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RESEARCH ARTICL

The prevalence and importance of frailty in heart failure with reduced ejection fraction – an analysis of PARADIGM-HF and ATMOSPHERE

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Aims Frailty, characterized by loss of homeostatic reserves and increased vulnerability to physiological decompensation, results from an aggregation of insults across multiple organ systems. Frailty can be quantified by counting the number of 'health deficits' across a range of domains. We assessed the frequency of, and outcomes related to, frailty in patients with heart failure and reduced ejection fraction (HFrEF).

Methods and results Using a cumulative deficits approach, we constructed a 42-item frailty index (FI) and applied it to identify frail patients enrolled in two HFrEF trials (PARADIGM-HF and ATMOSPHERE). In keeping with previous studies, patients with FI ≤0.210 were classified as non-frail and those with higher scores were divided into two categories using score increments of 0.100. Clinical outcomes were examined, adjusting for prognostic variables. Among 13 625 participants, mean (± standard deviation) FI was 0.250 (0.10) and 8383 patients (63%) were frail (FI >0.210). The frailest patients were older and had more symptoms and signs of heart failure. Women were frailer than men. All outcomes were worse in the frailest, with high rates of all-cause death or all-cause hospitalization: 40.7 (39.1–42.4) vs. 22.1 (21.2–23.0) per 100 person-years in the non-frail; adjusted hazard ratio 1.63 (1.53–1.75) ($P < 0.001$). The rate of all-cause hospitalizations, taking account of recurrences, was 61.5 (59.8–63.1) vs. 31.2 (30.3–32.2) per 100 person-years (incidence rate ratio 1.76; 1.62–1.90; $P < 0.001$).

Conclusion Frailty is highly prevalent in HFrEF and associated with greater deterioration in quality of life and higher risk of hospitalization and death. Strategies to prevent and treat frailty are needed in HFrEF.

Keywords Heart failure with reduced ejection fraction • Frailty • Outcomes

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Introduction

Frailty is defined as a multisystem disorder characterized by loss of homeostatic reserves, rendering affected individuals vulnerable to physiological decompensation and placing them at increased risk of adverse outcomes when exposed to a stressor.[1] Frailty is thought to result from an aggregation of insults across multiple organ systems.[2] Importantly, frailty is related to, but distinct from, both aging and comorbidity.[1,3] Younger individuals may be frail and frailty is often associated with problems not specific to a particular disease such as fatigue, poor appetite and reduced mobility.[1–4] There is particular interest in the relationship between frailty and cardiovascular disease for a number of reasons.[5] First, cardiovascular disease may accelerate development of frailty and frailty may worsen outcomes related to cardiovascular disease.[6] Both cardiovascular disease and frailty may share common pathophysiological mechanisms, like inflammation, and have common consequences, such as exercise intolerance, leading to a vicious cycle of decline. Moreover, frailty may be an 'effect modifier', adversely affecting the risk–benefit profile of both pharmacological and non-pharmacological interventions, for example surgery and device implantation.[7,8]

We have studied the prevalence and importance of frailty in heart failure (HF) with reduced ejection fraction (HFrEF) in the Prospective comparison of ARNI (Angiotensin Receptor–Neprilysin Inhibitor) with ACEI (Angiotensin-Converting Enzyme Inhibitor) to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF, ClinicalTrials.gov NCT01035255) and the Aliskiren Trial to Minimize OutcomeS in Patients with HEart failuRE trial (ATMOSPHERE, ClinicalTrials.gov NCT00853658) using the Rockwood cumulative deficit approach.[9–11]

Methods

Trials and participants

The inclusion and exclusion criteria of PARADIGM-HF and ATMOSPHERE were almost identical. Briefly, patients were eligible at screening if ≥18 years, New York Heart Association (NYHA) class II–IV, left ventricular ejection fraction (LVEF) ≤ 35% (changed from ≤40% in PARADIGM-HF by amendment), elevated natriuretic peptide (NP) level, taking an ACEI or angiotensin receptor blocker, beta-blocker (unless contraindicated/not tolerated) and mineralocorticoid receptor antagonist, if indicated.[9,10]

Exclusion criteria included symptomatic hypotension or systolic blood pressure <95 mmHg (<90 mmHg in ATMOSPHERE), estimated glomerular filtration rate <30 mL/min/1.73 m^2 (<35 mL/min/1.73 m^2 in ATMOSPHERE) and potassium >5.4 mmol/L (>5.2 mmol/L in ATMOSPHERE). Trials were approved by ethics committees at all participating centres and all patients provided written informed consent.

After a run-in period, patients were randomly assigned to double-blind therapy with sacubitril/valsartan or enalapril in 1:1 ratio in PARADIGM-HF, or enalapril, aliskiren or combination in 1:1:1 ratio in ATMOSPHERE.

Median duration of follow-up was 26.6 months in PARADIGM-HF (1 day to 4.2 years) and 36.7 months (1 day to 6.2 years) in ATMOSPHERE.

Frailty index

We used the cumulative deficits approach to construct a 42-item frailty index (FI) in patients in PARADIGM-HF and ATMOSPHERE. The FI was constructed as described by Rockwood where the index, ideally, should be made up of at least 30 items; variables included must be associated with health and not part of normal ageing such as presbyopia (but deficits should generally increase with age); items in the index should cover a range of body systems; items used must be applied similarly throughout the sample.[11–13] We used 15 questions (of 23) from the Kansas City Cardiomyopathy Questionnaire (KCCQ, see below) as proxy measures of disability (an important constituent of frailty and distinguishes it from multimorbidity) to form the basis for our index.[3] The remaining 27 items were derived from medical history, other patient characteristics and laboratory results, covering a range of body systems (online supplementary *Table S1*). We excluded eight questions from the KCCQ used to construct the symptom severity, frequency and burden domains to avoid defining the FI by HF symptoms.[14] Binary variables were scored 0/1 (absent/present); ordinal variables were scored from 0–1, 1 indicating greatest severity. Continuous variables were dichotomized and scored as 0/1 (normal/non-normal). Patients with ≥20% missing variables were excluded from the analysis.[15,16] FI score was calculated using the recommended approach, i.e. sum of the deficits divided by total number of non-missing deficits assessed. In this study, patients with FI ≤0.210 were classified as non-frail based on conventional cutoffs used by most authors; those with higher scores were further divided into two categories using increments in score of 0.100.[11,17]

