composite of CV death or HHF). As can be seen, there is a marked impact of higher grades of the FI of the frequency of the primary composite endpoint. Compared with the non-frail group, the higher grade frailty group showed a significantly higher risk of the primary outcome (P trend < 0.001), and also for total HHF (Figure 3) (P trend < 0.001), and the slope

Table 1 Demographics by frailty index

	Non-frail < 0.21 (n = 1514)	Mild frailty 0.21 to <0.3 (n = 2100)	Moderate frailty 0.3 to <0.4 (n = 1501)	Severe frailty ≥ 0.4 (n = 873)	P value for trend
Age, years	70.7 ± 10.0	72.2 ± 9.0	72.6 ± 9.3	71.9 ± 9.4	<0.001
Women, n (%)	599 (39.6)	848 (40.4)	743 (49.5)	486 (55.7)	<0.001
Race					<0.001
White	1053 (69.6)	1579 (75.2)	1185 (78.9)	725 (83.0)	
Black/African-American	47 (3.1)	76 (3.6)	72 (4.8)	63 (7.2)	
Asian	288 (19.0)	316 (15.0)	166 (11.1)	54 (6.2)	
Missing	0	2 (0.1)	0	0	
Region					<0.001
North America	130 (8.6)	217 (10.3)	215 (14.3)	157 (18.0)	
Latin America	425 (28.1)	498 (23.7)	345 (23.0)	247 (28.3)	
Europe	623 (41.1)	990 (47.1)	700 (46.6)	376 (43.1)	
Asia	250 (16.5)	267 (12.7)	135 (9.0)	34 (3.9)	
Other	86 (5.7)	128 (6.1)	106 (7.1)	59 (6.8)	
LV ejection fraction, %	54.4 ± 9.0	53.9 ± 8.7	54.7 ± 8.6	54.6 ± 8.7	0.204
BMI, kg/m ²	27.9 ± 5.2	29.5 ± 5.7	30.6 ± 5.8	32.7 ± 6.1	<0.001
Systolic BP, mmHg	127.8 ± 13.4	131.8 ± 15.1	133.3 ± 16.6	136.5 ± 16.9	<0.001
Diastolic BP, mmHg	75.7 ± 9.6	75.7 ± 10.4	75.5 ± 11.1	76.2 ± 11.7	0.700
Pulse pressure, mmHg	52.0 ± 12.6	56.0 ± 14.1	57.8 ± 15.1	60.3 ± 15.2	<0.001
eGFR, mL/min/1.73 m ²	67.2 ± 18.7	61.3 ± 19.3	57.2 ± 19.4	53.6 ± 20.2	<0.001
NT-proBNP (median, IQR), pg/mL	905 (483–1563)	935 (492–1703)	1052 (510–1828)	1042 (521–2084)	<0.001 ^a
NYHA functional class, n (%)					<0.001
I	1 (0.1)	1 (<0.1)	1 (0.1)	1 (0.1)	
II	1434 (94.7)	1849 (88.0)	1104 (73.6)	496 (56.8)	
III	79 (5.2)	248 (11.8)	391 (26.0)	365 (41.8)	
IV	0	2 (0.1)	5 (0.3)	11 (1.3)	
KCCQ-CSS	87.8 ± 10.4	77.3 ± 13.9	61.4 ± 16.2	39.1 ± 14.0	<0.001
KCCQ-TSS	90.9 ± 9.6	80.4 ± 14.7	64.5 ± 17.9	41.7 ± 17.3	<0.001
KCCQ-OSS	86.7 ± 9.7	76.1 ± 13.5	59.3 ± 15.7	37.2 ± 13.8	<0.001
Lab value					
Haemoglobin (g/dL)	13.6 ± 1.4	13.4 ± 1.6	13.2 ± 1.6	12.9 ± 1.7	<0.001
Fasting glucose (mmol/L)	6.1 ± 1.6	6.8 ± 2.6	7.1 ± 2.8	7.7 ± 3.4	<0.001
Potassium (mmol/L)	4.5 ± 0.5	4.5 ± 0.5	4.6 ± 0.5	4.6 ± 0.6	<0.001
Sodium (mEq/L)	141.2 ± 2.6	141.2 ± 3.0	141.0 ± 3.1	140.9 ± 3.3	0.017
Albumin (g/dL)	4.4 ± 0.3	4.4 ± 0.3	4.4 ± 0.4	4.3 ± 0.4	<0.001
Cause of heart failure					
Ischaemic	308 (20.3)	779 (37.1)	626 (41.7)	404 (46.3)	<0.001
Medical history					
History of HHF (in the last 12 months)	228 (15.1)	449 (21.4)	420 (28.0)	272 (31.2)	<0.001
Atrial fibrillation or flutter	762 (50.3)	1099 (52.3)	804 (53.6)	470 (53.8)	0.044
Coronary artery disease	222 (14.7)	757 (36.0)	676 (45.0)	439 (50.3)	<0.001
Diabetes	383 (25.3)	1052 (50.1)	875 (58.3)	628 (71.9)	<0.001
Hypertension	1229 (81.2)	1925 (91.7)	1428 (95.1)	842 (96.4)	<0.001
Myocardial infarction	233 (15.4)	626 (29.8)	563 (37.5)	358 (41.0)	<0.001
PCI or CABG	181 (12.0)	706 (33.6)	617 (41.1)	410 (47.0)	<0.001
COPD	104 (6.9)	237 (11.3)	247 (16.5)	207 (23.7)	<0.001
Stroke	70 (4.6)	199 (9.5)	197 (13.1)	144 (16.5)	<0.001
Heart failure medication					
ACEI	598 (39.5)	894 (42.6)	594 (39.6)	323 (37.0)	0.194
ARB	552 (36.5)	790 (37.6)	598 (39.8)	376 (43.1)	<0.001
ARNI	47 (3.1)	51 (2.4)	21 (1.4)	15 (1.7)	0.002
Any RASi (ACEI/ARB/ARNI)	1193 (78.8)	1721 (82.0)	1207 (80.4)	711 (81.4)	0.206
Beta-blocker	1279 (84.5)	1822 (86.8)	1304 (86.9)	762 (87.3)	0.037
MRA	549 (36.3)	779 (37.1)	559 (37.2)	357 (40.9)	0.062
Diuretic other than MRA	1085 (71.7)	1670 (79.5)	1266 (84.3)	788 (90.3)	<0.001
Hypolipidaemic medication	803 (53.0)	1528 (72.8)	1180 (78.6)	731 (83.7)	<0.001
Total number of medications					
<8	968 (63.9)	834 (39.7)	381 (25.4)	152 (17.4)	<0.001
8 to <12	462 (30.5)	925 (44.0)	677 (45.1)	373 (42.7)	
≥12	84 (5.5)	340 (16.2)	443 (29.5)	348 (39.9)	

