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Sacubitril/Valsartan and Frailty in Patients With Heart Failure and Preserved Ejection Fraction



Jawad H. Butt, MD,^{a,b} Pooja Dewan, MBBS, PhD,^a Pardeep S. Jhund, MBChB, MSc, PhD,^a Inder S. Anand, MD, DPHIL,^{c,d} Dan Atar, MD,^{e,f} Junbo Ge, MD,^g Akshay S. Desai, MD,^h Luis E. Echeverria, MD,ⁱ Lars Køber, MD, DMSc,^b Carolyn S.P. Lam, MBBS, PhD,^j Aldo P. Maggioni, MD,^k Felipe Martinez, MD,^l Milton Packer, MD,^m Jean L. Rouleau, MD,ⁿ David Sim, MD,^o Dirk J. Van Veldhuisen, MD, PhD,^p Bojan Vrtovc, MD,^q Faiez Zannad, MD,^r Michael R. Zile, MD,^{s,t} Jianjian Gong, PhD,^u Martin P. Lefkowitz, MD,^u Adel R. Rizkala, PHARM D,^u Scott D. Solomon, MD,^h John J.V. McMurray, MD^a

ABSTRACT

BACKGROUND Frailty is an increasingly common problem, and frail patients are less likely to receive new pharmacologic therapies because the risk-benefit profile is perceived to be less favorable than in nonfrail patients.

OBJECTIVES This study investigated the efficacy of sacubitril/valsartan according to frailty status in 4,796 patients with heart failure with preserved ejection fraction randomized in the PARAGON-HF (Prospective Comparison of ARNI With ARB Global Outcomes in Heart Failure With Preserved Ejection Fraction) trial.

METHODS Frailty was measured by using the Rockwood cumulative deficit approach. The primary endpoint was total heart failure hospitalizations or cardiovascular death.

RESULTS A frailty index (FI) was calculable in 4,795 patients. In total, 45.2% had class 1 frailty (FI \leq 0.210, not frail), 43.5% had class 2 frailty (FI 0.211-0.310, more frail), and 11.4% had class 3 frailty (FI \geq 0.311, most frail). There was a graded relationship between FI class and the primary endpoint, with a significantly higher risk associated with greater frailty (class 1: reference; class 2 rate ratio: 2.19 [95% CI: 1.85-2.60]; class 3 rate ratio: 3.29 [95% CI: 2.65-4.09]). The effect of sacubitril/valsartan vs valsartan on the primary endpoint from lowest to highest FI class (as a rate ratio) was: 0.98 [95% CI: 0.76-1.27], 0.92 [95% CI: 0.76-1.12], and 0.69 [95% CI: 0.51-0.95], respectively ($P_{\text{interaction}} = 0.23$). When FI was examined as a continuous variable, the interaction with treatment was significant for the primary outcome ($P_{\text{interaction}} = 0.002$) and total heart failure hospitalizations ($P_{\text{interaction}} < 0.001$), with those most frail deriving greater benefit.

CONCLUSIONS Frailty was common in heart failure with preserved ejection fraction and associated with worse outcomes. Compared with valsartan, sacubitril/valsartan seemed to show a greater reduction in the primary endpoint with increasing frailty, although this was not significant when FI was examined as a categorical variable. (Prospective Comparison of ARNI With ARB Global Outcomes in Heart Failure With Preserved Ejection Fraction [PARAGON-HF]; [NCT01920711](https://clinicaltrials.gov/ct2/show/study/NCT01920711)). (J Am Coll Cardiol 2022;80:1130-1143) © 2022 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).



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From the ^aBritish Heart Foundation Cardiovascular Research Centre, University of Glasgow, Glasgow, United Kingdom; ^bDepartment of Cardiology, Rigshospitalet Copenhagen University Hospital, Copenhagen, Denmark; ^cDepartment of Medicine, VA Medical Center, Minneapolis, Minnesota, USA; ^dUniversity of Minnesota Medical Center, University of Minnesota, Minneapolis, Minnesota, USA; ^eDepartment of Cardiology, Oslo University Hospital Ullevål, Oslo, Norway; ^fInstitute of Clinical Medicine, University of Oslo, Oslo, Norway; ^gShanghai Institute of Cardiovascular Diseases, Zhongshan Hospital, Fudan University, Shanghai, China; ^hDivision of Cardiovascular Medicine, Brigham and Women's Hospital, Boston, Massachusetts, USA; ⁱHeart Failure Unit and Cardiac Transplant Program, Fundación Cardiovascular de Colombia, Floridablanca, Santander, Colombia; ^jNational Heart Centre Singapore and Duke-National University of Singapore, Singapore; ^kAssociazione Nazionale Medici Cardiologi Ospedalieri, Florence, Italy; ^lUniversidad Nacional of Córdoba, Córdoba, Argentina; ^mBaylor Heart and Vascular Institute, Baylor University Medical Center, Dallas, Texas, USA; ⁿInstitut de Cardiologie de Montréal, Université de Montréal, Montréal,

Frailty is an emerging global health burden, with substantial implications for public health.¹⁻⁴ This syndrome is characterized by a decline in homeostatic reserves across several physiological systems, accompanied by increased vulnerability to endogenous and exogenous stressors. Frailty is related to both aging and comorbidity because physiological reserves decline with age and comorbidity burden. However, frailty can also occur in young individuals and people without comorbidities, and the manifestations of frailty, which include poor appetite, a decline in cognitive function, fatigue, and reduced mobility, are not specific to a particular disease. The consequences of frailty are substantial and include falls, disability, dependency, hospitalization, and premature death.

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Heart failure (HF) and frailty are 2 distinct, yet commonly associated conditions that share pathophysiological mechanisms, including dysregulation of neurohormonal, metabolic, inflammatory, and immunologic pathways. The imbalance between the anabolic and catabolic state in HF may accelerate the development of frailty, and patients with HF are up to 6 times more likely to be frail than the general population.⁵⁻⁸ HF with preserved ejection fraction (HFpEF) is of particular interest in relation to frailty, as both conditions can be viewed as a systemic “geriatric” syndrome for which aging and multimorbidity are central to the pathophysiology.⁹ Because frailty is associated with a substantial risk of adverse outcomes in patients with HF, there has been an increased focus, in the holistic management of HF, on reducing the risk of developing frailty, slowing its progression, and even reversing it, although whether the latter is achievable is uncertain.^{8,10-14} Recently, interest has been increasing in using frailty status to evaluate the efficacy and safety of new HF treatments. There is a common reluctance of clinicians to introduce new therapies in frail patients due to anticipation of a less favorable risk-benefit profile in these patients. Related concerns are that frail patients are exposed to more

polypharmacy, are more likely to experience drug interactions and adverse drug reactions, and are more likely to discontinue treatment than nonfrail patients.^{8,10,15-17} Although it is perceived that therapies are less effective in frail patients, there is little evidence supporting this assumption.^{10,11,18-20} Given the likely role of hospital admission in accelerating frailty, the absolute benefits of therapies might be even larger in more frail patients who are at particular high risk of hospitalizations.

In the PARAGON-HF (Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial, sacubitril/valsartan did not significantly reduce the primary outcome of a composite of total HF hospitalizations or cardiovascular death compared with valsartan in 4,796 patients with HFpEF; the treatment effect was of borderline statistical significance (rate ratio: 0.87; 95% CI: 0.75-1.01), however.²¹ In this post hoc analysis, we examined the efficacy and safety of sacubitril/valsartan according to frailty status, using the Rockwood cumulative deficit approach.²²⁻²⁴

METHODS

PARAGON-HF was a randomized, double-blind, parallel-group, active-controlled trial in patients with HFpEF, evaluating the efficacy and safety of sacubitril/valsartan compared with valsartan. The design and primary results of PARAGON-HF have been published.^{21,25} The trial protocol was approved by the Ethics Committee at all participating institutions, and all patients provided written informed consent.

