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Finerenone According to Frailty in Heart Failure
A Prespecified Analysis of the FINEARTS-HF Randomized Clinical Trial

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IMPORTANCE Patients with frailty are often perceived to have a less favorable benefit-risk profile for novel therapies and therefore may be less likely to receive these.

OBJECTIVE To examine the efficacy and safety of finerenone, compared with placebo, according to frailty status in patients with heart failure (HF) and mildly reduced ejection fraction (HFmrEF) or with HF and preserved ejection fraction (HFpEF).

DESIGN, SETTING, AND PARTICIPANTS This was a prespecified secondary analysis of a phase 3 randomized clinical trial, the Finerenone Trial to Investigate Efficacy and Safety Superior to Placebo in Patients With Heart Failure (FINEARTS-HF), conducted across 653 sites in 37 countries. Patients with HF with New York Heart Association functional class II through IV, a left ventricular ejection fraction of 40% or higher, evidence of structural heart disease, and elevated natriuretic peptide levels were randomized between September 2020 and January 2023. Data analysis was conducted from October 1 to November 30, 2024.

INTERVENTION Addition of once-daily finerenone or placebo to usual therapy.

MAIN OUTCOMES AND MEASURES The primary outcome was a composite of cardiovascular death and total worsening HF events. Frailty was measured using the Rockwood cumulative deficit approach.

RESULTS Of the 6001 patients randomized in FINEARTS-HF, a frailty index (FI) was calculable in 5952 patients (mean [SD] age, 72.0 [9.6] years; 3241 [54.4%] male). In total, 1588 patients (26.7%) had class I frailty (FI ≤0.210 [not frail]), 2141 (36.0%) had class II frailty (FI 0.211-0.310 [more frail]), and 2223 (37.3%) had class III frailty (FI ≥0.311 [most frail]). Compared with patients with class I frailty, those with class II and III frailty had a higher risk of the primary outcome (unadjusted rate ratio [RR], 1.88 [95% CI, 1.54-2.28] for class II and 3.86 [95% CI, 3.22-4.64] for class III). The effect of finerenone on the primary outcome did not vary significantly by frailty class (class I: RR, 1.07 [95% CI, 0.77-1.49]; class II: RR, 0.66 [95% CI, 0.52-0.83]; class III: RR, 0.91 [95% CI, 0.76-1.07]; *P* for interaction = .77). Frailty class did not modify the effects of finerenone on the components of the primary outcome, all-cause death, or improvement in the Kansas City Cardiomyopathy Questionnaire total symptom score. The effects of finerenone, compared with placebo, on experiencing hypotension, elevated creatinine level, hyperkalemia, or hypokalemia did not differ by frailty class.

CONCLUSIONS AND RELEVANCE In FINEARTS-HF, finerenone reduced the risk of total worsening HF events and cardiovascular death, and it improved symptoms; these effects were not modified by frailty status. In addition, the effects of finerenone on experiencing hypotension, elevated creatinine level, hyperkalemia, or hypokalemia did not differ by frailty status.

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Supplemental content

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Despite sharing pathophysiological mechanisms, frailty and heart failure (HF) are 2 distinct yet commonly associated conditions, and each increases the likelihood and complicates the course of the other.[1-6] The imbalance between the anabolic and catabolic states in HF may accelerate the development of frailty, and frailty is up to 6 times more common in individuals with HF than in the general population.[1-5] The presence of frailty in patients with HF is associated with a substantially higher risk of functional decline, hospital admissions, and death.[5,7-15]

There has been increasing interest in investigating the efficacy and safety of new HF treatments according to frailty status due to concerns that individuals with frailty obtain less benefit from evidence-based therapies, have more treatment intolerance, experience more adverse drug reactions and drug interactions, and are more likely to discontinue treatment than nonfrail patients.[5,16-18] Thus, clinicians may be more reluctant to initiate new therapies in these individuals due to anticipation of a less favorable benefit-risk profile in patients with frailty. However, this assumption is contrary to a growing body of evidence demonstrating that certain pharmacological therapies and aerobic exercise training may reduce the risk of worsening HF events and improve symptom burden and quality of life to a greater extent in frail individuals with HF than in nonfrail HF patients.[7,8,12-15,19-23]

In the Finerenone Trial to Investigate Efficacy and Safety Superior to Placebo in Patients With Heart Failure (FINEARTS-HF), the nonsteroidal mineralocorticoid receptor antagonist (MRA) finerenone reduced the risk of the primary composite outcome of cardiovascular death and total HF events and improved health-related quality of life in 6001 patients with HF with mildly reduced ejection fraction (HFmrEF) or HF with preserved ejection fraction (HFpEF).[24] In this prespecified secondary analysis, we examined the efficacy and safety of finerenone according to frailty status using the Rockwood cumulative deficit approach.

Key Points

Question Is finerenone, a nonsteroidal mineralocorticoid receptor antagonist, a safe and effective therapy in patients with heart failure (HF) with mildly reduced ejection fraction (HFmrEF) or HF with preserved ejection fraction (HFpEF), regardless of frailty status?

Findings In this prespecified secondary analysis of patients with HFmrEF or HFpEF in the Finerenone Trial to Investigate Efficacy and Safety Superior to Placebo in Patients With Heart Failure (FINEARTS-HF), frailty was common, and greater frailty was associated with more impairment in health status and worse clinical outcomes, including worsening HF events, hospitalizations, and death. Compared with placebo, finerenone reduced the risk of worsening HF events and cardiovascular deaths and improved symptoms in patients with HFmrEF or HFpEF across the range of frailty studied.

Meaning The favorable benefit-risk balance associated with frailty for finerenone should challenge any clinical reluctance to introduce this new treatment in patients considered to be frail.

Methods

FINEARTS-HF was a randomized, double-blind, placebo-controlled clinical trial in patients with symptomatic HFmrEF or HFpEF, investigating the efficacy and safety of finerenone compared with matching placebo in addition to usual therapy. The design, baseline characteristics, and primary results of FINEARTS-HF have been published.[24-26] The trial protocol (Supplement 1) was approved by the ethics committee at all participating institutions, and all patients provided written informed consent. Data analysis was conducted from October 1 to November 30, 2024. This study follows the Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines.