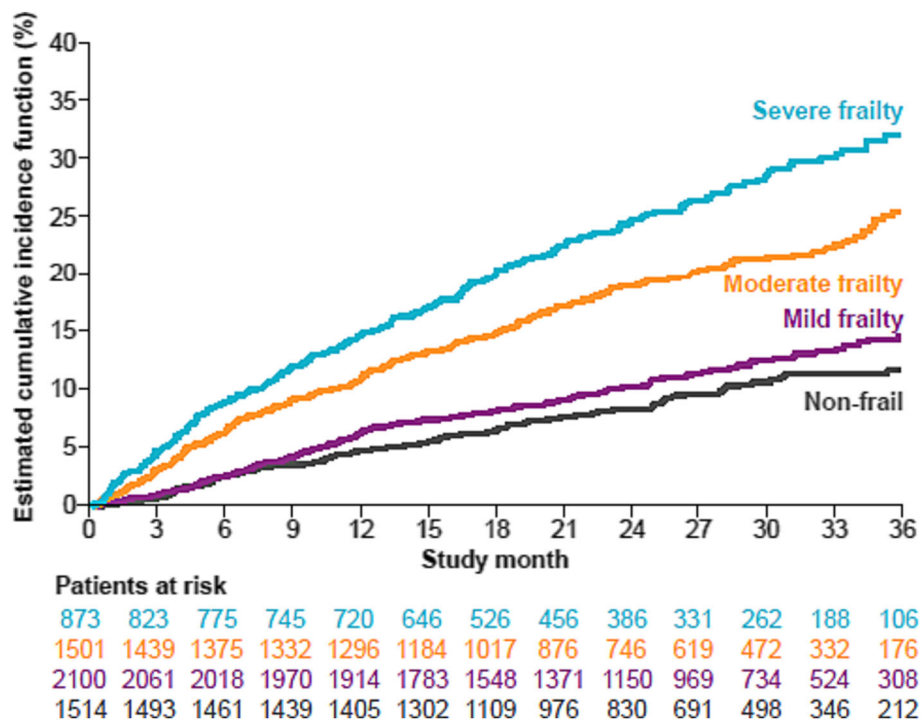
Note: Values are mean ± SD, median (interquartile range [IQR]) or n (%). Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; BMI, body mass index; BP, blood pressure; COPD, chronic obstructive pulmonary disease; CSS, Clinical Summary Score; eGFR, estimated glomerular filtration rate with Chronic Kidney Disease Epidemiology Collaboration formula; HHF, hospitalization for heart failure; KCCQ, the Kansas City Cardiomyopathy Questionnaire; LV, left ventricular; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; OSS, Overall Summary Score; PCI or CABG, percutaneous coronary intervention or coronary artery bypass grafting; RASi, renin angiotensin system inhibitor; TSS, Total Symptom Score.