STUDY PATIENTS AND TRIAL PROCEDURES. Men and women aged ≥ 50 years were eligible if they had signs and symptoms of HF (New York Heart Association [NYHA] functional class II-IV), left ventricular ejection fraction (LVEF) $\geq 45\%$ within 6 months of screening, elevated natriuretic peptide level (with different cutoffs depending on the occurrence of a recent HF hospitalization and the presence of atrial

ABBREVIATIONS AND ACRONYMS

FI = frailty index

HF = heart failure

HFpEF = heart failure with preserved ejection fraction

KCCQ-CSS = Kansas City Cardiomyopathy Questionnaire Clinical Summary Score

LVEF = left ventricular ejection fraction

MMSE = Mini-Mental State Examination

NT-proBNP = N-terminal pro-B-type natriuretic peptide

NYHA = New York Heart Association

Québec, Canada; ^oDepartment of Cardiology, National Heart Centre Singapore, Singapore; ^pDepartment of Cardiology, University Medical Centre Groningen, University of Groningen, Groningen, the Netherlands; ^qUniversity Medical Centre, Ljubljana, Slovenia; ^rInserm CIC 1433 and Université de Lorraine, Centre Hospitalier Régional Universitaire, Nancy, France; ^sMedical University of South Carolina, Charleston, South Carolina, USA; ^tRalph H. Johnson Veterans Administration Medical Center, Charleston, South Carolina, USA; and the ^uNovartis Pharmaceuticals Corporation, East Hanover, New Jersey, USA.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the [Author Center](#).

fibrillation/flutter), evidence of structural heart disease (left atrial enlargement or left ventricular hypertrophy), and diuretic therapy. Key exclusion criteria included any previous echocardiographic measurement of LVEF <40%; recent acute coronary syndrome, cardiac surgery, or percutaneous coronary intervention; acute decompensated HF at the time of screening; intolerance to either study drug (or similar classes) or a history of angioedema; systolic blood pressure >180 mm Hg or <110 mm Hg; estimated glomerular filtration <30 mL/min/1.73 m²; and a serum potassium level >5.2 mmol/L. A complete list of exclusion criteria is provided in the design paper.²⁵

During the single-blind run-in periods, all participants first received valsartan at one-half the target dose and then sacubitril/valsartan at one-half the target dose. If this dose was tolerated in both run-in phases, participants were then randomized to treatment with either sacubitril/valsartan (target dose: 97 mg/103 mg twice daily) or valsartan (target dose: 60 mg of valsartan twice daily) in a 1:1 ratio.

FRAILITY INDEX. We used the Rockwood cumulative deficit approach to construct a 41-item frailty index (FI). This approach has been described previously in detail.^{10,11,22-24} Overall, at least 30 items are required, and these should cover a range of body systems and be associated with health but not part of normal aging (although deficits should generally increase with age). The items included were derived from medical history, vital signs, the EuroQoL-5 Domain questionnaire (quality-of-life measures, including functional status), and laboratory data (Supplemental Table 1). Each patient was assigned a score for each non-missing item, and the FI score was calculated as the sum of these scores divided with the total number of nonmissing items, with higher scores indicating greater frailty. Binary variables were scored as 0/1 (absent/present); ordinal variables were scored from 0 to 1 (1 indicating the greatest severity); and continuous variables were categorized and scored as 0/1 (normal/abnormal). Patients with ≥20% missing items were excluded.^{10,11,26,27} Patients were divided into the following 3 subgroups: FI ≤0.210 (FI class 1 [classified as nonfrail patients, as defined previously]^{10,27}), FI 0.211 to 0.310 (FI class 2 [more frail]), and FI ≥0.311 (FI class 3 [most frail]).

TRIAL OUTCOMES. The primary outcome in PARAGON-HF was a composite of total (first and recurrent) HF hospitalizations or cardiovascular death. The secondary outcomes in the trial were: change in the Kansas City Cardiomyopathy Questionnaire Clinical Summary Score (KCCQ-CSS) from baseline to 8 months; change in NYHA functional

class from baseline to 8 months; the first occurrence of a decline in renal function (a composite of a reduction in estimated glomerular filtration ≥50%, end-stage renal disease, or death due to renal failure); and all-cause death. The present analysis also examined an expanded primary composite outcome (primary endpoint plus urgent HF visits), the components of the primary outcome, first HF hospitalization or cardiovascular death, first HF hospitalization, total cardiovascular hospitalizations, total all-cause hospitalization, and noncardiovascular death. In a subset of patients, the change in Mini-Mental State Examination (MMSE) score from baseline to 2 years was also examined.

Prespecified safety analyses included hypotension, an elevation of serum creatinine, an elevation of serum potassium, angioedema, and liver-related adverse events. We also examined falls and fractures using data from investigator-reported adverse events.

STATISTICAL ANALYSES. Baseline characteristics were summarized as frequencies with percentages, mean ± SD, or medians (IQR). Differences in baseline characteristics were tested by using the Cochran-Armitage trend test for binary variables, the Cochran-Mantel-Haenszel test for categorical variables, and the Jonckheere-Terpstra test and analysis of variance test for non-normal and normally distributed continuous variables, respectively.

Regardless of treatment allocation, total events were evaluated with Nelson-Aalen cumulative hazard curves and semiparametric proportional rates models, stratified according to geographic region, with treatment assignment as fixed effect factors. Time-to-event data were evaluated with the Kaplan-Meier estimator and Cox proportional hazards models, stratified according to region and adjusted for treatment assignment. In addition, HRs and rate ratios, stratified according to region and adjusted for treatment assignment, age, sex, log of N-terminal pro-B-type natriuretic peptide (NT-proBNP), HF duration, LVEF, and NYHA functional class were reported. Variables that were part of the FI were not adjusted for because the categorization of FI into the 3 classes was conditioned on these variables.

To compare the effects of sacubitril/valsartan vs valsartan, total events were evaluated with Nelson-Aalen cumulative hazard curves and semiparametric proportional rates models, stratified according to region. Time-to-event data were evaluated with the Kaplan-Meier estimator and Cox proportional hazards models, stratified according to region. The effect of sacubitril/valsartan was also examined according to continuous FI as a fractional

polynomial. Change from baseline to 8 months in KCCQ-CSS was analyzed by using a multilevel mixed effects linear regression model, together with a multilevel mixed effects logistic regression model for a 5-point or greater change in KCCQ-CSS. Both models were adjusted for baseline KCCQ-CSS, treatment, region, visit, and treatment-by-visit interaction. Change from baseline to 8 months in NYHA functional class was analyzed by using a multilevel mixed effects logistic regression model, adjusted for baseline NYHA functional class, region, treatment, visit, and treatment-by-visit interaction. Change from baseline to 2 years in MMSE score was analyzed by using a multilevel mixed effects linear regression model, together with a multilevel mixed effects logistic regression model for a 3-point or greater decrease in MMSE score. Both models were adjusted for MMSE baseline value, region, treatment, visit, treatment-by-visit interaction, age, baseline hypertension status, baseline diabetes status, and visit-by-MMSE baseline value interaction.

The analysis of the effect of sacubitril/valsartan according to frailty status was performed post hoc. All analyses were conducted by using SAS 9.4 (SAS Institute, Inc) and STATA 17.0 (StataCorp). A *P* value of 0.05 was considered statistically significant. *P* values and 95% CIs have not been adjusted for multiplicity, and the inferences drawn may therefore not be reproducible.