Trial Patients

Key inclusion criteria were age 40 years or older, diuretic treatment for at least 30 days before randomization, New York Heart Association (NYHA) class II through IV, left ventricular ejection fraction (LVEF) of at least 40%, evidence of structural heart disease, and elevated natriuretic peptide levels. Key exclusion criteria were estimated glomerular filtration rate (eGFR) less than 25 mL/min/1.73 m^2 or potassium level higher than 5.0 mEq/L (to convert to millimoles per liter, multiply by 1). A complete list of exclusion criteria is provided in the design article.[26] Race was self-reported and included the following categories: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, or not reported.

Eligible participants were randomized in a 1:1 ratio to finerenone or matching placebo (eFigure 1 in Supplement 2). Participants with an eGFR of 60 mL/min/1.73 m^2 or lower started 10 mg once daily with a maximum maintenance dose of 20 mg once daily, whereas participants with an eGFR higher than 60 mL/min/1.73 m^2 started 20 mg once daily with a maximum maintenance dose of 40 mg once daily.

Frailty Index

Frailty was assessed using the Rockwood cumulative deficit approach, and this approach has been described in detail previously.[7,8,12-15,27-29] Standard criteria for constructing a frailty index (FI) using this approach are the following: at least 30 items are required; items must be associated with health status; items must cover a range of body systems and not be isolated to 1 system; and items must not be part of normal aging or saturate too early (eg, presbyopia), but they should generally increase with age. We created a 50-item FI, and these items were derived from medical history, vital signs, laboratory data, the EQ-5D questionnaire, and the Kansas City Cardiomyopathy Questionnaire (KCCQ) (eTable 1 in Supplement 2). A score was assigned for each nonmissing item, and the FI score was calculated as the sum of these scores divided by the total number of nonmissing items, with higher scores indicating greater frailty. Binary variables (eg, history of sleep apnea) were scored as 0 or 1 (absent or present); ordinal variables (eg, quality-of-life measures) were scored from 0 to 1 in increments of 0.20 or 0.25, with a score of 1 indicating the greatest severity; and

continuous variables (eg, hemoglobin level) were categorized and scored as 0 or 1 (normal or abnormal). Patients with at least 20% missing items were excluded.[7,8,13,14,30-32] Patients were divided into the following 3 subgroups: FI of 0.210 or less (FI class I, nonfrail patients); FI of 0.211 to 0.310 (FI class II, more frail patients), and FI of 0.311 or higher (FI class III, most frail patients). An FI of 0.210 or less is generally considered not frail.[7,8,13,14,30-32] An FI of 0.310 was selected as the cutoff to classify patients as more and most frail because it has been used in frailty analyses of other HF trials, allowing a comparison between FINEARTS-HF and prior HF reports.

Trial Outcomes

The primary outcome in FINEARTS-HF was a composite of cardiovascular death and total (first and recurrent) HF events (HF hospitalization or urgent HF visit). The secondary outcomes were total (first and recurrent) HF events; improvement in NYHA class from baseline to 12 months; change in the KCCQ total symptom score (TSS) from baseline to 6, 9, and 12 months; composite kidney end point (defined as sustained decrease in eGFR ≥50% relative to baseline over ≥4 weeks, sustained eGFR decline <15 mL/min/1.73 m^2, or initiation of dialysis or kidney transplantation); and all-cause death. All deaths and potential primary nonfatal events were adjudicated by an independent clinical events committee. The composite kidney outcome was not explored further in the present analysis because there were few events overall. Noncardiovascular death, total (first and recurrent) hospitalizations for any reasons, and change in the KCCQ overall summary score (OSS) and KCCQ clinical summary score (CSS) were also examined in the present analysis.

Prespecified safety analyses included hyperkalemia, hypokalemia, hypotension, and elevations in serum creatinine levels. Safety analyses were performed only in patients who had received at least 1 dose of either finerenone or placebo.

Statistical Analysis

Baseline characteristics were summarized as frequencies with percentages, means with SDs, or medians with IQRs. Differences in baseline characteristics were tested 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 nonnormally and normally distributed continuous variables, respectively.

The association between frailty class and clinical outcomes was evaluated using Cox proportional hazards models for time-to-event data and semiparametric proportional rates models for total (first and recurrent) events.[33] Hazard ratios (HRs) and rate ratios (RRs), respectively, were stratified according to geographic region and LVEF stratification (<60% vs ≥60%) and adjusted for treatment assignment, age, sex, body mass index (BMI), log of N-terminal pro-B-type natriuretic peptide (NT-proBNP), LVEF, NYHA class, and prior HF hospitalization. Variables that were part of the FI were not adjusted for because the categorization of FI into the 3 frailty classes was conditioned on these variables.

To compare the effects of finerenone vs placebo on clinical outcomes according to frailty class, time-to-event data and total events were evaluated with Cox proportional hazards models and semiparametric proportional rates models, respectively; these models were stratified according to geographic region and LVEF stratification. The effect of finerenone vs placebo across the range of FI as a continuous variable was modeled using Poisson regression models adjusted for treatment and a restricted cubic spline of FI with 3 knots, using robust SEs and observed follow-up time as an offset term. Absolute rates (per 100 person-years) and differences were estimated across the range of FI using marginal predictions from this model under both treatment assignments.

The proportion of patients with improvement in NYHA class from baseline to 12 months was analyzed using a logistic regression model, adjusted for geographic region and LVEF stratification. Odds ratios (ORs) were reported.

The change in KCCQ scores from baseline to 12 months was summarized as mean and SD within each subgroup at 12 months. The effect of finerenone vs placebo on the change in KCCQ scores from baseline to 12 months was estimated using a linear regression model within each subgroup, adjusted for baseline KCCQ scores, geographic region, and LVEF stratification.

All analyses were conducted using SAS version 9.4 (SAS Institute Inc) and Stata version 17.0 (StataCorp LLC) statistical software. Two-tailed $P < .05$ was considered statistically significant.