Outcomes

Primary outcome for both trials was the composite of HF hospitalization or cardiovascular death. In this study, we analysed the primary outcome, its components, and cardiovascular, non-cardiovascular and overall hospitalizations. Recurrent hospitalizations for each of these causes and reduction in health-related quality of life, as measured by decrease in KCCQ at 12 months, are reported.[14]

Statistical analysis

Baseline characteristics are reported as means [± standard deviations (SD)], proportions, or medians (Q1–Q3). Statistical tests employed were ANOVA, Chi-square test and Kruskal–Wallis test, respectively.

The association between FI and age was compared between men and women using linear regression. Restricted cubic splines were employed to assess the relationship between FI and all-cause death, taking the lowest FI as the reference. Competing risks regression, using Fine–Gray method, was used to assess outcomes. Primary outcome and cardiovascular death were analysed accounting for competing risk of non-cardiovascular death. First HF, cardiovascular, non-cardiovascular and all-cause hospitalizations were analysed accounting for competing risk of all-cause death. Non-cardiovascular deaths were analysed accounting for competing risk of cardiovascular death. Crude sub-distribution hazard ratios (sHRs) and adjusted sHRs from models including age, sex, heart rate, N-terminal pro brain natriuretic peptide (NT-proBNP), NYHA class, LVEF, duration of HF and additionally previous hospitalization for HF are reported. For multivariable adjustment we chose clinically relevant variables shown in prior studies to be predictive of death and hospitalization, but which were not part of the FI (e.g. LVEF, NT-proBNP level). Furthermore, adjusting for aetiology of HF did not affect results. Cox regression was used to

assess risk of the composite outcome of all-cause hospitalization or all-cause death and all-cause death, with adjustment for variables listed above. Cox regression analysis was also done for 12 subgroups for the primary composite outcome and all-cause death. Consistency in treatment effects across the three classes in PARADIGM-HF was also assessed using the Cox model.

A decrease in KCCQ clinical summary score (CSS) from baseline to 12 months of ≥5 points was analysed using logistic regression and is reported as odds ratio adjusted for two models – model 1 for KCCQ-CSS at baseline and model 2 additionally adjusted for variables listed above.

Recurrent hospitalizations (HF, cardiovascular, non-cardiovascular and all-cause) were analysed using negative binomial regression model. Both crude incidence rate ratio (IRR) and IRR adjusted for the variables listed above, and previous HF hospitalization, are reported. We also did a sensitivity analysis for outcomes in patients ≥60 years of age.

All models were adjusted for randomized treatment and region.

All analyses were conducted using Stata version 15 (Stata Corp., College Station, TX, USA).

Results

In this HFrEF population, FI was calculable for 13 265 (86.0%) patients. Mean (± SD) and median (interquartile range) FI was 0.250 (0.10) and 0.244 (0.176–0.318), respectively. Range was 0.0–0.686 and 10th and 90th percentiles were 0.126 and 0.382, respectively.

Overall, 4882 patients were in FI class 1 (≤0.210), 4770 in FI class 2 (0.211–0.310) and 3613 in FI class 3 (>0.311).

Baseline characteristics and medical history

Age and proportion of women increased with increasing FI (*Table 1*). *Figure 1* shows density distribution of FI for women compared with men demonstrating a rightward shift in women. Mean and median FI in men were 0.247 (0.10) and 0.240 (0.173–0.315), respectively, and 0.261 (0.10) and 0.259 (0.289–0.330), respectively, in women ($P < 0.001$ for each, men vs. women). FI increased with age at a similar rate in both sexes (*Figure 2*).

Heart failure characteristics

The frailest patients had a longer duration of HF and higher rate of prior HF hospitalization (*Table 2*). NYHA class distribution was worst in the frailest: the proportion in NYHA class III/IV in least frail was 11% compared with 49% in the frailest category.

Congestion was more common in the frailest patients (*Table 2*). Fatigue was twice as common in the frailest patients compared to the non-frail (69% vs. 37%).

The EQ-5D questionnaire was completed by patients enrolled in PARADIGM-HF (online supplementary *Table S2*): 81% of non-frail patients reported no problems in walking, compared to 23% of the frailest patients; 40% of the frailest patients had problems with self-care and > 70% reported some problems with performing day-to-day activities (compared with 3% and 16% of the non-frail, respectively). Moderate/extreme levels of anxiety/depression were more common in the frailest patients (53% in frailest compared to 19% in the non-frail).

Biomarkers

N-terminal proBNP was notably higher in the frailest patients (*Table 2*). Levels of most biomarkers measured (in PARADIGM-HF) also increased with increasing frailty except for matrix metalloprotease-9 (online supplementary *Table S3*).

Baseline treatment

Frailer patients were prescribed more drugs (45% of the frailest group prescribed >4 drugs compared to 30% in the non-frail) (*Table 2*) and higher rates of implantation of a pacemaker, cardioverter-defibrillator and cardiac resynchronization therapy. Vaccination and disease management programme enrolment (in PARADIGM-HF) increased with increasing frailty (online supplementary *Table S4*).

Clinical outcomes

Heart failure specific outcomes

Risk of the primary composite outcome and its components was highest in the frailest, with unadjusted sHRs between 1.89 and 2.14 and adjusted sHRs of 1.69 to 1.75 (*Table 3* and *Figure 3*).