RESULTS

PATIENT CHARACTERISTICS. Of the 4,796 patients randomized in PARAGON-HF, FI was calculable for 4,795 patients. The distribution of FI is presented in [Supplemental Figure 1](#). Mean FI was 0.227 ± 0.091 , and median FI was 0.220 (IQR: 0.175-0.268; range: 0.061-0.537). In total, 2,165 (45.2%) patients were in class 1 frailty (FI ≤ 0.210 , not frail), 2,084 (43.5%) had class 2 frailty (FI 0.211-0.310, more frail), and 546 (11.4%) were in class 3 frailty (FI ≥ 0.311 , most frail).

Compared with patients with lower FI, those with higher FI were older and more often male, smokers, and resident in North America. Frailer patients were more likely to have cardiovascular and non-cardiovascular comorbidities, with steep gradients in diabetes, chronic obstructive pulmonary disease, and chronic kidney disease. They also had higher systolic blood pressure, pulse pressure, and body mass index but lower diastolic blood pressure and heart rate. Patients with higher FI were more likely to have coronary artery disease, longer duration of HF,

lower LVEF, and worse clinical signs/symptoms, including fatigue, NYHA functional class, and KCCQ scores. The average MMSE score was lower in those with greater frailty, as was the proportion of patients with cognitive impairment ([Table 1](#)).

Regarding biomarkers, patients with greater FI had higher levels of many biomarkers, including NT-proBNP, creatinine, uric acid, neutrophil/lymphocyte ratio, markers of collagen turnover, and high-sensitivity troponin T. Conversely, levels of other biomarkers were lower in frailer patients, including albumin, cholesterol, hemoglobin, platelets, and urinary cyclic guanosine monophosphate/creatinine ratio, a marker of tissue responsiveness to natriuretic peptides. There was also greater erythrocyte anisocytosis among frailer patients ([Supplemental Table 2](#)).

In terms of pharmacologic therapy, patients with higher FI were more often treated with a diuretic, beta-blocker, calcium-channel blocker, nitrate, statin, antiplatelet, and oral anticoagulant but less often with digoxin.

OUTCOMES ACCORDING TO FI. Compared with patients in FI class 1, those in FI classes 2 and 3 had a higher rate of total HF hospitalizations or cardiovascular death, even after adjustment for known prognostic variables (rate ratio: 2.19 [95% CI: 1.85-2.60] and 3.29 [95% CI: 2.65-4.09], respectively). Likewise, there was a graded relationship between FI class and the secondary outcomes, with a significantly higher risk in those with greater frailty, and these associations persisted after adjustment for known prognostic variables ([Figure 1](#), [Supplemental Table 3](#)). There was also a trend toward a greater decline in MMSE with increasing frailty (mean change in MMSE: FI class 1, reference; FI class 2, -0.06 [95% CI: -0.23 to 0.11]; FI class 3, -0.17 [95% CI: -0.46 to 0.12]).

EFFECT OF SACUBITRIL/VALSARTAN ON CLINICAL OUTCOMES ACCORDING TO FI. Primary composite outcome.

The rate ratios for the effect of sacubitril/valsartan vs valsartan on total HF hospitalizations or cardiovascular death from lowest to highest FI class were: 0.98 (95% CI: 0.76-1.27), 0.92 (95% CI: 0.76-1.12), and 0.69 (95% CI: 0.51-0.95), respectively. There was no statistically significant interaction between FI class and the effect of treatment ($P_{\text{interaction}} = 0.23$) ([Table 2](#), [Figure 2](#)). However, when examined as a continuous variable, there was a significant interaction between FI and the effect of sacubitril/valsartan ($P_{\text{interaction}} = 0.002$). Collectively, these findings suggest that, compared with valsartan, sacubitril/valsartan might have more benefit in more frail

TABLE 1 Baseline Characteristics of the Study Population According to the FI

	FI \leq 0.210 (Not Frail) (n = 2,165)	FI 0.211-0.310 (More Frail) (n = 2,084)	FI \geq 0.311 (Most Frail) (n = 546)	P Value
Age, y	71.3 \pm 8.7	73.8 \pm 8.1	74.6 \pm 7.7	<0.001
Sex				0.03
Female	1,145 (52.9)	1,078 (51.7)	256 (46.9)	
Male	1,020 (47.1)	1,006 (48.3)	290 (53.1)	
Geographic region				<0.001
Asia/Pacific and other	410 (18.9)	286 (13.7)	66 (12.1)	
Central Europe	828 (38.2)	752 (36.1)	135 (24.7)	
Latin America	216 (10.0)	137 (6.6)	17 (3.1)	
North America	145 (6.7)	257 (12.3)	157 (28.8)	
Western Europe	566 (26.1)	652 (31.3)	171 (31.3)	
Physiological measures				
Systolic blood pressure, mm Hg	126.8 \pm 13.3	132.9 \pm 16.1	136.4 \pm 17.1	<0.001
Diastolic blood pressure, mm Hg	74.9 \pm 9.5	74.4 \pm 11.1	71.9 \pm 11.9	<0.001
Pulse pressure, mm Hg	52.0 \pm 12.3	58.5 \pm 15.2	64.5 \pm 15.4	<0.001
Heart rate, beats/min	70.3 \pm 11.9	70.7 \pm 12.6	69.7 \pm 12.5	<0.001
BMI, kg/m ²	29.3 \pm 4.9	30.8 \pm 5.1	31.7 \pm 4.6	<0.001
Sign/symptoms				
Dyspnea on effort	1,993 (92.3)	1,930 (92.7)	501 (91.8)	0.95
Paroxysmal nocturnal dyspnea	62 (2.9)	78 (3.7)	51 (9.3)	<0.001
Orthopnea	284 (13.1)	436 (20.9)	166 (30.4)	<0.001
Edema	689 (31.9)	855 (41.1)	281 (51.5)	<0.001
Rales	129 (6.0)	168 (8.1)	48 (8.8)	0.003
Third heart sound	32 (1.5)	62 (3.0)	16 (3.0)	0.002
Jugular venous distention	210 (9.8)	327 (15.9)	117 (21.6)	<0.001
Fatigue	1,054 (48.8)	1,065 (51.2)	317 (58.1)	<0.001
MMSE score	27.7 \pm 2.8	27.3 \pm 3.0	27.0 \pm 3.2	<0.001
MMSE score	29 (26-30)	28 (26-29)	28 (26-29)	<0.001
MMSE breakdown				0.004
Cognitive impairment (score \leq 24)	293 (21.5)	305 (24.8)	73 (24.3)	
Borderline cognitive function (score 25-27)	170 (12.5)	192 (15.6)	53 (17.6)	
Normal cognitive function (score \geq 28)	899 (66.0)	735 (59.7)	175 (58.1)	
KCCQ-CSS	78.1 \pm 16.7	69.4 \pm 18.9	60.3 \pm 20.4	<0.001
KCCQ-OSS	76.8 \pm 16.7	68.8 \pm 19.0	59.9 \pm 20.2	<0.001
NYHA functional class				<0.001
I	70 (3.2)	52 (2.5)	15 (2.7)	
II	1,768 (81.7)	1,582 (75.9)	355 (65.0)	
III	319 (14.7)	440 (21.1)	173 (31.7)	
IV	7 (0.3)	9 (0.4)	3 (0.5)	
LVEF, %	57.6 \pm 8.1	57.5 \pm 7.7	57.3 \pm 7.5	<0.001
Duration of HF				<0.001
>0 to 3 months	394 (18.2)	320 (15.4)	59 (10.9)	
>3 to 6 months	308 (14.3)	231 (11.1)	47 (8.7)	
>6 to 12 months	301 (13.9)	256 (12.3)	59 (10.9)	
>1 to 2 y	289 (13.4)	319 (15.3)	71 (13.1)	
>2 to 5 y	427 (19.8)	415 (20.0)	150 (27.7)	
>5 y	442 (20.5)	539 (25.9)	156 (28.8)	
Current or former smoker	773 (36.1)	860 (41.4)	279 (51.3)	<0.001

Continued on the next page

patients and less, if any, benefit in nonfrail patients (Central Illustration).