^aBased on log-transformed results.

Table 2 Primary and secondary trial endpoints by frailty index and by treatment group

Outcome by frailty index subgroup	Empagliflozin (N = 2997)			Placebo (N = 2991)			HR (95% CI)	P trend
	n/N	%	Rate/100 person-years	n/N	%	Rate/100 person-years		
Primary outcome—Time to first event of CV death or HHF								
All patients	415/2997	13.8	6.86	511/2991	17.1	8.67	0.79 (0.69, 0.90)	0.097
Non-frail (<0.21)	55/770	7.1	3.41	88/744	11.8	5.85	0.59 (0.42, 0.83)	
Mild frailty (0.21 to <0.3)	105/1015	10.3	4.92	139/1085	12.8	6.31	0.79 (0.61, 1.01)	
Moderate frailty (0.3 to <0.4)	138/745	18.5	9.55	172/756	22.8	11.94	0.77 (0.61, 0.96)	
Severe frailty (≥0.4)	117/467	25.1	13.74	112/406	27.6	15.11	0.90 (0.69, 1.16)	
Key secondary outcome—First and recurrent HHF								
All patients	407	—	—	541	—	—	0.73 (0.61, 0.88)	0.077
Non-frail (<0.21)	49	—	—	89	—	—	0.50 (0.33, 0.77)	
Mild frailty (0.21 to <0.3)	80	—	—	128	—	—	0.66 (0.47, 0.92)	
Moderate frailty (0.3 to <0.4)	157	—	—	179	—	—	0.83 (0.61, 1.14)	
Severe frailty (≥0.4)	121	—	—	145	—	—	0.80 (0.54, 1.17)	
eGFR slope								
		Mean (SE) _t mL/min/1.73 m ² /year		Mean (SE) _t mL/min/1.73 m ² /year		Difference of rate of decline (95% CI)		P trend
All patients		−1.25 (0.11)		−2.62 (0.11)		1.36 (1.06, 1.66)		0.159
Non-frail (<0.21)		−1.27 (0.21)		−2.32 (0.21)		1.05 (0.47, 1.62)		
Mild frailty (0.21 to <0.3)		−1.25 (0.18)		−2.73 (0.17)		1.47 (0.98, 1.96)		
Moderate frailty (0.3 to <0.4)		−1.55 (0.22)		−2.73 (0.22)		1.18 (0.57, 1.80)		
Severe frailty (≥0.4)		−0.79 (0.30)		−2.80 (0.32)		2.01 (1.16, 2.85)		

Abbreviations: CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HHF, hospitalization for heart failure; HR, hazard ratio.

**Figure 2** Primary outcome by frailty index (treatment arms combined).

of eGFR over time (P trend = 0.002). Increasing FI was also associated with an increasing risk of CV death and first HHF when analysed separately, as well as of all-cause mortality (Figures S4–S6, respectively) (P trend < 0.001, respectively).

Changes in the frailty index over time

We saw a significant empagliflozin treatment effect on the FI over time. Compared with placebo, empagliflozin pa-