All-cause death and all-cause hospitalization

The rates of hospitalization for cardiovascular causes and for any reason were also significantly higher in the frailest patients, with sHRs of 1.69 (1.55–1.84, $P < 0.001$) and 1.60 (1.49–1.71, $P < 0.001$), respectively (*Table 3*). Risk of death from any cause was approximately twice as high in the frailest patients, compared to the non-frail, although the proportions of deaths that were cardiovascular and non-cardiovascular were similar across the FI categories (*Table 3*). Similar differences in risk of death and hospitalization were observed when frailty was examined across the different age groups, whether including the complete spectrum of age, or focussing only on those aged ≥60 years (online supplementary *Tables S5* and *S6*).

As shown in online supplementary *Figure S1*, the association between FI and mortality was most evident at a FI ≥0.20. Risk of each outcome also increased with every 0.01 increase in the FI (online supplementary *Table S7*).

Recurrent events

All outcomes of interest were more common in the frailest patients (*Table 3* and online supplementary *Table S8*). The adjusted IRR for HF hospitalization in the frailest participants was 1.90 (1.64–2.20); 1.76 (1.60–1.95) for cardiovascular hospitalization, 1.75 (1.58–1.94) for non-cardiovascular hospitalization, and 1.76 (1.62–1.90) for all-cause hospitalization.

Subgroup analysis

There were no differences in outcomes (primary composite outcome and all-cause death) among any of the subgroups analysed except for race as shown in online supplementary *Figure S2*.

Table 1 Baseline characteristics

	FI class 1 (≤0.210) (*n* = 4882)	FI class 2 (0.211–0.310) (*n* = 4770)	FI class 3 (≥0.311) (*n* = 3613)	*P*-value for trend
Age (years)	61.0 ± 11.7	64.9 ± 10.8	67.1 ± 10.3	<0.001
Female sex, *n* (%)	893 (18.3)	1059 (22.2)	882 (24.4)	<0.001
Region, *n* (%)				0.853
North America	199 (4.1)	265 (5.6)	295 (8.2)	
Latin America	1165 (23.9)	671 (14.1)	265 (7.3)	
Western Europe and other	1225 (25.1)	1385 (29.0)	1094 (30.3)	
Central Europe	1086 (22.2)	1789 (37.5)	1739 (48.1)	
Asia-Pacific	1207 (24.7)	660 (13.8)	220 (6.1)	
Race, *n* (%)				<0.001
White	2963 (60.7)	3644 (76.4)	3127 (86.6)	
Black	207 (4.2)	168 (3.5)	109 (3.0)	
Asian	1176 (24.1)	625 (13.1)	209 (5.8)	
Other	535 (11.0)	332 (7.0)	167 (4.6)	
Systolic blood pressure (mmHg)	119.0 ± 14.8	123.5 ± 16.6	127.2 ± 17.9	<0.001
Heart rate (bpm)	71.1 ± 11.7	72.0 ± 12.5	72.6 ± 12.5	<0.001
BMI[a] (kg/m^2)	26.4 (23.7–29.6)	27.7 (24.6–31.3)	29.1 (25.7–33.0)	<0.001
Comorbidities, *n* (%)				
Hypertension	2599 (53.2)	3460 (72.5)	3040 (84.1)	<0.001
Diabetes	982 (20.1)	1619 (33.9)	1635 (45.3)	<0.001
Atrial fibrillation	1242 (25.4)	1811 (38.0)	1910 (52.9)	<0.001
Valvular heart disease	202 (4.1)	257 (5.4)	200 (5.5)	0.002
Unstable angina	224 (4.6)	573 (12.0)	754 (20.9)	<0.001
Myocardial infarction	1409 (28.9)	2219 (46.5)	2105 (58.3)	<0.001
Stroke	183 (3.7)	385 (8.1)	495 (13.7)	<0.001
Peripheral arterial disease	86 (1.8)	249 (5.2)	436 (12.1)	<0.001
COPD	319 (6.5)	588 (12.3)	801 (22.2)	<0.001
Renal disease	351 (7.2)	664 (13.9)	874 (24.2)	<0.001
Current smoker	709 (14.5)	660 (13.8)	469 (13.0)	0.246

All values are reported as mean ± standard deviation except where indicated.
BMI, body mass index; COPD, chronic obstructive pulmonary disease; FI, frailty index.
[a]Median (interquartile range).

Effect of treatment with sacubitril/valsartan according to frailty index

In PARADIGM-HF only, there was no evidence of an interaction between treatment and frailty for the four endpoints (online supplementary *Figure S3*).

Adverse events

The risk of falls and factures increased as frailty increased, although the numbers of events were small (online supplementary *Table S9*). Study drug discontinuation due to adverse event was more common in the frailest patients (20% vs. 14% in non-frail) (online supplementary *Table S10*).

Discussion

Using an accepted methodology, we found that 63% of individuals (69% in patients ≥60 years) in this cohort of HFrEF were frail, even though they were relatively young and had been selected for inclusion in clinical trials.[11] Frail patients had worse baseline health-related quality of life (which was more likely to decline during follow-up) and were about twice as likely to die during follow-up. They were also significantly more likely to be hospitalized for cardiovascular and other reasons. The association between frailty and worse clinical outcomes persisted after adjustment for prognostically important factors and NT-proBNP, the single most powerful predictor of adverse outcomes in HFrEF.

