JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 85, NO. 2, 2025

Finerenone, Obesity, and Heart Failure With Mildly Reduced/ Preserved Ejection Fraction

Prespecified Analysis of FINEARTS-HF

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ABSTRACT

BACKGROUND Obesity is associated with excessive adipocyte-derived aldosterone secretion, independent of the classical renin-angiotensin-aldosterone cascade, and mineralocorticoid receptor antagonists may be more effective in patients with heart failure (HF) and obesity.

OBJECTIVES This study sought to examine the effects of the nonsteroidal mineralocorticoid receptor antagonist finerenone compared with placebo, according to body mass index (BMI) in FINEARTS-HF (FINerenone trial to investigate Efficacy and sAfety superioR to placebo in paTientS with Heart Failure).

METHODS A total of 6,001 patients with HF with NYHA functional class II, III, and IV, a left ventricular ejection fraction of ≥40%, evidence of structural heart disease, and elevated natriuretic peptide levels were randomized to finerenone or placebo. BMI (kg/m^2) was examined using World Health Organization categories, namely, underweight/normal weight (<25.0 kg/m^2; n = 1,306); overweight (25.0-29.9 kg/m^2; n = 1,990); obesity class I (30.0-34.9 kg/m^2; n = 1,546); obesity class II (35.0-39.9 kg/m^2; n = 751); and obesity class III (≥40 kg/m^2; n = 395). The primary outcome was cardiovascular death and total worsening HF events.

RESULTS Data on baseline BMI were available for 5,988 patients (median: 29.2 kg/m^2; Q1-Q3: 25.5-33.6 kg/m^2). Compared with patients who were underweight/normal weight, those with obesity class II or III had a higher risk of the primary outcome (underweight/normal weight, reference; overweight, unadjusted rate ratio: 0.96 [95% CI: 0.81-1.15]; obesity class I: 1.04 [95% CI: 0.86-1.26]; obesity class II-III: 1.26 [95% CI: 1.03-1.54]). The effect of finerenone on the primary outcome did not vary by baseline BMI (underweight/normal weight, rate ratio: 0.80 [95% CI: 0.62-1.04]; overweight: 0.91 [95% CI: 0.72-1.15]; obesity class I: 0.92 [95% CI: 0.72-1.19]; obesity class II-III: 0.67 [95% CI: 0.50-0.89]; $P_{interaction}$ = 0.32). However, when BMI was examined as a continuous variable, the beneficial effect of finerenone seemed to be greater in those with a higher BMI ($P_{interaction}$ = 0.005). A similar pattern was observed for total worsening HF events. Consistent effects across baseline BMI were observed for cardiovascular and all-cause death and improvement in the Kansas City Cardiomyopathy Questionnaire scores.

CONCLUSIONS In patients with HF with mildly reduced/preserved ejection fraction, the beneficial effects of finerenone on clinical events and symptoms were consistent, irrespective of BMI at baseline, possibly with a greater effect on the primary outcome in patients with higher BMI. (FINEARTS-HF [FINerenone trial to investigate Efficacy and sAfety superioR to placebo in paTientS with Heart Failure]; NCT04435626) (JACC. 2025;85:140–155) © 2025 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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ISSN 0735-1097 https://doi.org/10.1016/j.jacc.2024.10.111