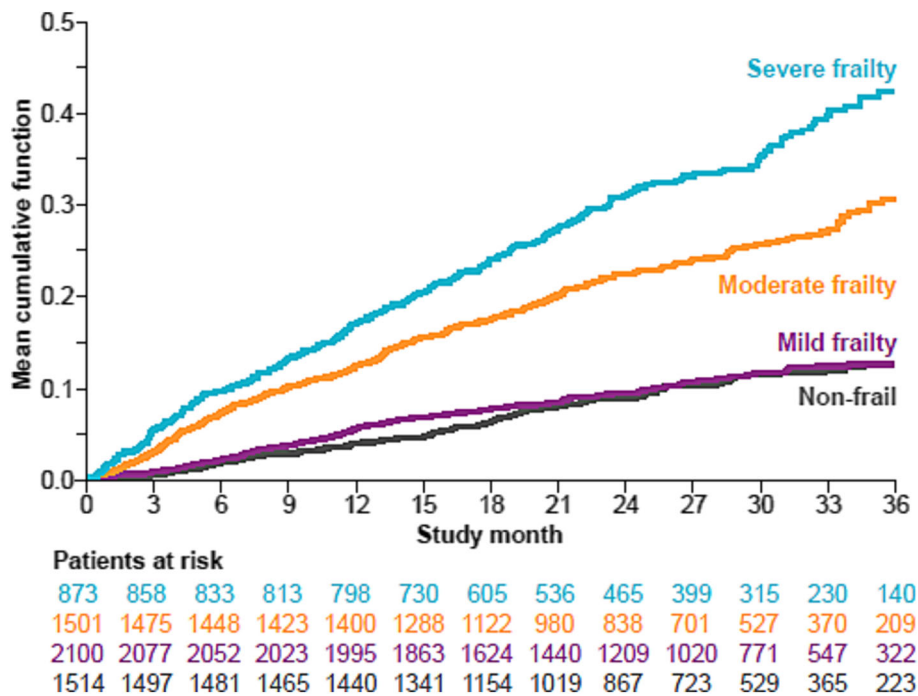


Figure 3 Total hospitalizations for heart failure by frailty index (treatment arms combined).

tients had a higher likelihood of being in a lower FI category at Weeks 12, 32 and 52, odds ratio: 1.12 [95% confidence interval, CI, 1.01–1.24], 1.21 [1.09–1.34] and 1.20 [1.09–1.33] at Week 12, 32 and 52; $P = 0.030$, <0.001 and <0.001 , respectively (Table 3). In a responder analysis, we saw a significant difference in the proportion of subjects who had a ≥ 1 class improvement in FI category between baseline and Week 12 in favour of the empagliflozin group compared with placebo (odds ratio: 1.13 [95% CI 1.00–1.28], $P = 0.046$), but there was no significant difference in the proportion of subjects who had a ≥ 1 class de-

terioration in FI category over the same time period. At Week 32, both ≥ 1 class improvement and ≥ 1 class deterioration in FI statistically significantly favoured empagliflozin compared with placebo, odds ratio for ≥ 1 class improvement: 1.15 [95% CI 1.01–1.30], $P = 0.035$ and odds ratio for ≥ 1 class deterioration: 0.80 [95% CI 0.69–0.91], $P = 0.001$. Similar significant differences were seen at Week 52 (Figure 4), which presents the odds ratios for empagliflozin versus placebo for a ≥ 1 class improvement in FI or a ≥ 1 class deterioration in FI from baseline to three time points in follow-up.

Table 3 Effect of empagliflozin versus placebo: Frailty status over time

	Empagliflozin ($N = 2997$)	Placebo ($N = 2991$)	Empagliflozin versus placebo	
	n (%)	n (%)	Odds ratio (95% CI)	P value
Week 12	$N = 2934$	$N = 2907$		
Non-frail	951 (32.4)	914 (31.4)	1.12 (1.01, 1.24)	0.030
Mild frailty	1044 (35.6)	1050 (36.1)		
Moderate frailty	606 (20.7)	594 (20.4)		
Severe frailty	333 (11.3)	349 (12.0)		
Week 32	$N = 2800$	$N = 2791$		
Non-frail	927 (33.1)	844 (30.2)	1.21 (1.09, 1.34)	<0.001
Mild frailty	927 (33.1)	958 (34.3)		
Moderate frailty	568 (20.3)	569 (20.4)		
Severe frailty	378 (13.5)	420 (15.0)		
Week 52	$N = 2710$	$N = 2695$		
Non-frail	855 (31.5)	794 (29.5)	1.20 (1.09, 1.33)	<0.001
Mild frailty	898 (33.1)	879 (32.6)		
Moderate frailty	566 (20.9)	615 (22.8)		
Severe frailty	391 (14.4)	407 (15.1)		

Abbreviation: CI, confidence interval.