As frailty is considered to result from an aggregation of insults across multiple organ systems, one approach to quantify frailty is counting the number of 'health deficits', assessed by symptoms, signs, diseases and disabilities, as well as laboratory, radiographic and electrocardiographic abnormalities, across a wide range of domains.[2,11] The more deficits accumulated, the more likely a patient will be frail. This 'deficit accumulation' approach allows calculation of a FI which has proved to be predictive of mortality, hospitalization and institutionalization in the general population, as well as in specific diseases.[2] Our FI appeared valid as higher scores were associated with poorer self-reported and physician-assessed

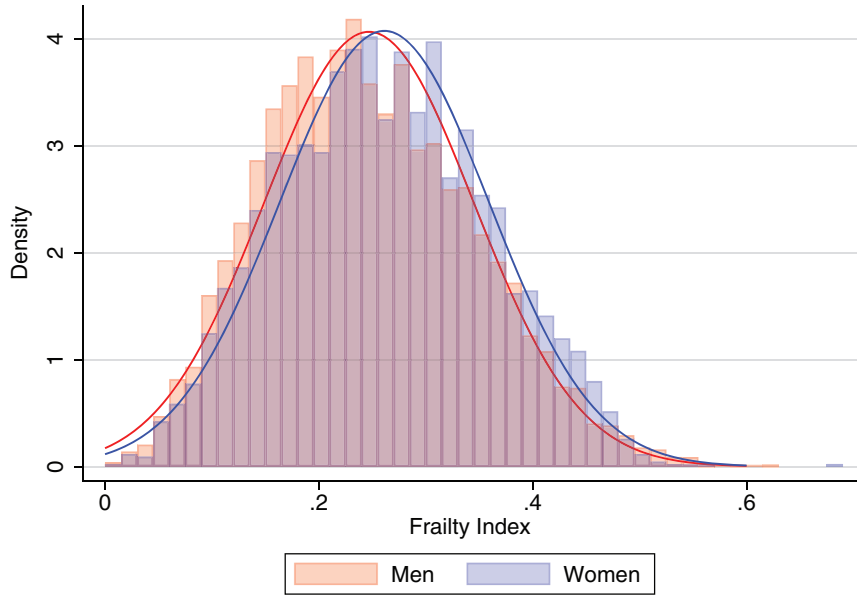

Figure 1 Density distribution of frailty index in men and women.

Figure 2 Frailty index according to age in men and women.

functional status and traditional frailty outcomes such as falls. Moreover, in our restricted cubic spline analysis, the significant point of inflection in risk of death related to FI was consistent with the conventional threshold defining frailty (FI ≥0.210).[11]

To give some context to our findings, the mean FI in the general population (UK Biobank, $n = 500\,336$), was 0.129 in those aged 60–65 and 0.139 in ≥65 years (compared with a mean of 0.250 in our patients, a higher score reflecting greater frailty).[18] In 2.69 million American Medicare beneficiaries >65 years without cancer, FI at age 66 was 0.198 and at age 70 was 0.197.[19] In two hypertension trials, the median FI in patients over 80 years was 0.17 and 0.18, respectively.[20,21] In the Systolic Blood Pressure Intervention Trial (SPRINT), 27% of patients were classified as frail. In general population studies, 20–30% of individuals are identified as frail, rising to 43% at the age of 85 years in a large Canadian study.[22] In our patients with a mean age of 64 years, 63% were frail. These striking differences between patients with HFrEF and those with hypertension, and the general population,

Table 2 Heart failure characteristics, clinical features, investigations and treatment

	FI class 1 (≤0.210) (*n* = 4882)	FI class 2 (0.211–0.310) (*n* = 4770)	FI class 3 (≥0.311) (*n* = 3613)	*P*-value for trend
HF aetiology				<0.001
Ischaemic	2122 (43.5)	2961 (62.1)	2675 (74.0)	
Non-ischaemic	2422 (49.6)	1643 (34.4)	857 (23.7)	
Other/unknown	338 (6.9)	166 (3.5)	81 (2.2)	
HF duration				<0.001
<1 year	1856 (38.0)	1336 (28.0)	763 (21.1)	
1–5 years	1756 (36.0)	1878 (39.4)	1434 (39.7)	
>5 years	1268 (26.0)	1555 (32.6)	1416 (39.2)	
Previous HF hospitalization	2835 (58.1)	2994 (62.8)	2412 (66.8)	<0.001
NYHA class				<0.001
I	302 (6.2)	99 (2.1)	25 (0.7)	
II	4021 (82.4)	3323 (69.7)	1808 (50.1)	
III	540 (11.1)	1320 (27.7)	1702 (47.2)	
IV	16 (0.3)	24 (0.5)	73 (2.0)	
KCCQ clinical summary score[a]	92.7 (85.4–97.9)	77.1 (65.6–85.9)	55.2 (43.3–67.7)	<0.001
KCCQ overall summary score[a]	89.6 (82.3–95.1)	73.2 (63.0–82.3)	51.3 (40.6–63.5)	<0.001
MAGGIC risk score[b]	19.5 ± 5.0	21.3 ± 5.4	23.1 ± 5.5	<0.001
Clinical features				
Dyspnoea on exertion	3901 (80.0)	4203 (88.2)	3383 (93.8)	<0.001
Orthopnoea	141 (2.9)	270 (5.7)	409 (11.3)	<0.001
PND	85 (1.7)	219 (4.6)	374 (10.4)	<0.001
Fatigue	1826 (37.4)	2574 (54.0)	2496 (69.2)	<0.001
Peripheral oedema	501 (10.3)	1010 (21.2)	1343 (37.2)	<0.001
Third heart sound	369 (7.6)	401 (8.4)	334 (9.3)	0.005
JVD	302 (6.2)	430 (9.0)	516 (14.3)	<0.001
Investigations				
Ejection fraction[b] (%)	28.5 ± 6.1	29.4 ± 5.9	29.8 ± 5.8	<0.001
NT-proBNP[a] (pg/mL)	1230 (713–2353)	1435 (787–2708)	1706 (894–3336)	<0.001
Haemoglobin[b] (g/L)	141.1 ± 14.1	139.1 ± 15.7	136.6 ± 17.6	<0.001
Creatinine[b] (μmol/L)	90.7 ± 21.6	96.9 ± 25.0	103.3 ± 30.5	<0.001
eGFR[b] (mL/min/1.73 m^2)	75.7 ± 22.5	69.0 ± 20.9	64.1 ± 20.5	<0.001
Sodium[b] (mmol/L)	140.6 ± 2.8	140.7 ± 3.1	141.0 ± 3.5	<0.001
Potassium[b] (mmol/L)	4.5 ± 0.4	4.5 ± 0.5	4.5 ± 0.5	0.063
ECG				
LVH	774 (15.9)	791 (16.6)	693 (19.2)	<0.001
Atrial fibrillation	861 (17.6)	1220 (25.6)	1218 (33.7)	<0.001
LBBB	1042 (21.3)	944 (19.8)	715 (19.8)	0.063
RBBB	325 (6.7)	348 (7.3)	337 (9.3)	<0.001
QRS duration[b] (ms)	118.1 ± 36.2	117.5 ± 34.9	118.1 ± 36.0	0.998
Treatment				
Diuretics	3677 (75.3)	3885 (81.4)	3104 (85.9)	<0.001
Digoxin	1495 (30.6)	1362 (28.6)	1060 (29.3)	0.149
ACEI	4352 (89.1)	4191 (87.9)	3188 (88.2)	0.154
ARB	551 (11.3)	612 (12.8)	460 (12.7)	0.032
MRA	2522 (51.7)	2288 (48.0)	1669 (46.2)	<0.001
CCB	283 (5.8)	472 (9.9)	473 (13.1)	<0.001
Statins	2301 (47.1)	2738 (57.4)	2287 (63.3)	<0.001
Aspirin	2418 (49.5)	2485 (52.1)	1920 (53.1)	0.001
Anticoagulants	1277 (26.2)	1610 (33.8)	1484 (41.1)	<0.001
≥5 drugs[c]	1468 (30.1)	1826 (38.3)	1606 (44.5)	<0.001
PCI	675 (13.8)	675 (13.8)	1064 (29.4)	<0.001
CABG	435 (8.9)	818 (17.1)	842 (23.3)	<0.001
Pacemaker	473 (9.7)	616 (12.9)	587 (16.2)	<0.001
ICD any	656 (13.4)	814 (17.1)	687 (19.0)	<0.001
ICD only	460 (9.4)	554 (11.6)	458 (12.7)	<0.001
CRT	266 (5.4)	339 (7.1)	298 (8.2)	<0.001