Aldosterone is secreted by the adrenal glands and regulated by circulating angiotensin II and serum potassium concentration, and the deleterious consequences of excessive production of this hormone (and mineralocorticoid receptor overactivation) on the heart, vasculature, and kidney are well-established.[1-5] However, aldosterone synthase is also expressed in adipocytes, which can secrete aldosterone, and angiotensin II is produced in adipose tissue and stimulates the production of aldosterone in a paracrine/autocrine manner.[1,2] Thus, there is evidence to suggest that adipose tissue secretes aldosterone, and obesity may lead to excessive adipocyte-derived aldosterone secretion, independent of the classical renin-angiotensin-aldosterone cascade. Given this endocrine role of adipose tissue, mineralocorticoid receptor antagonists (MRAs) may have an especially important therapeutic role in patients with obesity. In support of this hypothesis, a prior analysis of EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure) suggested that the benefit of the steroidal MRA, eplerenone, was greater in patients with heart failure (HF) with reduced ejection fraction (HFrEF) and obesity (defined by elevated waist circumference),[6] and in a more recent analysis of RALES (Randomized Aldactone Evaluation Study), body weight modified the beneficial effect of the steroidal MRA, spironolactone, with a greater risk reduction in heavier patients with HFrEF. If this hypothesis is correct, it could have important implications for the treatment of patients with heart failure with mildly reduced or preserved ejection fraction (HFmrEF/HFpEF) in whom obesity is more prevalent than in individuals with HFrEF.[7,8] Although a borderline interaction between adiposity (defined by a BMI of ≥30 kg/m^2) and the effect of treatment was observed in TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist) (Americas only), this trial did not show a significant benefit of spironolactone overall.[9]

SEE PAGE 156

Consequently, we tested this hypothesis in a pre-specified analysis of FINEARTS-HF (Finerenone Trial to Investigate Efficacy and Safety Superior to Placebo in Patients with Heart Failure), which demonstrated that the nonsteroidal MRA, finerenone, compared with placebo, decreased the risk of the primary composite outcome of total (first and repeat) worsening HF events and cardiovascular death, and improved health-related quality of life, in 6,001 patients with HFmrEF/HFpEF.[10] Specifically, in a pre-specified analysis, we examined the efficacy and safety of finerenone, compared with placebo, according to body mass index (BMI) and other anthropometric indices. We also addressed the long-standing question of whether adiposity, defined by conventional BMI categories, is associated with better survival in patients with established HF (ie, the obesity survival paradox) or whether this counterintuitive epidemiologic observation reflects the many limitations of BMI as a measure of adiposity and the lack of adjustment for N-terminal pro-B-type natriuretic peptides (NT-proBNP), the single strongest predictor of adverse outcomes in HF.[11-19]

METHODS

FINEARTS-HF was a randomized, double-blinded, placebo-controlled trial in patients with symptomatic

ABBREVIATIONS AND ACRONYMS

BMI = body mass index

CSS = clinical summary score

eGFR = estimated glomerular filtration rate

HF = heart failure

HFmrEF/HFpEF = heart failure with mildly reduced or preserved ejection fraction

HFrEF = heart failure with reduced ejection fraction

KCCQ = Kansas City Cardiomyopathy Questionnaire

LVEF = left ventricular ejection fraction

MRA = mineralocorticoid receptor antagonist

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

OSS = overall summary score

TSS = total symptom score

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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.

Manuscript received October 10, 2024; revised manuscript received October 29, 2024, accepted October 30, 2024.

HFmrEF/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 are published elsewhere.[10,20,21] The trial protocol was approved by the ethics committee at all participating institutions, and all patients provided written informed consent.

TRIAL PATIENTS. Key inclusion criteria were age ≥40 years; diuretic treatment for ≥30 days before randomization; NYHA functional class II, III, or IV; a left ventricular ejection fraction (LVEF) ≥40%; evidence of structural heart disease (either left atrial enlargement or left ventricular hypertrophy); and elevated natriuretic peptide levels (NT-proBNP ≥300 pg/mL [B-type natriuretic peptide ≥100 pg/mL] for patients in sinus rhythm or NT-proBNP ≥900 pg/mL [B-type natriuretic peptide ≥300 pg/mL] for patients in atrial fibrillation), measured within 30 days before randomization in those without a recent worsening HF event or within 90 days in those with a recent worsening HF event. Both ambulatory and hospitalized patients were eligible for enrolment. Patients with a prior LVEF of <40% with subsequent improvement to ≥40% were also eligible for enrolment provided that ongoing HF symptoms were present. Key exclusion criteria were an estimated glomerular filtration rate (eGFR) of <25 mL/min/1.73 m^2 or serum/plasma potassium of >5.0 mmol/L at screening or randomization. A complete list of exclusion criteria is provided in the design paper.[21]