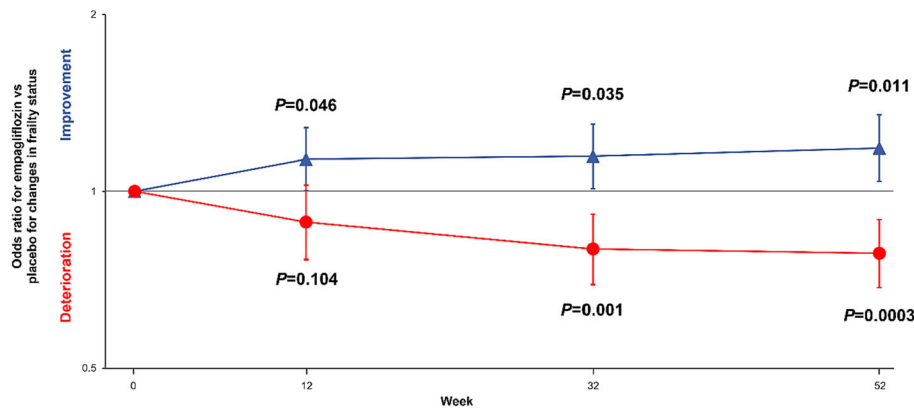


Figure 4 Effect of empagliflozin versus placebo ≥ 1 class improvement or deterioration in frailty index over time. Frailty index was calculated using 41 variables that were available during follow-up.

Safety analyses

As expected, AEs increased with increased frailty grades. Especially for SAEs, the incidence significantly increased in the mild/moderate/severe frailty categories compared with the non-frail group. For some specific AEs, which are considered to be important for SGLT2 inhibitors such as UTI, genital infection and hypotension, the incidence tended to be higher in empagliflozin, but the *P* trend values were not significant (Table 4).

Discussion

In this post hoc analysis of the EMPEROR-Preserved trial, we report several key findings.

First, this analysis confirms the high frequency of frailty in HFpEF and that an increasing severity of frailty was associ-

ated with female gender, higher BMI and SBP, lower eGFR, higher NT-proBNP and higher NYHA class III–IV, although the age effect was not marked, perhaps because in this trial of HFpEF, very elderly frail patients were not so frequently recruited. Despite this, there was a very high rate of frailty overall; previous reports using similar Rockwood cumulative deficit FI scores showed frailty rates (defined as rates of $FI \geq 0.21$) of 50% in HFpEF¹⁶ and 55–62% in HFpEF,^{18,23} compared with 74.7% in EMPEROR-Preserved.

In the DELIVER trial, 38% of patients were considered non-frail ($FI < 0.21$) and in PARAGON-HF, it was 45%, whereas in our report of EMPEROR-Preserved, this proportion was only 25.3%; therefore, with a frailty rate of nearly 75%, this study recruited considerably more frail patients compared with the previous two large HFpEF trials. This increased severity of frailty was the reason for us to define in this analysis four classes and introduce a category of highest frailty ($FI \geq 0.40$) that constituted 14.6% of our patients compared with the worst frailty class in DELIVER

Table 4 Adverse events according to baseline frailty index categories

	Non-frail		Mild frailty		Moderate frailty		Severe frailty		<i>P</i> trend
	Empagliflozin (<i>N</i> =770) <i>n</i> (%)	Placebo (<i>N</i> =743) <i>n</i> (%)	Empagliflozin (<i>N</i> =1015) <i>n</i> (%)	Placebo (<i>N</i> =1084) <i>n</i> (%)	Empagliflozin (<i>N</i> =745) <i>n</i> (%)	Placebo (<i>N</i> =756) <i>n</i> (%)	Empagliflozin (<i>N</i> =466) <i>n</i> (%)	Placebo (<i>N</i> =406) <i>n</i> (%)	
Any adverse event	624 (81.0)	597 (80.3)	856 (84.3)	924 (85.2)	666 (89.4)	680 (89.9)	428 (91.8)	384 (94.6)	0.208
Serious adverse events	282 (36.6)	289 (38.9)	443 (43.6)	534 (49.3)	409 (54.9)	446 (59.1)	302 (64.8)	274 (67.5)	0.889
Acute renal failure	52 (6.8)	59 (8.0)	103 (10.1)	115 (10.6)	125 (16.8)	119 (15.8)	83 (17.8)	91 (22.4)	0.685
Urinary tract infections	48 (6.2)	51 (6.9)	95 (9.4)	69 (6.4)	86 (11.5)	77 (10.2)	68 (14.6)	46 (11.3)	0.339
Genital infections	12 (1.6)	2 (0.3)	20 (2.0)	8 (0.7)	22 (3.0)	3 (0.4)	13 (2.8)	9 (2.2)	0.163
Lower limb amputations	0 (0)	2 (0.3)	5 (0.5)	2 (0.2)	4 (0.5)	8 (1.1)	3 (0.6)	5 (1.2)	NC
Bone fractures	28 (3.6)	25 (3.4)	36 (3.5)	46 (4.2)	44 (5.9)	34 (4.5)	26 (5.6)	21 (5.2)	0.582
Hypoglycaemia	11 (1.4)	10 (1.3)	15 (1.5)	22 (2.0)	26 (3.5)	24 (3.2)	21 (4.5)	22 (5.4)	0.837
Symptomatic hypotension	34 (4.4)	33 (4.4)	56 (5.5)	51 (4.7)	66 (8.9)	36 (4.8)	41 (8.8)	36 (8.9)	0.582
Hypotension	61 (7.9)	57 (7.7)	94 (9.3)	85 (7.8)	95 (12.8)	63 (8.3)	61 (13.1)	52 (12.8)	0.592