All values are reported as *n* (%) except where indicated.

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CABG, coronary artery bypass graft; CCB, calcium channel blocker; CRT, cardiac resynchronization therapy; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; FI, frailty index; ICD, implantable cardioverter-defibrillator; JVD, jugular venous distension; KCCQ, Kansas City Cardiomyopathy Questionnaire; LBBB, left bundle branch block; LVH, left ventricular hypertrophy; MAGGIC, Meta-Analysis Global Group in Chronic Heart Failure; MRA, mineralocorticoid receptor antagonist; NLR, neutrophil lymphocyte ratio; NT-proBNP, N-terminal pro brain natriuretic peptide; NYHA, New York Heart Association; PCI, primary coronary intervention; PND, paroxysmal nocturnal dyspnoea; RBBB, right bundle branch block.

[a]Median (interquartile range).

[b]Mean ± standard deviation.

[c]Only cardiovascular drugs listed in the table taken into account.

Table 3 Clinical outcomes according to frailty

	FI class 1 (≤0.210) (*n* = 4882)	FI class 2 (0.211–0.310) (*n* = 4770)	FI class 3 (≥0.311) (*n* = 3613)
Primary outcome			
Events, *n* (%)	1104 (22.6)	1328 (27.8)	1314 (36.4)
Event rate per 100 pt-years (CI)	8.8 (8.3–9.3)	11.6 (11.0–12.3)	17.1 (16.2–18.0)
Unadjusted sHR	1.00 (ref)	1.35 (1.25–1.47) <0.001	1.99 (1.83–2.16) <0.001
Adjusted sHR	1.00 (ref)	1.24 (1.14–1.35) <0.001	1.71 (1.56–1.88) <0.001
First HF hospitalization			
Events, *n* (%)	625 (12.8)	759 (15.9)	787 (21.8)
Event rate per 100 pt-years	5.0 (4.6–5.4)	6.6 (6.2–7.1)	10.2 (9.5–11.0)
Unadjusted sHR	1.00 (ref)	1.29 (1.16–1.44) <0.001	1.89 (1.69–2.11) <0.001
Adjusted sHR	1.00 (ref)	1.20 (1.07–1.34) 0.001	1.69 (1.50–1.90) <0.001
CV death			
Events, *n* (%)	701 (14.4)	842 (17.7)	875 (24.2)
Event rate per 100 pt-years	5.3 (4.9–5.7)	6.8 (6.3–7.3)	10.0 (9.4–10.7)
Unadjusted sHR	1.00 (ref)	1.38 (1.25–1.53) <0.001	2.14 (1.92–2.38) <0.001
Adjusted sHR	1.00 (ref)	1.25 (1.12–1.39) <0.001	1.75 (1.56–1.96) <0.001
First CV hospitalization			
Events, *n* (%)	1306 (26.8)	1605 (33.6)	1477 (40.9)
Event rate per 100 pt-years	12.8 (12.1–13.5)	18.2 (17.4–19.2)	26.5 (25.2–27.9)
Unadjusted sHR	1.00 (ref)	1.33 (1.24–1.43) <0.001	1.79 (1.65–1.93) <0.001
Adjusted sHR	1.00 (ref)	1.29 (1.19–1.39) <0.001	1.69 (1.55–1.84) <0.001
Non-CV death			
Events, *n* (%)	137 (2.8)	176 (3.7)	188 (5.2)
Event rate per 100 pt-years	1.0 (0.9–1.2)	1.4 (1.2–1.6)	2.2 (1.9–2.5)
Unadjusted sHR	1.00 (ref)	1.34 (1.07–1.68) 0.012	1.94 (1.53–2.45) <0.001
Adjusted sHR	1.00 (ref)	1.26 (1.00–1.60) 0.053	1.75 (1.35–2.25) <0.001
First non-CV hospitalization			
Events, *n* (%)	1088 (22.3)	1261 (26.4)	1158 (32.1)
Event rate per 100 pt-years	10.7 (10.0–11.3)	14.3 (13.6–15.1)	20.8 (19.6–22.0)
Unadjusted sHR	1.00 (ref)	1.22 (1.13–1.33) <0.001	1.62 (1.48–1.77) <0.001
Adjusted sHR	1.00 (ref)	1.17 (1.08–1.28) <0.001	1.52 (1.38–1.67) <0.001
All hospitalization/all death			
Events, *n* (%)	2251 (46.1)	2569 (53.9)	2271 (62.9)
Event rate per 100 pt-years	22.1 (21.2–23.0)	29.2 (28.1–30.3)	40.7 (39.1–42.4)
Unadjusted HR	1.00 (ref)	1.29 (1.22–1.37) <0.001	1.77 (1.67–1.89) <0.001
Adjusted HR	1.00 (ref)	1.23 (1.16–1.31) <0.001	1.63 (1.53–1.75) <0.001
First all-cause hospitalization			
Events, *n* (%)	1969 (40.3)	2268 (47.5)	2024 (56.0)
Event rate per 100 pt-years	19.3 (18.5–20.2)	25.8 (24.7–26.9)	36.3 (34.7–37.9)
Unadjusted sHR	1.00 (ref)	1.27 (1.19–1.34) <0.001	1.71 (1.60–1.82) <0.001
Adjusted sHR	1.00 (ref)	1.21 (1.14–1.29) <0.001	1.60 (1.49–1.71) <0.001
All-cause death			
Events, *n* (%)	838 (17.2)	1018 (21.3)	1063 (29.4)
Event rate per 100 pt-years	6.3 (5.9–6.7)	8.2 (7.7–8.7)	12.2 (11.5–13.0)
Unadjusted HR	1.00 (ref)	1.39 (1.27–1.53) <0.001	2.19 (1.99–2.41) <0.001
Adjusted HR	1.00 (ref)	1.26 (1.14–1.39) <0.001	1.80 (1.62–2.00) <0.001
Recurrent HF hospitalizations			
Total events, *n*	1021	1280	1426
Events per 100 pt-years	7.7 (7.2–8.2)	10.3 (9.6–10.9)	16.4 (15.5–17.2)
Unadjusted IRR	1.00 (ref.)	1.41 (1.24–1.61) <0.00	2.40 (2.09–2.76) <0.001
Adjusted IRR	1.00 (ref.)	1.25 (1.09–1.42) <0.001	1.90 (1.64–2.20) <0.001
Recurrent CV hospitalizations			
Total events, *n*	2441	3050	3118
Events per 100 pt-years	18.3 (17.6–19.1)	24.6 (23.7–25.4)	35.8 (34.6–37.1)
Unadjusted IRR	1.00 (ref.)	1.36 (1.25–1.49) <0.001	2.03 (1.85–2.22) <0.001
Adjusted IRR	1.00 (ref.)	1.26 (1.16–1.38) <0.001	1.76 (1.60–1.95) <0.001