Secondary outcomes. The effect of sacubitril/valsartan vs valsartan was consistent across FI classes for any of the secondary clinical outcomes examined (Table 2). However, there was a trend toward a greater

reduction in total HF admissions and hospitalizations due to cardiovascular or any causes with sacubitril/valsartan in patients with FI class 3 (most frail). When examined as a continuous variable, there was an interaction between FI and the effect of treatment on total HF admissions ($P_{\text{interaction}} < 0.001$). As with the

TABLE 1 Continued

	FI ≤0.210 (Not Frail) (n = 2,165)	FI 0.211-0.310 (More Frail) (n = 2,084)	FI ≥0.311 (Most Frail) (n = 546)	P Value
Medical history				
Previous MI	297 (13.7)	553 (26.5)	233 (42.7)	<0.001
PCI/CABG	340 (15.7)	668 (32.1)	313 (57.3)	<0.001
Unstable angina	92 (4.2)	176 (8.5)	100 (18.3)	<0.001
History of atrial fibrillation/flutter	990 (45.8)	1,210 (58.1)	361 (66.1)	<0.001
Atrial fibrillation/flutter on ECG at randomization	601 (27.8)	675 (32.4)	164 (30.0)	0.02
Any atrial fibrillation/flutter	996 (46.0)	1,216 (58.4)	363 (66.5)	<0.001
Left bundle branch block	81 (3.7)	128 (6.1)	58 (10.6)	<0.001
Pacemaker	109 (5.0)	229 (11.0)	121 (22.2)	<0.001
Hypertension	2,020 (93.3)	2,023 (97.1)	540 (98.9)	<0.001
Carotid artery disease	47 (2.2)	146 (7.0)	100 (18.5)	<0.001
Stroke	115 (5.3)	267 (12.8)	126 (23.2)	<0.001
Peripheral artery disease	37 (1.7)	123 (5.9)	99 (18.2)	<0.001
Diabetes at randomization	571 (26.4)	1,095 (52.5)	402 (73.6)	<0.001
Hospitalization for HF	945 (43.6)	1,044 (50.1)	317 (58.1)	<0.001
Chronic obstructive pulmonary disease	156 (7.2)	333 (16.0)	181 (33.2)	<0.001
Renal disease	231 (10.7)	656 (31.6)	337 (61.9)	<0.001
Dyslipidemia	1,131 (52.5)	1,349 (64.9)	418 (76.6)	<0.001
Osteoporosis	111 (5.2)	230 (11.2)	81 (15.1)	<0.001
Obstructive sleep apnea	64 (3.0)	168 (8.1)	132 (24.5)	<0.001
Anemia	175 (8.1)	341 (16.4)	191 (35.0)	<0.001
Cancer	122 (5.6)	219 (10.5)	92 (16.9)	<0.001
Treatment				
ACE inhibitor/ARB	1,870 (86.4)	1,814 (87.0)	455 (83.3)	0.27
Beta-blocker	1,703 (78.7)	1,667 (80.0)	450 (82.4)	0.049
Mineralocorticoid receptor antagonist	583 (26.9)	516 (24.8)	140 (25.6)	0.22
Diuretic	2,038 (94.1)	2,010 (96.4)	536 (98.2)	<0.001
Calcium-channel blocker	648 (29.9)	762 (36.6)	230 (42.1)	<0.001
Digoxin	213 (9.8)	203 (9.7)	34 (6.2)	0.046
Nitrate	243 (11.2)	318 (15.3)	138 (25.3)	<0.001
Statin	1,241 (57.3)	1,376 (66.0)	437 (80.0)	<0.001
Antiplatelet	221 (10.2)	308 (14.8)	105 (19.2)	<0.001
Oral anticoagulant	600 (27.7)	746 (35.8)	205 (37.5)	<0.001

Values are mean ± SD, n (%), or median (25th-75th percentile). Mini-Mental State Examination (MMSE) at randomization, N = 2,895.
 ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BMI = body mass index; CABG = coronary artery bypass graft surgery; CSS = Clinical Summary Score; ECG = electrocardiogram; FI = frailty index; HF = heart failure; KCCQ = Kansas City Cardiomyopathy Questionnaire; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NYHA = New York Heart Association; OSS = Overall Summary Score; PCI = percutaneous coronary intervention.

primary outcome, these findings suggest that, compared with valsartan, sacubitril/valsartan might have more benefit in more frail patients and less, if any, benefit in nonfrail patients. There was no interaction between FI as a continuous variable and the effect of treatment on cardiovascular or all-cause mortality ($P_{\text{interaction}} = 0.78$ and 0.74 , respectively).

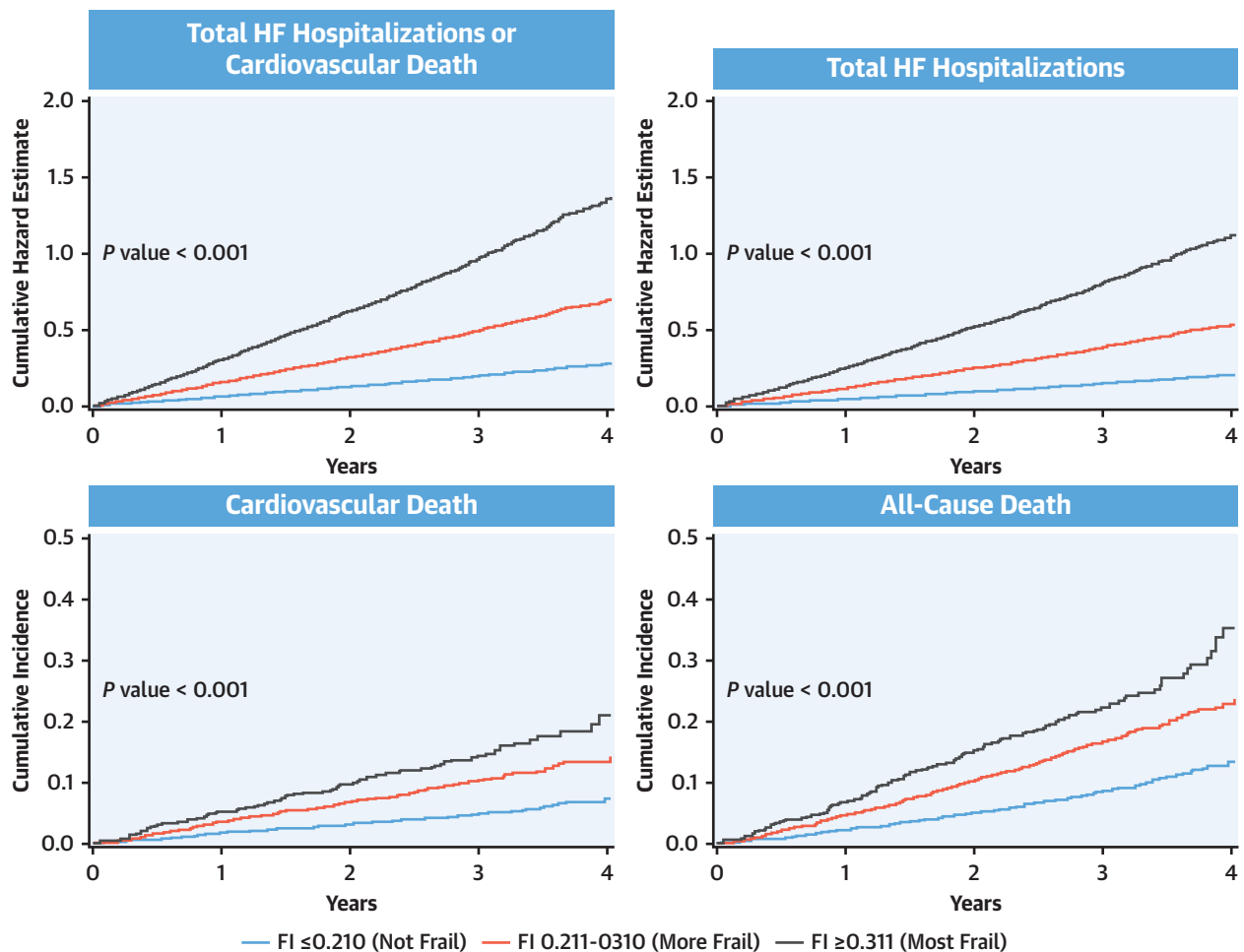
The beneficial effect of sacubitril/valsartan on the change in KCCQ-CSS and NYHA functional class from baseline to 8 months was consistent across FI classes (Table 2).