Results

Of the 6001 patients randomized in FINEARTS-HF, an FI was calculable for 5952 patients (mean [SD] age, 72.0 [9.6] years; 3241 [54.4%] male). The numbers of patients with missing data for individual components of the FI are shown in eTable 2 and eTable 3 in Supplement 2. The mean (SD) FI was 0.284 (0.104), and the median FI was 0.274 (IQR, 0.207-0.353; range, 0.033-0.633) (eFigure 2 in Supplement 2). In total, 1588 patients (26.7%) had class I frailty (FI ≤0.210; not frail), 2141 (36.0%) had class II frailty (FI 0.211-0.310; more frail), and 2223 (37.3%) had class III frailty (FI ≥0.311; most frail).

Patient Characteristics According to Frailty

Compared with patients with a lower FI (the least frail), those with a higher FI (the frailest) were older, more often female, more often White, less often Asian, and more likely to have cardiovascular and noncardiovascular comorbidities (**Table 1**). They also had higher systolic blood pressure, heart rate, BMI, NT-proBNP level (irrespective of atrial fibrillation on electrocardiography), and urinary albumin to creatinine ratio and lower eGFR. Patients with a higher FI were more likely to have a higher LVEF and worse NYHA functional class and KCCQ scores than those with a lower FI.

Regarding pharmacological therapy at baseline, patients with a higher FI were more frequently treated with an angiotensin-receptor blocker (ARB), β-blocker, sodium-glucose cotransporter 2 (SGLT2) inhibitor, loop diuretic, and lipid-lowering drug but less often with angiotensin receptor-neprilysin inhibitor (ARNI) compared with those with a lower FI.

Table 1. Baseline Characteristics According to Frailty Index (FI) Class

Characteristic	FI class			*P* value
	I, Not frail (n = 1588)	II, More frail (n = 2141)	III, Most frail (n = 2223)	
Age, mean (SD), y	69.4 (10.2)	72.3 (9.5)	73.5 (9.0)	<.001
Sex, No. (%)				
Men	987 (62.2)	1193 (55.7)	1061 (47.7)	<.001
Women	601 (37.8)	948 (44.3)	1162 (52.3)	
Race, No. (%)[a]				
Asian	459 (28.9)	364 (17.0)	169 (7.6)	<.001
Black	21 (1.3)	26 (1.2)	40 (1.8)	
White	1043 (65.7)	1684 (78.7)	1965 (88.4)	
Other	65 (4.1)	67 (3.1)	49 (2.2)	
Geographic region, No. (%)				
Asia	455 (28.7)	360 (16.8)	164 (7.4)	<.001
Eastern Europe	602 (37.9)	992 (46.3)	1044 (47.0)	
Latin America	207 (13.0)	216 (10.1)	212 (9.5)	
North America	84 (5.3)	154 (7.2)	224 (10.1)	
Western Europe, Oceania, and others	240 (15.1)	419 (19.6)	579 (26.0)	
Physiological measures				
Blood pressure, mean (SD), mm Hg				
Systolic	126.3 (14.8)	129.7 (14.7)	131.3 (16.0)	<.001
Diastolic	75.6 (9.5)	75.9 (10.3)	74.9 (11.0)	.02
Pulse pressure, mean (SD), mm Hg	50.7 (12.9)	53.8 (13.2)	56.4 (14.7)	<.001
Heart rate, mean (SD), bpm	70.7 (11.7)	71.0 (11.7)	72.4 (12.0)	<.001
BMI, median (IQR)	27.0 (24.1-31.2)	28.9 (25.5-32.8)	31.2 (27.2-35.7)	<.001
Left bundle branch block on ECG, No (%)	52 (3.3)	80 (3.7)	103 (4.6)	.03
Smoking status, No. (%)				
Never	953 (60.0)	1336 (62.4)	1382 (62.2)	<.001
Former	459 (28.9)	646 (30.2)	670 (30.1)	
Current	176 (11.1)	159 (7.4)	171 (7.7)	
LVEF, %				
Mean (SD)	52.0 (8.0)	52.7 (7.7)	52.9 (7.8)	.001
No. (%)				
<50	655 (41.3)	751 (35.1)	750 (33.8)	<.001
50-59	653 (41.1)	983 (46.0)	1011 (45.6)	
≥60	279 (17.6)	404 (18.9)	458 (20.6)	
NYHA class, No. (%)				
II	1381 (87.0)	1632 (76.3)	1105 (49.7)	<.001
III	203 (12.8)	505 (23.6)	1084 (48.8)	
IV	4 (0.3)	3 (0.1)	34 (1.5)	
KCCQ score, mean (SD)				
TSS	87.9 (11.5)	72.2 (17.4)	47.3 (20.4)	<.001
CSS	85.6 (11.3)	70.6 (15.7)	46.0 (18.2)	<.001
OSS	82.8 (11.3)	68.0 (15.4)	43.5 (17.8)	<.001
Biomarkers				
NT-proBNP, median (IQR), pg/mL	827 (372-1514)	980 (434-1828)	1298 (560-2497)	<.001
Atrial fibrillation or flutter on ECG	1499 (1117-2255)	1634 (1075-2548)	1989 (1303-3339)	<.001
No atrial fibrillation or flutter on ECG	506 (272-994)	560 (302-1168)	735 (362-1629)	<.001
Creatinine, mean (SD), mg/dL	1.01 (0.26)	1.11 (0.38)	1.23 (0.39)	<.001
eGFR, mL/min/1.73 m^2				
Mean (SD)	70.3 (18.2)	62.7 (18.8)	55.7 (19.4)	<.001
No. (%)				
≥60	1134 (71.4)	1128 (52.7)	824 (37.1)	<.001
<60	454 (28.6)	1013 (47.3)	1399 (62.9)	
Sodium, mean (SD), mEq/L	140.8 (2.6)	140.8 (2.9)	140.4 (3.4)	<.001
Potassium, mean (SD), mEq/L	4.4 (0.4)	4.4 (0.5)	4.4 (0.5)	.15
Hemoglobin, mean (SD), g/dL	13.9 (1.4)	13.5 (1.6)	13.0 (1.7)	<.001

(continued)

Table 1. Baseline Characteristics According to Frailty Index (FI) Class (continued)