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

TRIAL OUTCOMES. The primary outcome in FINEARTS-HF was the composite of cardiovascular death and total (first and recurrent) HF events (ie, HF hospitalization or urgent HF visit). The secondary outcomes were total (first and recurrent) HF events; improvement in NYHA functional class from baseline to 12 months; change in the Kansas City Cardiomyopathy Questionnaire (KCCQ) total symptom score (TSS) from baseline to 6, 9, and 12 months; composite kidney endpoint (defined as a sustained decrease in eGFR of ≥50% relative to baseline over ≥4 weeks, or a sustained eGFR decline of <15 mL/min/1.73 m^2, or initiation of dialysis or renal 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, making subgroup analysis unreliable. In addition to KCCQ-TSS, the change in the KCCQ overall summary score (OSS) and clinical summary score (CSS) was also examined in the present analysis.

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

ANTHROPOMETRIC MEASURES. As prespecified in the academic statistical analysis plan, the primary outcome and secondary outcomes were analyzed by anthropometric measures obtained at the randomization visit and examined as categorical (using recognized categories) and continuous variables. The following anthropometric measures were evaluated: BMI, waist-to-height ratio, body weight, waist circumference, waist-to-hip ratio, relative fat mass, body shape index, body roundness index, and weight-adjusted-waist index. The calculation of each of these measures is described in Supplemental Table 1.

In the analyses using BMI, patients were divided according to the categories recommended by the World Health Organization: underweight (<18.5 kg/m^2), normal weight (18.5-24.9 kg/m^2), overweight (25.0-29.9 kg/m^2), obesity class I (30.0-34.9 kg/m^2), obesity class II (35.0-39.9 kg/m^2), and obesity class III (≥40 kg/m^2).[22,23] The underweight group was pooled with the normal weight group because only 65 patients who were underweight were enrolled in the trial. In the analyses using waist-to-height ratio, patients were divided according to categories recommended by the National Institute for Health and Care Excellence guidelines: low risk (<0.5), intermediate risk (0.5-0.59), and high risk (≥0.6).[23] All the other anthropometric measures were only assessed continuously.

Data on body weight were collected at baseline, 1 month, 3, months, 6 months, 9 months, and 12 months, and every fourth month hereafter.

STATISTICAL ANALYSES. Baseline characteristics were summarized as frequencies with percentages, mean ± SD, or median (Q1-Q3), and differences were tested using the chi-square test for binary or categorical variables and the Kruskal-Wallis test and analysis of variance test for non-normal and normally distributed continuous variables, respectively.

The association between anthropometric measures 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,[24] and HRs and rate ratios (RRs), respectively, were stratified according to geographic region and LVEF stratification (<60% vs ≥60%) and adjusted for treatment assignment. In addition, HRs and RRs, stratified by geographic region and LVEF stratification and adjusted for treatment assignment, age, sex, systolic blood pressure, heart rate, eGFR, LVEF, NYHA functional class, prior HF hospitalization, type 2 diabetes, myocardial infarction or coronary revascularization, atrial fibrillation/flutter, and log of NT-proBNP, were reported. The relationship between anthropometric measurements as continuous variables and the risk of outcomes was also examined in restricted cubic spline analyses with the median value as the reference (unless otherwise stated). The proportional hazards assumption was examined with scaled Schoenfeld residuals and log(-log[survival]) curves and was not violated.

To compare the effects of finerenone vs placebo on clinical outcomes according to anthropometric measures, time-to-event data and total events were evaluated with Cox proportional hazards models and semiparametric proportional rates models, respectively, and these models were stratified according to geographic region and LVEF stratification. The effect of finerenone was also examined according to continuous anthropometric measures using fractional polynomial models, restricted cubic spline models, or linear regression models, whichever had the lowest Akaike information criterion score. The proportional hazards assumption was not violated.