Overall, MMSE changed little between baseline and 2 years, and the mean difference between treatments in FI classes 1, 2, and 3 was -0.03 (-0.27 to 0.22), 0.02 (-0.27 to 0.33), and -0.14 (-0.88 to 0.59) points, respectively ($P_{\text{interaction}} = 0.96$).

SAFETY ANALYSES. Increasing frailty was associated with an increased risk of adverse events, except for hypotension, which was inversely associated with frailty, and discontinuation of trial treatment (both sacubitril/valsartan and valsartan) (Supplemental Table 4). Notably, greater frailty was associated with a significantly higher risk of falls. However, there was no difference between assigned treatments (sacubitril/valsartan vs valsartan) in terms of adverse events, which were similar across FI classes (Supplemental Table 5).

DISCUSSION

In this post hoc analysis of PARAGON-HF, ~55% of patients were deemed frail, and greater frailty was

FIGURE 1 Outcomes According to the FI

Cumulative hazard estimate for total heart failure (HF) hospitalizations or cardiovascular death, and total HF hospitalizations, and the cumulative incidence of cardiovascular death and all-cause death according to the frailty index (FI). *P* values and 95% CIs have not been adjusted for multiplicity.

associated with more impairment in health status and worse clinical outcomes, including hospitalizations and death. Frailer patients also had more impairment of cognitive function and were more likely to experience falls. There was a greater reduction in the primary composite endpoint, and total HF hospitalizations, with sacubitril/valsartan, compared with valsartan, in the frailest patients. Adverse events, while more frequent in frailer patients, were not more common in those randomized to receive sacubitril/valsartan compared with valsartan.

PREVALENCE OF AND OUTCOMES ACCORDING TO FRAILITY. In the present study, the mean FI using the Rockwood cumulative deficits approach was 0.227. To place these findings in context, an FI ≤ 0.210 is

considered nonfrail, and the mean FI in individuals aged >65 years from the UK Biobank was 0.129.²⁸ In a recent trial conducted in the United States and Australia, comparing aspirin with placebo in 19,114 people aged ≥70 years (≥65 years in U.S. minorities) and free of cardiovascular disease, persistent physical disability, and dementia, the mean FI was 0.11, and 8.1% of patients were categorized as frail.²⁹ This was lower than in other community-based studies, which have reported a mean FI of 0.14 to 0.16, probably due to the trial inclusion and exclusion criteria.^{30,31} In 2 hypertension trials, median FI in patients aged ≥80 years was 0.17 and 0.18, respectively.^{32,33}

The considerably higher FI in our patients with HF, compared with patients in these other studies, suggests that frailty is substantially more common in

patients with HF and that frailty is not confined to the very elderly (the average age of patients in PARAGON-HF was 73 years). However, the FI in PARAGON-HF was lower than in TOPCAT-Americas (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist [in the Americas]), in which the mean FI was 0.37. This may be due to the differences in the components used to create the FI (particularly the inclusion of HF-specific questions from the KCCQ in the TOPCAT analysis).¹¹ Although there are standard criteria for constructing an FI, direct comparison with other trials is difficult given the inclusion of different components, and this highlights the need for a standardized FI in clinical trials of HF.

A unique aspect of this report is the extensive range of biomarkers measured in PARAGON-HF. Chronic low-grade inflammation has been linked with frailty^{34,35} and, consistent with this, we found that the neutrophil/lymphocyte ratio increased with increasing frailty. Interestingly, we also found elevation of biomarkers reflecting collagen turnover in frailer patients and higher concentrations of high-sensitivity troponin T, possibly reflecting ongoing myocyte necrosis and, therefore, a mechanism whereby frailty might be related to progressive worsening of HF over time. A further intriguing find was that the urinary cyclic guanosine monophosphate/creatinine ratio declined with increasing frailty. This ratio reflects tissue responsiveness to natriuretic peptides and may be relevant to the possible interaction between frailty and treatment³⁶ (discussed further later in this section).

In line with previous findings, we found a graded relationship between FI and conventional HF outcomes (HF hospitalizations and cardiovascular death), and we also found associations with broader clinical outcomes (cardiovascular hospitalizations, all-cause hospitalizations, and noncardiovascular death). The associations between FI and hospitalization and death persisted after adjustment for NT-proBNP level and other prognostic variables.^{8,10-14} In particular, greater frailty was strongly associated with a substantial risk of total HF hospitalizations. This finding is not surprising as deterioration in HF and resultant hospitalization represents one of the most common external stressors in these patients, which in turn may lead to progression of frailty, thus creating a vicious cycle.

Importantly, we found an association between FI and other outcomes reflecting loss of homeostatic function such as falls and a decline in kidney function. Indeed, arguably, the biomarker data indicate an association between frailty and not just kidney

dysfunction but also liver (lower albumin) and pancreatic (elevated glycosylated hemoglobin) dysfunction and possibly impaired bone marrow function (erythrocyte anisocytosis, low lymphocyte and platelet counts). We also showed an association between frailty and cognitive function in patients with HFpEF. The latter findings are novel, and we think they validate the cumulative deficit approach as a measure of frailty in HF.

The strong association between frailty status and the wide range of adverse outcomes examined underlines the importance of preventing and treating (even reversing) frailty in HF, which has recently become a key goal in the management of these patients.^{8,37} Targeted interdisciplinary and multifaceted treatment programs, including nutritional, exercise, and other lifestyle interventions, have been investigated for the management of frailty in HF, although specialized comprehensive geriatric assessment may be the most effective intervention of this type.^{20,38,39} Conventional therapies may also be important in reducing the impact of frailty by decreasing risk of HF hospitalization and improving symptoms.^{8,40,41}

TREATMENT EFFECT OF SACUBITRIL/VALSARTAN ACCORDING TO FRAILTY.