Abbreviation: NC, not calculated.

(FI > 0.31) that represented 23.8% of their patients. In our report, 39.7% of patients had an FI of ≥ 0.30 . Thus, the present report is more informative of more marked frailty severity HFpEF patients, because it recruited more patients with severe frailty compared with previous reports. This increase of the classic FI intervals from three to four classes is justifiable given that patients were older and with more co-morbidity and in order to grade degrees of severity beyond the typical highest 0.30 cut-off; however, this variation may require future validation in a similarly very frail group in future HFpEF trials as the FI has typically only been assessed using three classes of FI.

Second, we demonstrate the significant impact of frailty in HFpEF on poor QoL and on the incidence of subsequent adverse clinical outcomes. The KCCQ-CSS at baseline of 87.8 ± 10.4 , 77.3 ± 13.9 , 61.4 ± 16.2 and 39.1 ± 14.0 in the four FI categories were substantially lower and covered a considerably wider range of severity than reported in the three categories used in the DELIVER analysis (75.3 ± 18.5 , 67.9 ± 20.0 and 57.9 ± 20.6) or in previous PARAGON-HF and DAPA-HF frailty analyses, demonstrating the greater severity of frailty in this report.

For the entire trial cohort, the primary outcome of time to first CV death or HHF was significantly related to frailty with increasing frailty being associated with higher risk of primary events. A similar relationship was seen between frailty severity and the key secondary endpoints of total HHF and slope of decline in eGFR; also, the secondary endpoint of composite renal endpoint did significantly increase with increasing frailty severity. These results confirm the major clinical impact of frailty severity in HF and extend them to a second positive outcome trial in HFpEF. In the DELIVER trial, it was noted that renal AEs increased in frequency as FI increased, suggesting a possibly similar impact of frailty on adverse kidney outcomes in this trial as well.¹⁸

Third, we made important observations on the treatment effects of empagliflozin across the wider range of frailty severity than seen in previous reports of SGLT2 inhibitors, giving us greater confidence that empagliflozin maintains its clinical benefits even in very severely frail HFpEF patients and in those with a very poor initial QoL as assessed by KCCQ. Frailty is reported to be a significant predictor for HF progression, and the vicious cycle between frailty and HF has been reported in the literature, so an effective therapy in high-risk HFpEF patients, irrespective of frailty severity, is of clinical benefit for an underserved population, who otherwise are considered high risk for multiple proposed therapies and interventions.^{24,25}

KCCQ is a well-detailed measurement of the QoL of HF patients, and one reported to be correlated with prognosis.^{26,27} As previously suggested, increased frailty was associated with worse baseline KCCQ scores and also worse outcomes. Compared with placebo, empagliflozin consistently increased KCCQ score across FI categories even in a

trial with more severe frailty than was reported in the DELIVER or PARAGON trials. The beneficial effect of empagliflozin on HHF has the capacity to favourably affect the components of symptom frequency/burden/physical limitation and may explain in part the consistent improvement in KCCQ assessed QoL. It should be considered whether using KCCQ scores causes the improved FI seen in this report, which we need to consider both from the conceptual basis of whether it is appropriate to present KCCQ as part of the FI, given that we have previously already reported the effects on KCCQ,²⁸ and from the perspective of whether the KCCQ change is the primary driver of the improved FI. Despite the fact that the effects on KCCQ in EMPEROR-Preserved have already been reported, we believe it is still appropriate to use patient-reported outcomes (in the form of KCCQ) in generating an FI as patient symptomatology and patient-reported limitations are an important aspect of deriving a cumulative deficits FI. With regard to the question of whether the KCCQ change is the sole cause for the improved, we tested this assumption by performing a sensitivity analysis excluding all 15 KCCQ items from our FI, and there was still a significant effect of empagliflozin on the trends in FI seen at Weeks 32 and 52 with a similar trend at Week 12, although no longer statistically significant at week 12 (results not shown).