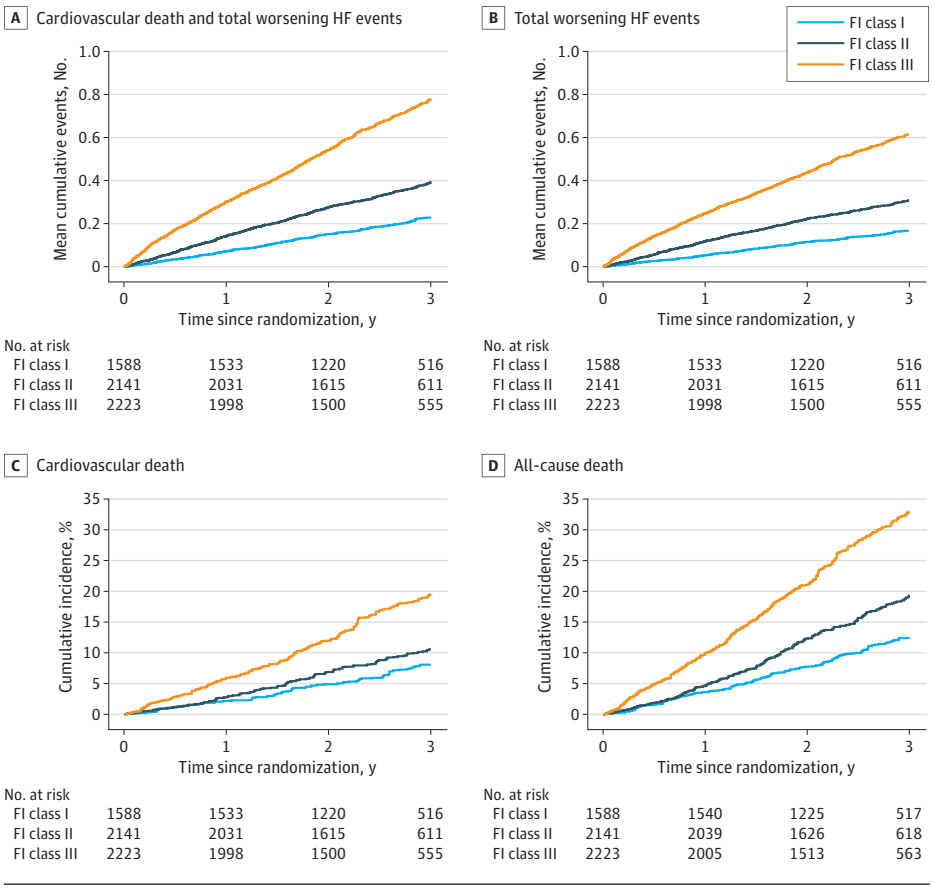
Characteristic	FI class			*P* value
	I, Not frail (n = 1588)	II, More frail (n = 2141)	III, Most frail (n = 2223)	
Alanine aminotransferase, mean (SD), U/L	20.8 (15.1)	20.6 (13.1)	20.6 (13.1)	.73
Total bilirubin, mean (SD), mg/dL	0.6 (0.3)	0.6 (0.4)	0.6 (0.4)	.36
Alkaline phosphatase, mean (SD), U/L	80.7 (27.1)	84.2 (31.5)	91.5 (39.5)	<.001
Blood urea nitrogen, mean (SD), mg/dL	19.3 (6.4)	22.0 (8.7)	25.8 (11.2)	<.001
Platelet count, mean (SD), $\times 10^3/\mu L$	215.6 (58.5)	217.0 (66.3)	225.7 (76.3)	<.001
White blood cell count, mean (SD), /μL	6500 (1700)	6800 (2800)	7300 (6200)	<.001
Hemoglobin A_{1c}, mean (SD), % of total hemoglobin	6.1 (0.9)	6.4 (1.1)	6.7 (1.3)	<.001
Urine albumin to creatinine ratio, mg/g				
Median (IQR)	10.0 (5.0-25.0)	17.0 (6.5-54.5)	36.0 (10.7-146.0)	<.001
No. (%)				
<30	1197 (78.0)	1327 (63.7)	981 (45.3)	<.001
30-299	292 (19.0)	584 (28.0)	830 (38.4)	
≥300	46 (3.0)	173 (8.3)	353 (16.3)	
Medical history, No. (%)				
Hospitalization for HF	876 (55.2)	1252 (58.5)	1457 (65.5)	<.001
Time from last HF hospitalization				
No prior HF hospitalization	712 (44.8)	889 (41.5)	766 (34.5)	<.001
0-7 d	122 (7.7)	339 (15.8)	534 (24.0)	
8 d to 3 mo	509 (32.1)	560 (26.2)	534 (24.0)	
>3 to 12 mo	99 (6.2)	134 (6.3)	164 (7.4)	
>1 y	146 (9.2)	219 (10.2)	225 (10.1)	
Myocardial infarction	321 (20.2)	549 (25.6)	659 (29.6)	<.001
PCI or CABG	411 (25.9)	737 (34.4)	879 (39.5)	<.001
Peripheral arterial occlusive disease	59 (3.7)	195 (9.1)	280 (12.6)	<.001
Atrial fibrillation or flutter in history or on ECG	747 (47.2)	1199 (56.1)	1350 (60.7)	<.001
Type 2 diabetes	314 (19.8)	827 (38.7)	1277 (57.7)	<.001
Hypertension	1239 (78.0)	1937 (90.5)	2106 (94.7)	<.001
Chronic obstructive pulmonary disease	101 (6.4)	253 (11.8)	412 (18.5)	<.001
Stroke	129 (8.1)	280 (13.1)	415 (18.7)	<.001
Sleep apnea	44 (2.8)	103 (4.8)	251 (11.3)	<.001
Treatment, No. (%)				
Total No. of medications				
<8	1092 (68.8)	1023 (47.8)	707 (31.8)	<.001
8-11	412 (25.9)	802 (37.5)	919 (41.3)	
≥12	84 (5.3)	316 (14.8)	597 (26.9)	
ACEI	591 (37.2)	779 (36.4)	770 (34.6)	.09
ARB	467 (29.4)	797 (37.2)	824 (37.1)	<.001
ARNI	208 (13.1)	160 (7.5)	139 (6.3)	<.001
β-Blocker	1318 (83.0)	1821 (85.1)	1917 (86.2)	.007
SGLT2i	163 (10.3)	271 (12.7)	378 (17.0)	<.001
Loop diuretic	1310 (82.5)	1855 (86.6)	2028 (91.2)	<.001
Any diuretic	1569 (98.8)	2123 (99.2)	2190 (98.5)	.32
Lipid-lowering drug	937 (59.0)	1488 (69.5)	1689 (76.0)	<.001
Digoxin	116 (7.3)	171 (8.0)	181 (8.1)	.36
Pacemaker, CRT, or ICD	51 (3.2)	144 (6.7)	212 (9.5)	<.001

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CABG, coronary artery bypass graft; CRT, cardiac resynchronization therapy; CSS, clinical summary score; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; HF, heart failure; ICD, implantable cardioverter-defibrillator; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro–B-type natriuretic peptide; NYHA, New York Heart Association; OSS, overall summary score; PCI, percutaneous coronary intervention; SGLT2i, sodium-glucose cotransporter 2 inhibitor; TSS, total symptom score.