There are concerns that the risk-benefit profile of pharmacologic treatments may be less favorable in frail patients, and effective therapies may be underutilized (and even discontinued) in these individuals.^{18,42} However, previous studies investigating the treatment effect of pharmacologic interventions according to frailty status in various settings, including diabetes and hypertension populations, have shown conflicting results.^{32,43}

Regarding HF therapies, the beneficial effects of sacubitril/valsartan on clinical outcomes in patients with HF with reduced ejection fraction were independent of baseline frailty class in PARADIGM-HF (Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure).¹⁰ Similarly, the favorable effects of dapagliflozin in DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure), another trial in HF with reduced ejection fraction, were consistent, irrespective of frailty class, although the improvement in symptom burden, physical function, and quality of life with dapagliflozin appeared even more pronounced in patients with greater frailty.⁴⁴

The efficacy and safety of new therapies according to frailty status have only been investigated once before in patients with HFpEF. In TOPCAT-Americas, the effect of spironolactone, compared with placebo, on cardiovascular death or HF hospitalization (and

TABLE 2 Effects of Sacubitril/Valsartan Compared With Valsartan on Outcomes According to FI

	FI \leq 0.210 (Not Frail) (n = 2,165)		FI 0.211-0.310 (More Frail) (n = 2,084)		FI \geq 0.311 (Most Frail) (n = 546)		P Value for Interaction
	Valsartan (n = 1,081)	Sacubitril/Valsartan (n = 1,084)	Valsartan (n = 1,030)	Sacubitril/Valsartan (n = 1,054)	Valsartan (n = 277)	Sacubitril/Valsartan (n = 269)	
Primary outcome (total HF hospitalizations or cardiovascular death)							0.23
No. of events	211	208	507	485	290	201	
Event rate per 100 person-years (95% CI)	6.7 (5.8 to 7.6)	6.5 (5.7 to 7.5)	17.2 (15.8 to 18.7)	16.0 (14.7 to 17.5)	37.9 (33.8 to 42.5)	26.9 (23.4 to 30.9)	
RR (95% CI) ^a	0.98 (0.76 to 1.27)		0.92 (0.76 to 1.12)		0.69 (0.51 to 0.95)		
Primary outcome and urgent HF visits							0.31
No. of events	227	216	531	505	305	213	
Event rate per 100 person-years (95% CI)	7.2 (6.3 to 8.2)	6.8 (5.9 to 7.7)	18.0 (16.5 to 19.6)	16.7 (15.3 to 18.2)	39.8 (35.6 to 44.6)	28.5 (24.9 to 32.6)	
RR (95% CI) ^a	0.95 (0.73 to 1.22)		0.92 (0.76 to 1.11)		0.70 (0.51 to 0.96)		
Total HF hospitalizations							0.16
No. of events	158	152	390	379	248	159	
Event rate per 100 person-years (95% CI)	5.0 (4.3 to 5.8)	4.8 (4.1 to 5.6)	13.2 (12.0 to 14.6)	12.5 (11.3 to 13.9)	32.4 (28.6 to 36.7)	21.3 (18.2 to 24.8)	
RR (95% CI) ^a	0.95 (0.71 to 1.29)		0.93 (0.75 to 1.16)		0.64 (0.45 to 0.91)		
Total cardiovascular hospitalizations							0.10
No. of events	469	511	786	778	414	314	
Event rate per 100 person-years (95% CI)	14.8 (13.5 to 16.2)	16.0 (14.7 to 16.5)	26.6 (24.8 to 28.6)	25.7 (24.0 to 27.6)	54.1 (49.1 to 59.5)	42.0 (37.6 to 46.9)	
RR (95% CI) ^a	1.08 (0.91 to 1.29)		0.96 (0.82 to 1.11)		0.77 (0.60 to 0.99)		
Total all-cause hospitalizations							0.13
No. of events	985	1,032	1,655	1,631	820	652	
Event rate per 100 person-years (95% CI)	31.1 (29.2 to 33.1)	32.4 (30.5 to 34.4)	56.1 (53.5 to 58.9)	53.9 (51.4 to 56.6)	107.1 (100.0 to 114.7)	87.2 (80.8 to 94.2)	
RR (95% CI) ^a	1.04 (0.91 to 1.19)		0.95 (0.85 to 1.07)		0.81 (0.67 to 0.99)		
Cardiovascular death							0.69
n (%)	53 (4.9)	56 (5.2)	117 (11.4)	106 (10.1)	42 (15.2)	42 (15.6)	
Event rate per 100 person-years (95% CI)	1.7 (1.3 to 2.2)	1.8 (1.4 to 2.3)	4.0 (3.3 to 4.7)	3.5 (2.9 to 4.2)	5.5 (4.0 to 7.4)	5.6 (4.1 to 7.6)	
HR (95% CI) ^a	1.06 (0.73 to 1.54)		0.88 (0.68 to 1.15)		1.01 (0.66 to 1.56)		
Noncardiovascular death							0.93
n (%)	42 (3.9)	42 (3.9)	68 (6.6)	73 (6.9)	26 (9.4)	23 (8.6)	
Event rate per 100 person-years (95% CI)	1.3 (1.0 to 1.8)	1.3 (1.0 to 1.8)	2.3 (1.8 to 2.9)	2.4 (1.9 to 3.0)	3.4 (2.3 to 5.0)	3.1 (2.0 to 4.6)	
HR (95% CI) ^a	1.00 (0.65 to 1.53)		1.03 (0.74 to 1.43)		0.92 (0.52 to 1.63)		
All-cause death							0.89
n (%)	95 (8.8)	98 (9.0)	185 (18.0)	179 (17.0)	68 (24.5)	65 (24.2)	
Event rate per 100 person-years (95% CI)	3.0 (2.4 to 3.7)	3.1 (2.5 to 3.7)	6.3 (5.4 to 7.2)	5.9 (5.1 to 6.8)	8.9 (7.0 to 11.3)	8.7 (6.8 to 11.1)	
HR (95% CI) ^a	1.03 (0.78 to 1.37)		0.94 (0.76 to 1.15)		0.98 (0.69 to 1.38)		
First HF hospitalization or cardiovascular death							0.22
n (%)	149 (13.8)	152 (14.0)	283 (27.5)	276 (26.2)	124 (44.8)	98 (36.4)	
Event rate per 100 person-years (95% CI)	4.9 (4.2 to 5.8)	5.0 (4.3 to 5.9)	10.8 (9.6 to 12.1)	10.2 (9.0 to 11.4)	20.4 (17.1 to 24.4)	15.3 (12.6 to 18.7)	
HR (95% CI) ^a	1.01 (0.81 to 1.27)		0.93 (0.79 to 1.10)		0.73 (0.56 to 0.95)		
First HF hospitalization							0.13
n (%)	106 (9.8)	112 (10.3)	222 (21.6)	215 (20.4)	104 (37.5)	78 (29.0)	
Event rate per 100 person-years (95% CI)	3.5 (2.9 to 4.3)	3.7 (3.1 to 4.4)	8.4 (7.4 to 9.6)	7.9 (6.9 to 9.1)	17.1 (14.1 to 20.8)	12.2 (9.8 to 15.2)	
HR (95% CI) ^a	1.05 (0.80 to 1.37)		0.93 (0.77 to 1.12)		0.68 (0.51 to 0.92)		