We utilized 15 of the 23 items of KCCQ in our 44-item FI, in a similar way as was done for the TOPCAT frailty analysis paper where KCCQ contributed 15 of the 39 measures included, whereas the DAPA-HF analysis used only EQ-5D (which contributed only 5 of the 32 measures included). There is a systematic difference between DAPA-HF (and DELIVER) frailty papers, which used only 5 of 32 (or 30) patient-reported items in their FI, representing only 15.6–16.7% of the FI, compared to our analysis (34%), TOPCAT (38%) and the analysis of frailty in PARADIGM-HF and ATMOSPHERE, which also used KCCQ, as 15 of the 42 items used (36%).

In terms of safety, as in previous reports, the side effect event rate of the SGLT2 inhibitor increased as frailty worsened.²⁵ Especially severe AEs were significantly increased in all frailty categories compared with the non-frail group, and in some specific AEs such as UTI/genital infection, the incidence tended to be higher in patients randomized to empagliflozin, but the *P* trend value was not significant. The benefit of empagliflozin on rates of HHF may have reflected a better clinical stabilizing effect in these HFpEF patients' condition in terms of AE incidence.

Lastly, there was a statistically and clinically important improvement compared with placebo assessed by a proportional odds model and responder analysis for ≥ 1 class improvement/deterioration at each assessed time point. Several previous reports have suggested that not only baseline FI but also its change is associated with an increased risk of mortality and hospitalization,^{29,30} regardless of age, and so this effect of empagliflozin may be useful.

Strengths and limitations

Strengths of this report include its large sample size in a prospective study as part of a clinical trial evaluating a therapy that is both effective in HFpEF but also one for which concern had been expressed about the possibility of worsening frailty status. The FI is an established method used in previous studies, and therefore, the current results can be compared with previous studies, which have used a similar approach to assess frailty. On the other hand, its limitations must also be recognized.

Limitations include the fact that the patients included in this analysis were those selected for a clinical trial and therefore not fully representative of the general population and that this was a post hoc analysis and not prespecified in advance. The cut-off values of FI of 0.3 and 0.4 investigated in this paper have not been validated fully in literature, and the applicability of these cut-off values should be investigated in future studies. The follow-up period in EMPEROR-Preserved was not long (26 months), and longer chronological changes in frailty cannot therefore be guaranteed.

Acknowledgements

The authors were fully responsible for all content and editorial decisions, were involved at all stages of development and have approved the final version. Graphical assistance, supported financially by Boehringer Ingelheim, was provided by 7.4 Limited. All authors certify that they comply with the ethical guidelines for authorship and publishing in the *Journal of Cachexia, Sarcopenia and Muscle*.³¹

Conflict of interest statement

Dr. Coats reports consulting fees from AstraZeneca, Boehringer Ingelheim, Edwards, Menarini, Novartis, Servier, Vifor, Abbott, Actimed, Arena, Cardiac Dimensions, Corvia, CVRx, Enopace, ESN Cleer, Faraday, Impulse Dynamics, Respicardia and Viatrix. Dr Butler reports consulting fees from Abbott, American Regent, Amgen, Applied Therapeutic, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Cardiac Dimension, Cardior, CVRx, Cytokinetics, Edwards, Element Science, Innolife, Impulse Dynamics, Imbria, Inventiva, Lexicon, Lilly, LivaNova, Janssen, Medtronics, Merck, Occlutech, Novartis, Novo Nordisk, Pfizer, Pharmacosmos, Pharmain, Roche, Sequana, SQ Innovation and Vifor. Dr. Tsutsui reports receiving consultancy from Boehringer Ingelheim Co., Ltd., Bayer Yakuhi, Ltd., Novartis Pharma K.K., Ono Pharmaceutical Co., Ltd., and AstraZeneca Co., Ltd.; remuneration from MSD K.K., Astellas Pharma Inc., Pfizer Japan Inc., Bristol Myers Squibb Company, Otsuka Phar-