Table 3 (Continued)

	FI class 1 (≤0.210) (*n* = 4882)	FI class 2 (0.211–0.310) (*n* = 4770)	FI class 3 (≥0.311) (*n* = 3613)
Recurrent non-CV hospitalizations			
Total events, *n*	1713	2132	2235
Events per 100 pt-years	12.9 (12.3–13.5)	17.2 (16.5–17.9)	25.7 (24.6–26.8)
Unadjusted IRR	1.00 (ref.)	1.30 (1.19–1.42) <0.001	1.93 (1.76–2.12) <0.001
Adjusted IRR	1.00 (ref.)	1.21 (1.11–1.33) <0.001	1.75 (1.58–1.94) <0.001
Recurrent all-cause hospitalizations			
Total events, *n*	4154	5182	5353
Events per 100 pt-years	31.2 (30.3–32.2)	41.7 (40.6–42.9)	61.5 (59.8–63.1)
Unadjusted IRR	1.00 (ref.)	1.35 (1.26–1.44) <0.001	2.00 (1.86–2.16) <0.001
Adjusted IRR	1.00 (ref.)	1.24 (1.16–1.33) <0.001	1.76 (1.62–1.90) <0.001
Fall in KCCQ clinical summary score ≥ 5 at 12 months			
n (%)	1598 (33.8)	1628 (35.6)	1230 (36.3)
Adjusted OR1	1.00 (ref.)	1.32 (1.20–1.45) <0.001	1.83 (1.60–2.10) <0.001
Adjusted OR2	1.00 (ref.)	1.22 (1.10–1.35) <0.001	1.62 (1.40–1.87) <0.001

CV, cardiovascular; FI, frailty index; HF, heart failure; HR, hazard ratio; IRR, incidence rate ratio; KCCQ, Kansas City Cardiomyopathy Questionnaire; OR, odds ratio; pt, patient; sHR, sub-distribution hazard ratio.
sHRs with 95% confidence interval (HR for all-cause death). All sHRs adjusted for region and randomized treatment at baseline. Adjusted sHRs additionally adjusted for sex, age, heart rate, N-terminal pro brain natriuretic peptide, New York Heart Association class I/II vs. II/IV, duration of HF and ejection fraction.
Event rates per 100 patient-years with 95% confidence interval.
HF hospitalization additionally adjusted for previous hospitalization for HF.
IRRs with 95% confidence interval. All IRRs adjusted for region and randomized treatment at baseline. Adjusted IRRs additionally adjusted for sex, age, heart rate, N-terminal pro brain natriuretic peptide, New York Heart Association class I/II vs. II/IV, duration of HF, hospitalization for HF and ejection fraction.
OR with 95% confidence interval. ORs adjusted for region and randomized treatment at baseline. Adjusted OR1 additionally adjusted for KCCQ clinical summary score at baseline. Adjusted OR2 additionally adjusted for sex, age, heart rate, N-terminal pro brain natriuretic peptide, New York Heart Association class and ejection fraction.