SI conversion factors: To convert creatinine to micromoles per liter, multiply by 88.4; sodium and potassium to millimoles per liter, multiply by 1; hemoglobin to grams per liter, multiply by 10; alanine aminotransferase and alkaline phosphatase to microkatals per liter, multiply by 0.0167; total bilirubin to micromoles per liter, multiply by 17.104; blood urea nitrogen to millimoles per liter, multiply by 0.357; platelet count to $\times 10^9$ per liter, multiply by 1; white blood cell count to $\times 10^9$ per liter, multiply by 0.001; hemoglobin A_{1c} to proportion of total hemoglobin, multiply by 0.01.

[a] Race (as reported by participants) was captured on a dedicated demographics case report and included the following categories: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, or not reported. Other included American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, and not reported.

Figure 1. Outcomes According to Frailty Index (FI) Class



The cumulative hazard for the primary composite outcome of cardiovascular death and total worsening heart failure (HF) events (A) and total worsening HF events (B) and the cumulative incidence for cardiovascular death (C) and all-cause death (D) are shown.

Outcomes According to Frailty

Compared with patients in FI class I (the least frail), those in FI classes II and III (the frailest) had a higher risk of the primary composite of cardiovascular death and total worsening HF events (class II: unadjusted RR, 1.88 [95% CI, 1.54-2.28]; class III: RR, 3.86 [95% CI, 3.22-4.64]), each of its components (for worsening HF events, class II: RR, 2.02 [95% CI, 1.61-2.54]; class III: RR, 4.20 [95% CI, 3.39-5.21]; for cardiovascular death, class II: HR, 1.46 [95% CI, 1.11-1.93]; class III: HR, 2.93 [95% CI, 2.26-3.81]), all-cause death (class II: HR, 1.64 [95% CI, 1.34-2.01]; class III: HR, 3.30 [95% CI, 2.73-3.99]), and total hospitalizations (class II: RR, 1.53 [95% CI, 1.37-1.72]; class III: RR, 2.41 [95% CI, 2.16-2.70]), even after adjustment for known prognostic variables (**Figure 1**; eTable 4 in Supplement 2).

Effects of Finerenone on Outcomes According to Frailty

Compared with placebo, finerenone reduced the risk of total worsening HF events and cardiovascular death, with no interaction between FI class and the effect of finerenone (class I: RR, 1.07 [95% CI, 0.77-1.49]; class II: RR, 0.66 [95% CI, 0.52-0.83]; class III: RR, 0.91 [95% CI, 0.76-1.07]; *P* for interaction = .77). The effects of finerenone on secondary clinical outcomes were not modified by FI class (**Table 2**).

The analyses of FI as a continuous variable yielded similar findings for the primary composite outcome, each of its components, and all-cause death (**Figure 2**; eFigure 3 in Supplement 2). The absolute rate reduction in the primary outcome and total worsening HF events with finerenone tended to be greater with increasing frailty.

The mean increase in KCCQ scores from baseline to 12 months was greater with finerenone compared with placebo, with no effect modification of FI class (Table 2). The difference in mean change in KCCQ-TSS from baseline to 12 months for patients receiving finerenone compared with those receiving placebo was 1.30 (95% CI, −0.03 to 2.64) for FI class I, 1.07 (95% CI, −0.42 to 2.56) for class II, and 2.88 (95% CI, 0.95 to 4.80) for class III (*P* for interaction = .18). This difference for KCCQ-OSS was 0.99 (95% CI, −0.33 to 2.30) for class I, 0.46 (95% CI, −0.98 to 1.91) for class II, and 1.80 (95% CI, 0.00 to 3.60) for class III (*P* for interaction = .49). The difference for KCCQ-CSS was 0.83 (95% CI, −0.46 to 2.11) for class I, 0.77 (95% CI, −0.65 to 2.19) for class II, and 2.10 (95% CI, 0.32 to 3.89) for class III (*P* for interaction = .29). The effect of finerenone on improvement in NYHA class from baseline to 12 months was not modified by FI class (class I: OR, 0.95 [95% CI, 0.74 to 1.23]; class II: OR, 1.13 [95% CI, 0.90 to 1.43]; class III: OR, 0.96 [95% CI, 0.78 to 1.18]; *P* for interaction = .89).

Patients with greater frailty were more likely to experience an increase in creatinine levels, hyperkalemia, and hypokalemia but less likely to experience a decrease in systolic blood pressure (to <100 mm Hg) than those with less (or no) frailty. The effects of finerenone, compared with placebo, on

Table 2. Effects of Finerenone Compared With Placebo on Outcomes According to Frailty Index (FI) Class