Continued on the next page

TABLE 2 Continued

	FI ≤0.210 (Not Frail) (n = 2,165)		FI 0.211-0.310 (More Frail) (n = 2,084)		FI ≥0.311 (Most Frail) (n = 546)		P Value for Interaction
	Valsartan (n = 1,081)	Sacubitril/Valsartan (n = 1,084)	Valsartan (n = 1,030)	Sacubitril/Valsartan (n = 1,054)	Valsartan (n = 277)	Sacubitril/Valsartan (n = 269)	
Renal composite outcome							0.51
n (%)	14 (1.3)	5 (0.5)	38 (3.7)	24 (2.3)	12 (4.3)	4 (1.5)	
Event rate per 100 person-years (95% CI)	0.4 (0.3 to 0.7)	0.2 (0.1 to 0.4)	1.3 (0.9 to 1.8)	0.8 (0.5 to 1.2)	1.6 (0.9 to 2.8)	0.5 (0.2 to 1.4)	
HR (95% CI) ^a	0.36 (0.13 to 0.99)		0.59 (0.36 to 0.99)		0.37 (0.12 to 1.15)		
Change in KCCQ-CSS from baseline to 8 months							0.54
Mean change in KCCQ-CSS	-1.94 (0.49)	-1.66 (0.49)	-3.63 (0.61)	-1.43 (0.61)	-1.49 (1.22)	-1.62 (1.20)	
Mean difference in KCCQ-CSS ^b	0.28 (-1.08 to 1.64)		2.20 (0.50 to 3.89)		-0.13 (-3.51 to 3.24)		
≥5-point increase in KCCQ-CSS							0.37
Proportion of patients	298 (28.8)	304 (29.5)	276 (28.9)	348 (35.8)	84 (35.6)	91 (36.7)	
OR (95% CI) ^b	1.11 (0.78 to 1.57)		1.60 (1.18 to 2.18)		1.07 (0.58 to 1.98)		
Change in NYHA functional class from baseline to 8 months							0.89
Improved, n (%)	144 (13.6)	168 (15.9)	115 (11.7)	146 (14.5)	30 (11.6)	33 (12.9)	
Worsened, n (%)	62 (5.9)	64 (6.1)	114 (11.6)	97 (9.7)	45 (17.4)	41 (16.0)	
Unchanged, n (%)	851 (80.5)	823 (78.0)	758 (76.8)	762 (75.8)	183 (70.9)	182 (71.1)	
OR for improvement (95% CI) ^c	1.51 (0.91 to 2.51)		1.69 (0.98 to 2.91)		1.23 (0.46 to 3.29)		

P values and 95% CIs have not been adjusted for multiplicity. ^aStratified by region. ^bAdjusted for region, baseline KCCQ-CSS, visit, and treatment-by-visit interaction. ^cAdjusted for region, baseline NYHA functional class, visit, and treatment-by-visit interaction.
 RR = rate ratio; other abbreviations as in Table 1.

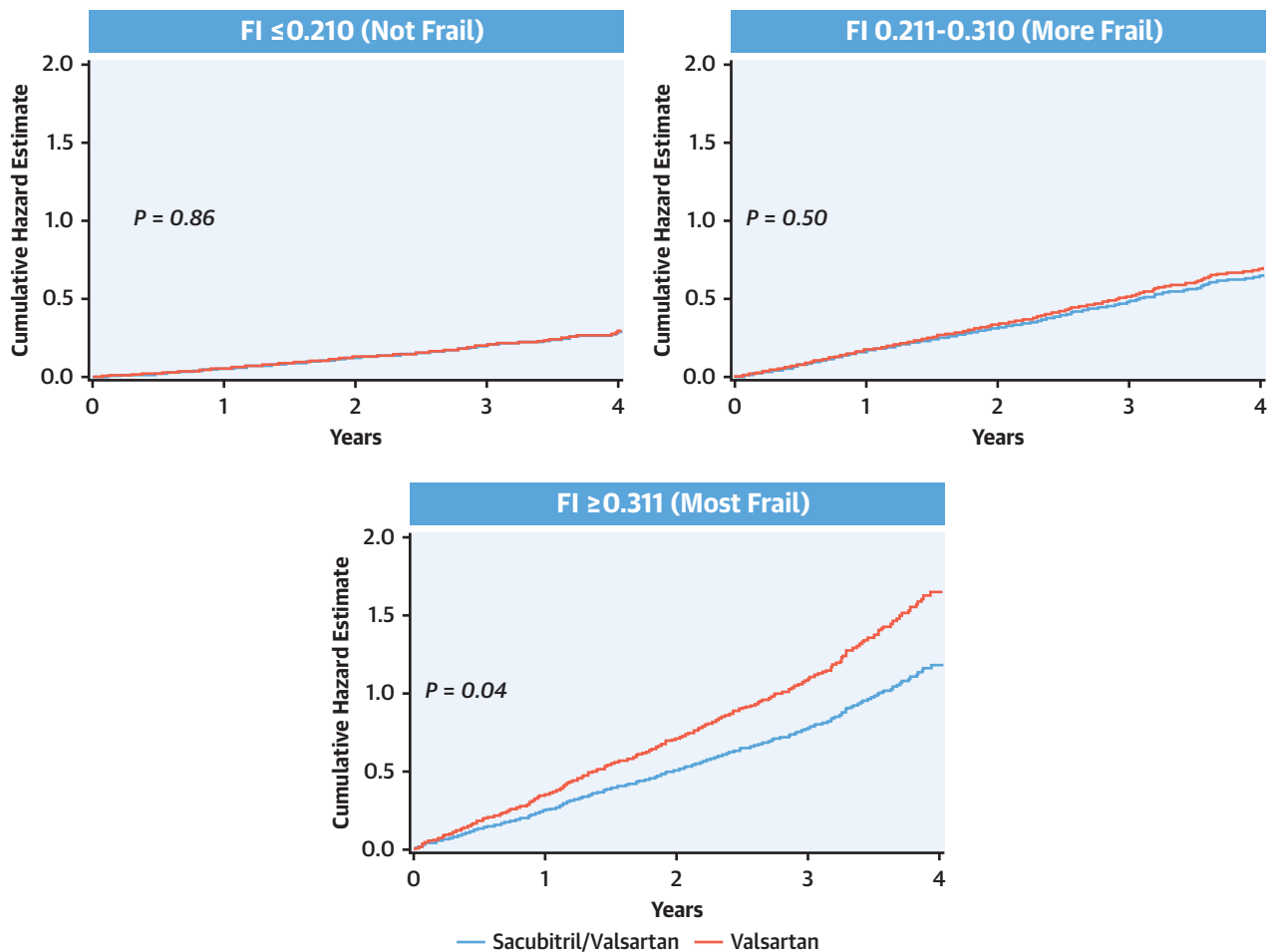
each of these individually) was not modified by frailty class.¹¹ Similarly, there was no statistically significant interaction between frailty and the effects of sacubitril/valsartan, compared with valsartan, for any of the outcomes assessed in our categorical analysis of PARAGON-HF. However, in the statistically more powerful analysis of FI as a continuous variable, sacubitril/valsartan seemed to be more effective in frailer patients. The lower baseline urinary cyclic guanosine monophosphate/creatinine ratio in more frail patients adds some biological plausibility to this finding. A substantial reduction in hospitalizations with sacubitril/valsartan in the most vulnerable individuals, if true, is of considerable potential importance given the reluctance of clinicians to introduce medications in patients perceived to be frail and the likely role of hospital admission in accelerating frailty.^{8,15-17}

Improving “health-related quality of life” or health status is a key goal of the management of patients with HF, especially in the frailest patients, who have a markedly greater symptom burden, more physical limitations, and worse quality of life than nonfrail patients, as clearly shown in the present study.^{10,11,14,37} Frailty status did not modify the beneficial effects of sacubitril/valsartan, compared with valsartan, on the change in KCCQ-CSS and

NYHA functional class. These findings are important because symptom control and maintenance of physical function may help prevent frailty and the progression of existing frailty.^{8,45}

Due to a greater comorbidity burden, polypharmacy, and reduced tolerance to treatments, frail patients may experience more adverse drug reactions and be more likely to discontinue treatment.^{8,10,15-17} In keeping with this, we found a strong and graded relationship between FI and adverse events (except hypotension) and discontinuation of randomized trial treatment (both sacubitril/valsartan and valsartan). Reassuringly, none of the prespecified adverse events, falls and fractures, or discontinuation of trial therapy were more common in the sacubitril/valsartan group, compared with the valsartan group, in any frailty class. Taken together, these data underline the safety and tolerability of sacubitril/valsartan, irrespective of frailty class.