are an important reminder that frailty is not confined to the very elderly. The high prevalence of frailty in our relatively young HFrEF population is also consistent with the hypothesis that frailty partly reflects accelerated ageing – essentially our patients have a prevalence of frailty usually only found in extreme old age. Moreover, frailty seems to be particularly prevalent in HF compared with other diseases; for example, lower frailty indices, and lower proportion of patients classified as frail, have been reported in chronic kidney disease, chronic obstructive pulmonary disease, and acute coronary syndrome.[23–32] Only in myeloma patients, with a mean age of 76 years, did we find similar levels of frailty: median FI 0.24, with 52% categorized as frail.[19]

Chronic inflammation, sarcopenia and general reduction in physiological reserves are implicated in the pathogenesis of the frailty syndrome.[23–32] Interestingly, we found that increasing frailty was associated with higher levels of inflammation and tissue turnover related biomarkers, especially, growth differentiation factor 15, one of a core panel of frailty biomarkers, thought to reflect mitochondrial dysfunction and cellular senescence, increased with increasing frailty.[33–38]

Consistent with previous studies, a higher proportion of women in this study were frail (68% vs. 62%), which has been attributed to their lower muscle mass. Quality of life, overall, was lower in women and whether this is a marker of frailty or a contributor to frailty is unknown.

Several studies have examined frailty in HF, although most were small and many used different methods to define frailty; additionally, some focused on hospitalized patients or HF with preserved ejection fraction (HFpEF) patients or included patients without LVEF measurement. Only three prior studies in ambulatory patients were large (>1000 participants) and reported clinical outcomes. In a Spanish study, 44% of 1314 HF outpatients (76% HFrEF and 24% HFpEF, mean age 67 years) were categorized as frail using an approach based on four geriatric scales.[39] Frailty was independently predictive of all-cause mortality, although the multivariable model did not include natriuretic peptides. No other outcomes were reported. Recently, an electronic FI (eFI), calculated for 6360 patients with a diagnosis of HF (but without LVEF or natriuretic peptides) in a large UK primary care dataset, was predictive of any hospitalization at 1 year but not of HF hospitalization.[40] Mortality was not reported. Of these patients (mean age not reported but 83% ≥65 years), only 15% were categorized as frail using an eFI cut-point of 0.24 compared to 51% using this threshold in our study. Patients in the UK study had been diagnosed with HF within the past 3 years whereas 36% of the patients in our study were diagnosed with HF more than 5 years previously. In our patients diagnosed with HF less than 2 years before enrolment, only 19% of the patients had an FI ≥0.24 whereas, of those diagnosed less than 5 years before enrolment, 33% had an FI ≥0.24. Using an approach similar to ours, the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) investigators reported a mean FI of 0.37 ± 0.11 (median 0.36; interquartile range 0.29–0.44) in 1767 patients with HFpEF from North and South America (mean age 71.5 years, 49% female).[13] A remarkable 94% had a FI >0.21. As in this study, a higher FI was associated with higher rates of HF hospitalization, cardiovascular death and