Outcome	FI class						*P* value for interaction[a]
	I, Not frail (n = 1588)		II, More frail (n = 2141)		III, Most frail (n = 2223)		
	Finerenone (n = 827)	Placebo (n = 761)	Finerenone (n = 1048)	Placebo (n = 1093)	Finerenone (n = 1102)	Placebo (n = 1121)	
Cardiovascular death and total worsening HF events							
Events, No.	159	138	269	426	639	708	
Event rate, No./100 person-years (95% CI)	7.6 (6.1-9.5)	7.1 (5.6-9.0)	10.3 (8.7-12.3)	15.8 (13.5-18.5)	25.2 (22.1-28.7)	27.7 (24.7-31.1)	
Rate ratio (95% CI)[b]	1.07 (0.77-1.49)		0.66 (0.52-0.83)		0.91 (0.76-1.07)		.77
Total worsening HF events							
Events, No.	119	100	199	351	511	564	
Event rate, No./100 person-years (95% CI)	5.7 (4.4-7.4)	5.1 (3.9-6.8)	7.6 (6.3-9.3)	13.0 (1.9-15.6)	20.1 (17.4-23.3)	22.0 (19.4-25.1)	
Rate ratio (95% CI)[b]	1.10 (0.75-1.62)		0.59 (0.45-0.77)		0.91 (0.75-1.10)		.61
Cardiovascular death or worsening HF event							
Events, No. (%)	111 (13.4)	87 (11.4)	166 (15.8)	244 (22.3)	338 (3.7)	380 (33.9)	
Event rate, No./100 person-years (95% CI)	5.6 (4.7-6.7)	4.7 (3.8-5.7)	6.8 (5.8-7.9)	9.9 (8.7-11.2)	15.2 (13.7-16.9)	17.6 (15.9-19.5)	
Hazard ratio (95% CI)[b]	1.20 (0.90-1.59)		0.69 (0.56-0.84)		0.87 (0.75-1.00)		.37
First worsening HF event							
Events, No. (%)	80 (9.7)	63 (8.3)	125 (11.9)	195 (17.8)	266 (24.1)	308 (27.5)	
Event rate, No./100 person-years (95% CI)	4.0 (3.2-5.0)	3.4 (2.6-4.3)	5.1 (4.3-6.1)	7.9 (6.9-9.1)	12.0 (10.6-13.5)	14.3 (12.8-16.0)	
Hazard ratio (95% CI)[b]	1.19 (0.86-1.66)		0.65 (0.51-0.81)		0.84 (0.71-0.99)		.45
Cardiovascular death							
Events, No. (%)	40 (4.8)	38 (5.0)	70 (6.7)	75 (6.9)	129 (11.7)	145 (12.9)	
Event rate, No./100 person-years (95% CI)	1.9 (1.4-2.6)	2.0 (1.4-2.7)	2.7 (2.1-3.4)	2.8 (2.2-3.5)	5.1 (4.3-6.0)	5.7 (4.8-6.7)	
Hazard ratio (95% CI)[b]	0.99 (0.63-1.54)		0.96 (0.69-1.33)		0.90 (0.71-1.14)		.72
All-cause death							
Events, No. (%)	70 (8.5)	72 (9.5)	138 (13.2)	157 (14.4)	273 (24.8)	285 (25.4)	
Event rate, No./100 person-years (95% CI)	3.4 (2.7-4.2)	3.7 (2.9-4.6)	5.3 (4.5-6.2)	5.8 (5.0-6.8)	10.7 (9.5-12.0)	11.1 (9.9-12.5)	
Hazard ratio (95% CI)[b]	0.90 (0.65-1.26)		0.90 (0.72-1.13)		0.96 (0.81-1.13)		.67
Improvement in NYHA class from baseline to 12 mo							
No. (%)	151 (18.3)	143 (18.8)	182 (17.4)	172 (15.7)	219 (19.9)	232 (2.7)	
Odds ratio (95% CI)[c]	0.95 (0.74-1.23)		1.13 (0.90-1.43)		0.96 (0.78-1.18)		.89
Change in KCCQ score from baseline to 12 mo							
TSS							
Change, mean (SD)	0.65 (13.82)	−0.50 (14.33)	6.73 (18.96)	6.31 (19.94)	17.98 (24.94)	15.69 (24.12)	
Difference in mean (95% CI)[d]	1.30 (−0.03 to 2.64)		1.07 (−0.42 to 2.56)		2.88 (0.95 to 4.80)		.18
OSS							
Change, mean (SD)	1.30 (13.61)	0.02 (13.78)	5.34 (16.89)	4.92 (18.04)	14.22 (21.62)	13.12 (22.18)	
Difference in mean (95% CI)[d]	0.99 (−0.33 to 2.30)		0.46 (−0.98 to 1.91)		1.80 (0.00 to 3.60)		.49
CSS							
Change, mean (SD)	0.28 (12.97)	−0.77 (13.00)	4.59 (16.43)	4.02 (17.72)	13.23 (21.89)	12.04 (21.92)	
Difference in mean (95% CI)[d]	0.83 (−0.46 to 2.11)		0.77 (−0.65 to 2.19)		2.10 (0.32 to 3.89)		.29

Abbreviations: CSS, clinical summary score; HF, heart failure; KCCQ, Kansas City Cardiomyopathy Questionnaire; NYHA, New York Heart Association; OSS, overall summary score; TSS, total symptom score.

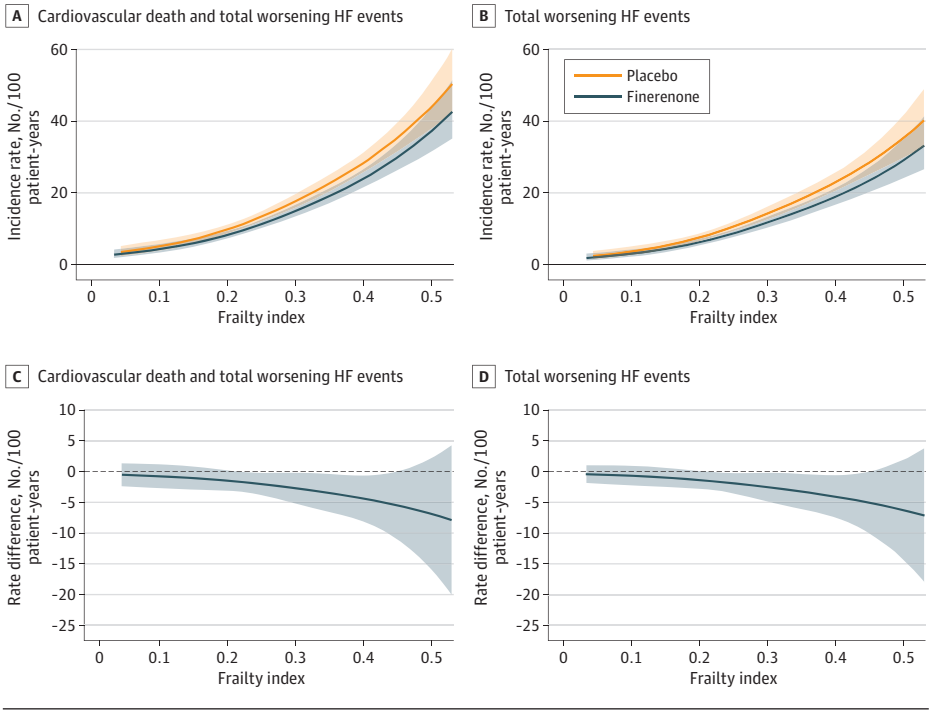
[a] FI class was included as an ordinal variable.