STUDY LIMITATIONS. This was a post hoc analysis. We were not able to test other types of frailty scores due to the lack of tests of muscle strength and functional capacity in PARAGON-HF. The prespecified inclusion and exclusion criteria precluded the enrollment of very-high-risk patients, and trial participants may be less frail than the general HFpEF

FIGURE 2 Effects of Sacubitril/Valsartan and Valsartan According to the FI

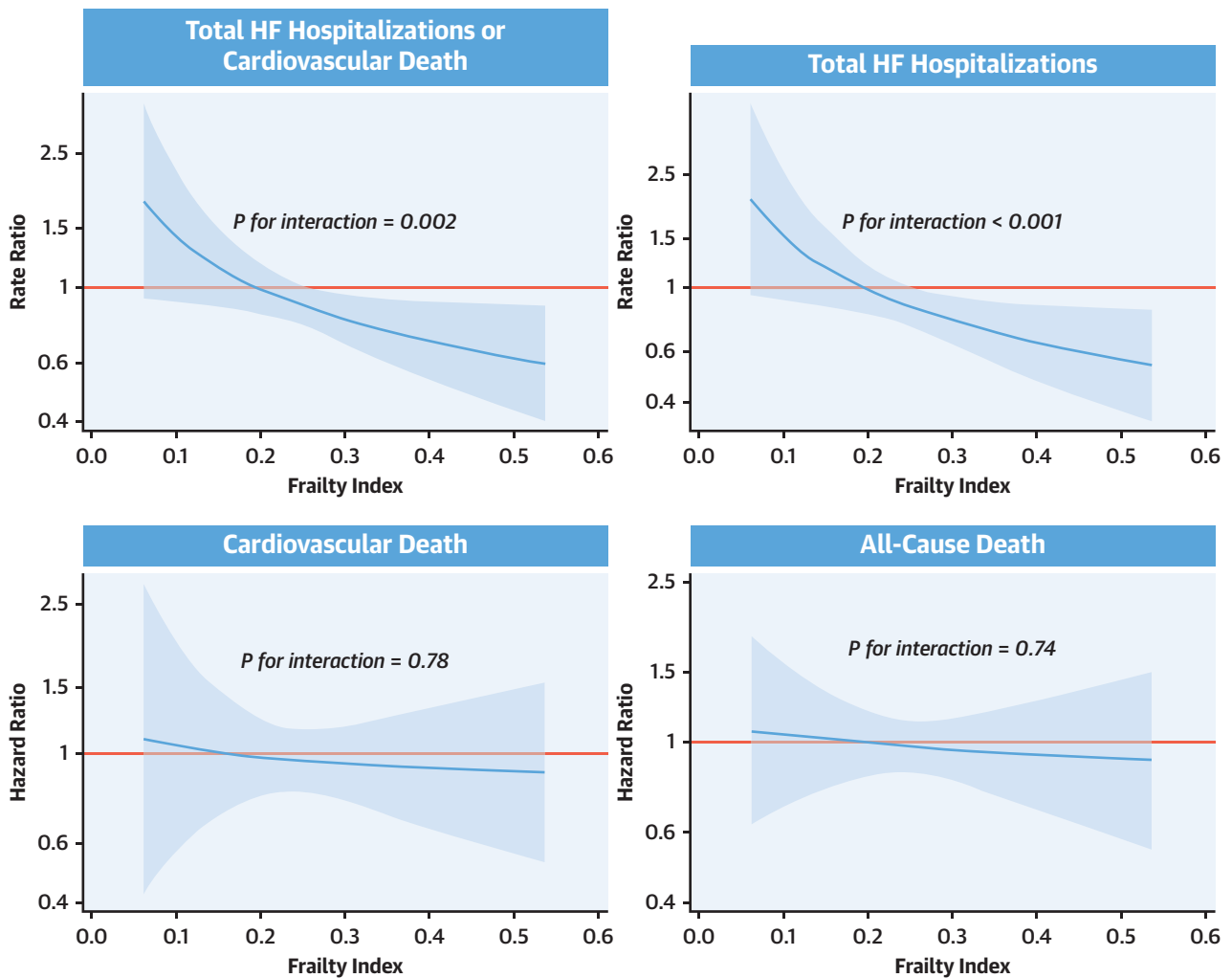
Cumulative hazard estimate for total heart failure hospitalizations or cardiovascular death in the sacubitril/valsartan and valsartan arm, respectively, according to the frailty index (FI). *P* values and 95% CIs have not been adjusted for multiplicity.

population. Thus, patients enrolled in clinical trials may not be fully representative of the general HFpEF population, which might affect the generalizability of our results. For example, the slight male preponderance of frailty we observed is not consistent with the view that the prevalence of frailty is generally higher in women, and we did not find that a higher FI was associated with underuse of medical therapy, which is usually expected in relation to frailty. Although most of the endpoints examined in the present study were prespecified, the large number of outcomes likely increases the risk of type I error. Finally, measures related to quality of life, activities of daily living, and physical function were under-represented in our FI.

CONCLUSIONS

In PARAGON-HF, greater frailty was associated with more impairment of health status and cognitive function and worse clinical outcomes. There seemed to be a greater reduction in the primary outcome and HF hospitalizations with sacubitril/valsartan, compared with valsartan, with increasing frailty when FI was analyzed as a continuous variable, although this was not significant when FI was examined as a categorical variable. Adverse events were not more common in individuals randomized to receive sacubitril/valsartan compared with valsartan, irrespective of frailty class. Therefore, the risk-benefit balance related to frailty may be more

CENTRAL ILLUSTRATION Effects of Sacubitril/Valsartan Compared With Valsartan According to the Frailty Index



Butt JH, et al. *J Am Coll Cardiol.* 2022;80(12):1130-1143.

Fractional polynomial analysis showing the effect of sacubitril/valsartan vs valsartan across the range of the frailty index. HF = heart failure.

favorable than expected. These findings challenge the common reluctance of clinicians to introduce new therapies to patients who are perceived to be frail because of doubts about the benefit of treatments in these patients. More education is needed about the importance of frailty, its assessment, and implications in cardiology.

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ADDRESS FOR CORRESPONDENCE: Dr John J.V. McMurray, British Heart Foundation Cardiovascular Research Centre, University of Glasgow, 126 University Place, Glasgow G12 8TA, United Kingdom. E-mail: john.mcmurray@glasgow.ac.uk.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In patients with heart failure and preserved left ventricular ejection fraction (HFpEF), increasing frailty is associated with a greater reduction in the composite outcome of cardiovascular death or heart failure hospitalization with sacubitril/valsartan compared to valsartan without the neprilysin inhibitor.

TRANSLATIONAL OUTLOOK: Future studies should seek to delineate the factors contributing to frailty in patients with HFpEF that respond favorably to treatment of heart failure.

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APPENDIX For supplemental tables and a figure, please see the online version of this paper.