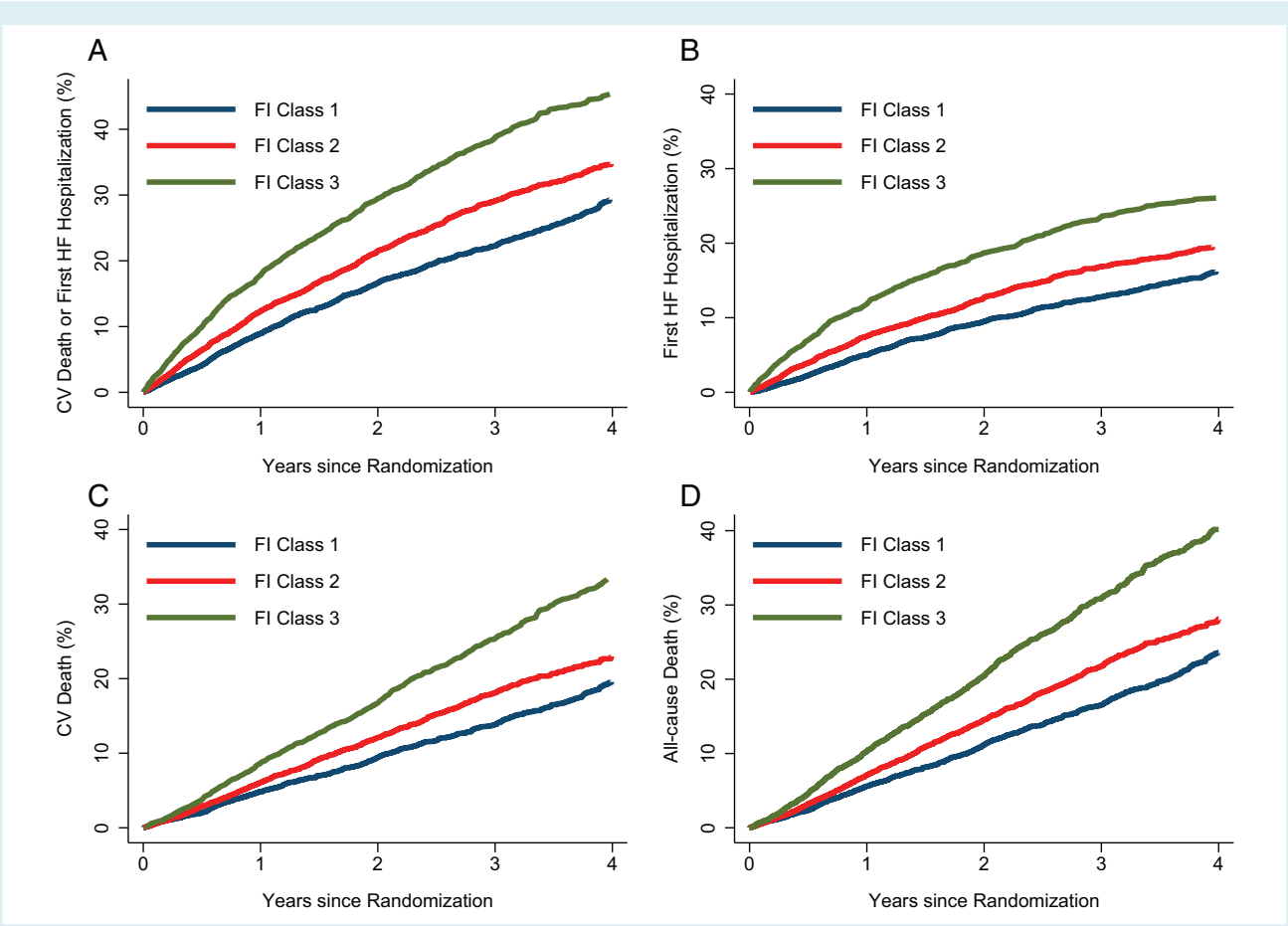

Figure 3 Clinical outcomes according to frailty index (FI) in heart failure (HF) with reduced ejection fraction. (*A*) Cumulative incidence curve of risk of first HF hospitalization or cardiovascular (CV) death. (*B*) Cumulative incidence curve of risk of first HF hospitalization. (*C*) Cumulative incidence curve of risk of CV death. (*D*) Kaplan–Meier curve of all-cause death.

all-cause death, although these outcomes were not adjusted for other predictive variables. A greater proportion of the patients in TOPCAT had diabetes and hypertension, along with a much lower mean KCCQ overall summary score (58.1 ± 23.4 vs. 72.3 ± 19.5 in our patients), which could have contributed to a higher proportion of their patients being described as frail.[13] Patients with HFrEF were also less likely to be frail than HFpEF patients in a smaller recent study assessing different frailty tools in HF.[41]

The high prevalence of frailty in HFrEF is highly clinically relevant, as reflected in the worse outcomes seen in frail patients. Frail patients have reduced ability to cope with stressors that may precipitate worsening of HF, meaning that exacerbations become more frequent and increasingly difficult to recover from. We certainly found a marked difference in the rate of HF hospitalization when comparing frail to non-frail patients. However, rates of admission and deaths from other reasons were also higher in frail individuals, although the proportion of deaths that was attributed to non-cardiovascular causes (around 19%) was similar across FI categories. Importantly, the absolute risks in the frailest patients were remarkably high – e.g. 4 in 10 of the frailest individuals were admitted to hospital at least once or died during each year of follow-up. In addition, when repeat admissions were accounted for, the rate of hospitalization was 62 episodes per 100 patient-years. Two recent studies using the same FI (the Hospital Frailty Risk Score) in patients hospitalized with HF have shown that frailty is also associated with higher rates of short and long-term mortality after discharge; a third confirmed the distinction between frailty and comorbidity by demonstrating a poor correlation between the Hospital Frailty Risk Score and the Charlson Comorbidity Index.[42–44]

Frailty may also reduce a patient's ability to self-care and impair adherence because of associated cognitive impairment.[36–38] Polypharmacy increased with increasing frailty, not only causing concerns about adherence but also about drug-related adverse effects and interactions. Consistent with this, study drug discontinuation was significantly more common in frailer patients.

The obvious question is what, if anything, can be done to prevent or treat frailty? Frailty is believed to evolve over time, with initially fit individuals progressing through a pre-frail stage to overt frailty and ultimately terminal disability and death.[1–5,45] Often, early frailty may be undetected as limitations in daily activities (and associated symptoms such as fatigue) are often attributed to the normal

consequences of ageing by patients and their caregivers. It is easy to see how this could be especially so in HF. Identifying frailty early may be important as some of the limitations caused by it may be amenable to nutritional and lifestyle interventions and, if employed at the pre-frail stage, these may delay progression to frailty.[1,5,45–47] In this respect, cardiac rehabilitation and exercise training programmes may be particularly relevant, yet the latter was prescribed in only around one in 10 patients in our study.[48] However, as frailty seems to reflect a number of insults to multiple systems, a multifaceted approach to its prevention and treatment may be required.

Concerns regarding the inclusion of the elderly and the frail in clinical trials, either due to the perceived burden to the frail patients or due to doubts regarding the benefit of such therapies to the elderly and frail, exist.[49] We did not see any evidence of an interaction between treatment and frailty in the PARADIGM-HF patients in this analysis. Similarly, other studies have also shown that frailty does not alter the effect of therapy.[20]

The FI lends itself to incorporation into routine datasets, including patient electronic health records. It is possible to conceive of how a hospital admission record or outpatient/primary care electronic health record might automatically calculate a FI and alert the physician/nurse to individuals with a high score, although, as alluded to above, we do not know, yet, whether identification of frailty should trigger any monitoring or therapeutic intervention. Likewise, in nationwide audits and comparison of outcomes, FI might be an important determinant of differences in outcome that could be adjusted for in between institution or other comparisons.

It would also be of interest to compare the Fried and Rockwood (and other) approaches to assessing frailty and how the prevalence of frailty varies according to the measure used and whether different approaches are similarly predictive of outcomes.

Strengths and limitations

Our study has strengths and limitations. The patients were those selected for inclusion in clinical trials and not fully representative of the general population. It is likely that frailty is even more prevalent in an unselected cohort of patients with HFrEF. Our FI is not an independently validated prediction model and may not be applicable to other cohorts. Also we could not test other types of frailty scores which include tests of muscle strength and functional capacity and we recognize that in the absence of these factors, our current FI may be viewed as a surrogate measure of frailty. On the other hand, we had detailed and near complete collection of baseline variables enabling us to create the 42-item FI. We also had careful collection of long-term adjudicated outcomes.

Conclusions

Frailty was highly prevalent in HFrEF, even in ambulatory patients with mainly mild symptoms. Frailty was associated with greater deterioration in quality of life and higher risk of hospitalization and death. Frailty, did not, however, modify the effect of sacubitril/valsartan. Strategies to prevent and treat frailty are needed in HFrEF.

Supplementary Information

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

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