[b] Models were stratified for geographic region and left ventricular ejection fraction stratification.

[c] Models were adjusted for geographic region and left ventricular ejection fraction stratification.

[d] Models were adjusted for baseline value, geographic region, and left ventricular ejection fraction stratification.

Figure 2. Effects of Finerenone Compared With Placebo on the Primary Composite Outcome and Total Worsening Heart Failure (HF) Events According to Frailty Index



The association between frailty index and the incidence rate for the primary composite outcome of cardiovascular death and total worsening HF events (A) and total worsening HF events (B) is shown, and the absolute benefit of finerenone across the range of frailty index for the primary composite outcome of cardiovascular death and total worsening HF events (C) and total worsening HF events (D) is shown. The shaded areas represent the 95% CIs.

the incidence of abnormal laboratory measurements and vital signs were not modified by FI class (**Table 3**).

Discussion

In this prespecified analysis of FINEARTS-HF, frailty was common in patients with HFmrEF or HFpEF, and greater frailty was associated with more impairment in health status and worse clinical outcomes, including worsening HF events, hospitalizations, and death. Finerenone reduced the risk of total worsening HF events and cardiovascular death and improved symptoms; these effects were not modified by frailty status. The effects of finerenone on experiencing hypotension, elevated creatinine level, hyperkalemia, or hypokalemia did not differ by frailty status. The favorable benefit-risk balance related to frailty for finerenone should challenge any clinical reluctance to introduce this new treatment in patients considered to be frail.

Prevalence and Outcomes According to Frailty

The mean FI in FINEARTS-HF, using the Rockwood cumulative deficits approach, was 0.284. The substantially higher FI in the present analysis, as compared with large population studies and clinical trials of older individuals with other conditions such as hypertension, confirms that frailty is much more prevalent in patients with HFmrEF or HFpEF than in individuals without this condition.[34-39]

FINEARTS-HF enrolled participants with a higher-risk clinical profile than most contemporary trials in HFmrEF and HFpEF.[25] It is therefore not surprising that the proportion of patients deemed to be frail (defined as an FI >0.210) in FINEARTS-HF (73.3% [4364 of 5952 patients]) was higher than that in the Prospective Comparison of ARNI With ARB Global Outcomes in HF With Preserved Ejection Fraction (PARAGON-HF) trial (55%)[14] and the Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure (DELIVER) trial (62%).[13] The proportion of patients with frailty in FINEARTS-HF was similar to that in the Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction (EMPEROR-Preserved; 75%)[15] but lower than that in the much smaller Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist–Americas (TOPCAT-Americas) trial (94%).[8] Although there are standard criteria for constructing an FI, the difference in the prevalence of frailty between these trials could also be due to the inclusion of different components in the FI (for example, questions from the KCCQ were included in the FI in FINARTS-HF, EMPEROR-Preserved, and TOPCAT-Americas but not in DELIVER or PARAGON-HF). For this reason, a direct comparison with other trials is difficult, and this highlights the need for a standardized FI in clinical trials of HF.

In keeping with reports from other HF trials,[7,8,12-15] there was a strong and graded relationship between the degree of frailty and the wide range of adverse outcomes examined (ie, the rates of worsening HF events, hospitalizations, and death were greater with increasing frailty). These findings emphasize the more general effect of frailty on health and the importance of preventing and treating (and even reversing) frailty in HF, which has become a key goal in the management of these patients.[5,40]

Table 3. Effects of Finerenone Compared With Placebo on Laboratory Measures and Systolic Blood Pressure According to Frailty Index (FI) Class[a]

Measure	FI class						*P* value for interaction[b]
	I, Not frail (n = 1584)		II, More frail (n = 2135)		III, Most frail (n = 2220)		
	Finerenone (n = 824)	Placebo (n = 760)	Finerenone (n = 1046)	Placebo (n = 1089)	Finerenone (n = 1099)	Placebo (n = 1121)	
Creatinine ≥2.5 mg/dL							
Events, No./total No. (%)	20/809 (2.5)	6/749 (0.8)	30/1014 (3.0)	28/1050 (2.7)	89/1050 (8.5)	53/1067 (5.0)	
Odds ratio (95% CI)[c]	3.14 (1.25-7.89)		1.12 (0.66-1.89)		1.79 (1.26-2.55)		.80
Creatinine ≥3 mg/dL							
Events, No./total No. (%)	8/809 (1.0)	0/749	11/1014 (1.1)	9/1050 (0.9)	36/1050 (3.4)	24/1067 (2.2)	
Odds ratio (95% CI)[c]	NA		1.31 (0.54-3.18)		1.56 (0.92-2.65)		.14
Potassium >5.5 mEq/L							
Events, No./total No. (%)	90/809 (11.1)	31/748 (4.1)	150/1014 (14.8)	77/1051 (7.3)	170/1051 (16.2)	87/1068 (8.1)	
Odds ratio (95% CI)[c]	2.80 (1.83-4.29)		2.23 (1.67-2.99)		2.21 (1.67-2.91)		.42
Potassium >6 mEq/L							
Events, No./total No. (%)	20/809 (2.5)	5/748 (0.7)	34/1014 (3.4)	14/1051 (1.3)	30/1051 (2.9)	21/1068 (2.0)	
Odds ratio (95% CI)[c]	3.66 (1.36-9.84)		2.61 (1.39-4.91)		1.47 (0.83-2.60)		.09
Potassium <3.5 mEq/L							
Events, No./total No. (%)	26/809 (3.2)	64/748 (8.6)	38/1014 (3.7)	98/1051 (9.3)	62/1051 (5.9)	118/1068 (11.0)	
Odds ratio (95% CI)[c]	0.37 (0.23-0.59)		0.38 (0.25-0.55)		0.50 (0.36-0.69)		.20
Systolic blood pressure <100 mm Hg							
Events, No./total No. (%)	193/810 (23.8)	117/749 (15.6)	179/1020 (17.5)	128/1058 (12.1)	158/1057 (15.0)	113/1075 (10.5)	
Odds ratio (95% CI)[c]	1.92 (1.46-2.54)		1.62 (1.25-2.10)		1.53 (1.17-2.00)		.35

Abbreviation: NA, not applicable.