maceutical Co., Ltd., Daiichi Sankyo Co., Ltd., Mitsubishi Tanabe Pharma Corporation, Boehringer Ingelheim Co., Ltd., Takeda Pharmaceutical Company Limited, Bayer Yakuhi, Ltd., Novartis Pharma K.K., Kowa Pharmaceutical Co. Ltd. and Teijin Pharma Ltd.; manuscript fees from Medical View and Nippon Rinsho; research funding from Actelion Pharmaceuticals Japan Ltd., Japan Tobacco Inc., Mitsubishi Tanabe Pharma Corporation, Nippon Boehringer Ingelheim Co., Ltd., Daiichi Sankyo Co., Ltd., IQVIA Services Japan and Omron Healthcare; and scholarship funds from Astellas Pharma Inc., Novartis Pharma K.K., Daiichi Sankyo Co., Ltd., Takeda Pharmaceutical Company Limited, Mitsubishi Tanabe Pharma Corporation, Teijin Pharma Ltd. and MSD K.K. Dr. Doehner reports consulting fees from Boehringer Ingelheim related to work on clinical events committee during the conduct of the study. Dr. Filippatos reports lecture fees and/or committee member contributions in clinical trials sponsored by Bayer, Medtronic, Vifor, Servier, Novartis, Amgen and Boehringer Ingelheim and research support from the European Union. Dr. Ferreira reports consultancy fees from Boehringer Ingelheim. Dr. Böhm reports support by the Deutsche Forschungsgemeinschaft (German Research Foundation; TTR 219, project number 322900939) and reports personal fees from Abbott, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Cytokinetics, Medtronic, Novartis, ReCor, Servier and Vifor during the conduct of the study. Dr. Chopra reports speaking fees from Novartis, Sanofi, Astra, Boehringer, Novo Nordisk, Pfizer, Sun Pharma, Mankind and Lupin. Dr. Verma holds a tier 1 Canada Research Chair in cardiovascular surgery and reports receiving research grants and/or speaking honoraria from Amarin, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly, HLS Therapeutics, Janssen, Merck, Novartis, Novo Nordisk, Sanofi, Sun Pharmaceuticals, PhaseBio and the Toronto Knowledge Translation Working Group. He is the president of the Canadian Medical and Surgical Knowledge Translation Research Group, a federally incorporated not-for-profit physician organization. Dr. Nordaby is an employee of Boehringer Ingelheim. Ms. Iwata is an employee of Boehringer Ingelheim. Dr. Nitta is an employee of Nippon Boehringer Ingelheim. Dr. Ponikowski reports personal fees from Boehringer Ingelheim, AstraZeneca, Servier, BMS, Amgen, Novartis, Merck, Pfizer and Berlin Chemie and grants and personal fees from Vifor Pharma. Dr. Zannad reports personal fees from Applied Therapeutics, Bayer, Boehringer, BMS, CVRx, Cardior, Cereno Pharmaceutical, Cellprothera, CEVA, Merck, Novartis, Novo Nordisk, Owkin, Pfizer and Servier, having stock options at G3 Pharmaceuticals and equities at Cereno Pharmaceutical, Cardiorenal and Eshmoun Clinical Research and being the founder of Cardiovascular Clinical Trialists. Dr Packer reports consulting fees from 89bio, AbbVie, Altimmune, Alnylam, Amarin, Amgen, Ardelyx, AstraZeneca, Boehringer Ingelheim, Caladrius, Casana, CSL Behring, Cytokinetics, Imara, Lilly, Medtronic, Moderna,

Novartis, Reata, Relypsa and Salamandra. Dr. Anker reports grants and personal fees from Vifor and Abbott Vascular and personal fees for consultancies, trial committee work and/or lectures from Actimed, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, BioVentrix, Brahms, Cardiac Dimensions, Cardior, Cordio, CVRx, Cytokinetics, Edwards, Faraday Pharmaceuticals, GSK, HeartKinetics, Impulse Dynamics, Novartis, Occlutech, Pfizer, Repairon, Sensible Medical, Servier, Vectorious and V-Wave and is named co-inventor of two patent applications regarding MR-proANP (DE 102007010834 and DE 102007022367), but he does not benefit personally from the related issued patents.

Data availability statement

To ensure independent interpretation of clinical study results and enable authors to fulfil their role and obligations under the ICMJE criteria, Boehringer Ingelheim grants all external authors access to relevant clinical study data. In adherence

with the Boehringer Ingelheim Policy on Transparency and Publication of Clinical Study Data, scientific and medical researchers can request access to clinical study data after publication of the primary manuscript in a peer-reviewed journal; regulatory activities are normally within 1 year after the marketing application has been granted by major Regulatory Authorities. Researchers should use the <https://vivli.org/link> to request access to study data and visit <https://www.mystudywindow.com/msw/datasharing> for further information.

Online supplementary material

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

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