SI conversion factors: To convert creatinine to micromoles per liter, multiply by 88.4; potassium to millimoles per liter, multiply by 1.

[a] A total of 13 randomized patients were excluded from the safety analysis, as these were performed in patients who had undergone randomization and received at least 1 dose of finerenone or placebo.

[b] FI class was included as an ordinal variable.

[c] Models were adjusted for geographic region and left ventricular ejection fraction stratification.

Effects of Finerenone on Clinical Outcomes According to Frailty

There is a common perception that the benefit-risk profile of evidence-based pharmacological therapies may be less favorable in patients with frailty, and clinicians may be more reluctant to initiate, and perhaps even more likely to discontinue, effective therapies in these individuals.[5,16-18] However, there is little evidence to support these concerns in patients with HF. Indeed, in 2 trials of patients with HF with reduced ejection fraction, the favorable effects of sacubitril-valsartan (Prospective Comparison of ARNI With ACEi to Determine Impact on Global Mortality and Morbidity in Heart Failure [PARADIGM-HF])[7] and dapagliflozin (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure [DAPA-HF])[12] were consistent, regardless of the degree of frailty. Similarly, the beneficial effects of the SGLT2 inhibitors dapagliflozin and empagliflozin were observed across the range of frailty studied in patients with HFmrEF or HFpEF enrolled in the DELIVER and EMPEROR-Preserved trials, although there was a trend toward a diminished effect in very frail patients in the latter trial (and the opposite trend in the former trial).[13,15] In 2 other trials of patients with HFmrEF or HFpEF, frailty status did not modify the effects of the steroidal MRA spironolactone (TOPCAT-Americas) or sacubitril-valsartan (PARAGON-HF), although neither trial showed a significant benefit of treatment overall.[8,14]

In the present analysis of approximately 6000 patients with HFmrEF or HFpEF enrolled in FINEARTS-HF, the efficacy of the nonsteroidal MRA finerenone was not diminished in patients with the greatest degree of frailty. Indeed, there was a trend toward a greater effect of finerenone, compared with placebo, on the primary outcome and total worsening HF events in patients with a greater degree of frailty, a finding consistent with what was observed with sacubitril-valsartan in PARAGON-HF and dapagliflozin in DELIVER. This finding is not surprising, as deterioration in HF and subsequent hospitalization represents one of the most common external stressors in these patients, which in turn may lead to the progression of frailty, thus creating a vicious cycle. Because patients with the greatest degree of frailty were at higher absolute risk, their absolute benefit with treatment was substantially greater. These findings should challenge any clinical reluctance to introduce this new treatment in patients considered to be frail.

In keeping with findings from prior trials in HFmrEF and HFpEF, the benefit of finerenone on clinical outcomes was mainly driven by a reduction in worsening HF events in FINEARTS-HF.[41-43] However, the finding that frailty status did not modify the beneficial effect of finerenone on worsening

HF events is of great importance in frail individuals given the role of hospital admission in accelerating frailty.

Improvement of health status is a key goal of the management of patients with HF,[40,44] and this is all the more important in patients with a greater degree of frailty, who have a much greater symptom burden and worse physical function and quality of life than individuals without frailty, as evidenced by the extremely low baseline mean KCCQ scores in the frailest patients. In FINEARTS-HF, the improvements in symptoms, physical function, and quality of life (as assessed by the change in KCCQ scores from baseline to 12 months) with finerenone, compared with placebo, were not modified by frailty status. These findings are important because symptom control, maintenance of physical function, and continuation of daily activities may help prevent or slow the development of frailty and progression of existing frailty in these individuals.[5,45]

Kidney dysfunction, hyperkalemia, and hypotension are often particular concerns in frail individuals and may lead to reluctance to initiate treatment (or discontinuation of treatment). As expected, patients with greater frailty were more likely to experience an increase in creatinine levels, hyperkalemia, and hypokalemia, but they were less likely to experience hypotension. While these adverse events (except hypokalemia) occurred more frequently with finerenone compared with placebo, reassuringly there was no significant interaction between frailty status and the effect of treatment on these events.

Limitations

This study has several limitations. First, patients enrolled in clinical HF trials are not fully representative of the general HF population (eg, the use of evidence-based, disease-modifying therapy is greater in clinical trials), which may affect the generalizability of our results to a real-world HF population. Second, the most frail patients with HF are excluded from clinical HF trials or only compose a small proportion of the trial population, and this may affect the generalizability of our results to the very frail patients. Although the effect of finerenone on the risk for the primary outcome was not modified by frailty status across the range of FI studied (0.033 to 0.633) and a larger absolute risk reduction was observed in the most frail patients, it is possible that the beneficial effects of this therapy may be attenuated in very frail patients. Third, data on muscle strength and functional capacity were not collected in FINEARTS-HF, and we were therefore not able to test other frailty scores that include assessments of these measures. Fourth, laboratory monitoring in FINEARTS-HF (and similar clinical trials) was protocol driven, and protocolized surveillance and follow-up may not reflect clinical practice. Fifth, due to the observational nature of the analyses on the association between the FI and outcomes, the possibility of unmeasured confounding remains, despite adjustment for known prognostic variables.

Conclusions

In patients with HFmrEF or HFpEF, the beneficial effects of finerenone on reducing the risk of total worsening HF events and cardiovascular death and on improving symptoms were not modified by frailty status. The effects of finerenone on experiencing hypotension, elevated creatinine level, hyperkalemia, or hypokalemia did not differ by frailty status. The favorable benefit-risk balance related to frailty for finerenone should challenge any clinical reluctance to introduce this new treatment in patients considered to be frail.

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