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

The change in KCCQ scores from baseline to 12 months was summarized as mean ± SD within each subgroup at 12 months, and the effect of finerenone versus 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.

The change in body weight at each visit from baseline to 12 months was analyzed using mixed effect models for repeated measurements, adjusted for baseline value, visit, treatment-by-visit interaction, geographic region, and LVEF stratification. The least-squares mean differences with 95% CI between treatment groups were reported.

All analyses were conducted using STATA version 18.0.

RESULTS

Of the 6,001 patients validly randomized in FINEARTS-HF, data on BMI were available for 99.8% of participants, and data on waist-to-height ratio were available in 99.3% (as were data on waist-to-hip ratio, relative fat mass, body roundness index, body shape index, and weight-adjusted-waist index). Data on body weight and waist circumference were available in 99.9% and 99.4% of participants, respectively.

BASELINE CHARACTERISTICS ACCORDING TO ANTHROPOMETRIC MEASURES. BMI. The median BMI was 29.2 kg/m^2 (Q1-Q3: 25.5-33.6 kg/m^2). In total, 65 patients (1.1%) had a BMI of <18.5 kg/m^2 (underweight); 1,241 (20.7%) patients had a BMI between 18.5 and 24.9 kg/m^2 (normal weight); 1,990 (33.2%) patients had a BMI between 25.0 and 29.9 kg/m^2 (overweight); 1,546 (25.8%) patients had a BMI between 30.0 and 34.9 kg/m^2 (obesity class I); 751 (12.5%) patients had a BMI between 35.0 and 39.9 kg/m^2 (obesity class II); and 395 (6.6%) patients had a BMI of ≥40 kg/m^2 (obesity class III).

The baseline characteristics of patients according to BMI category are shown in **Table 1**. Compared with patients who were underweight/normal weight, those with a higher BMI were younger, more often female, and White, and they had higher systolic blood pressure, but lower NT-proBNP levels. Despite no difference in eGFR across BMI categories, patients with a higher BMI had a higher urine albumin-to-creatinine ratio. They also had a higher LVEF, worse NYHA functional class, and much lower KCCQ scores. Compared with patients who had lower BMI, those with a higher BMI were less likely to have a prior HF hospitalization, stroke, and ischemic heart disease, but they were more likely to have hypertension, diabetes, chronic obstructive pulmonary disease, and sleep apnea.

Regarding pharmacological therapy, patients with a higher BMI were treated more frequently with an angiotensin receptor blocker and a loop diuretic and less frequently with an angiotensin receptor-neprilysin inhibitor and digoxin.

Waist-to-height ratio. The median waist-to-height ratio was 0.62 (Q1-Q3: 0.56-0.69). In total, 376 patients had a waist-to-height ratio of <0.5 (low risk); 1,908 patients between 0.50 and 0.59 (intermediate

TABLE 1 Baseline Characteristics According to Body Mass Index Category

	<25.0 kg/m² (n = 1,306)	25.0-29.9 kg/m² (n = 1,990)	30.0-34.9 kg/m² (n = 1,546)	≥35.0 kg/m² (n = 1,146)	*P* Value
Age, y	74.3 ± 9.7	72.7 ± 9.6	71.3 ± 9.2	69.0 ± 9.4	<0.001
Sex					<0.001
Men	728 (55.7)	1,187 (59.6)	854 (55.2)	492 (42.9)	
Women	578 (44.3)	803 (40.4)	692 (44.8)	654 (57.1)	
Race					<0.001
White	711 (54.4)	1,579 (79.3)	1,377 (89.1)	1,060 (92.5)	
Black	16 (1.2)	19 (1.0)	19 (1.2)	30 (2.6)	
Asian	532 (40.7)	325 (16.3)	109 (7.1)	29 (2.5)	
Other	47 (3.6)	67 (3.4)	41 (2.7)	27 (2.4)	
Geographic region					<0.001
Western Europe, Oceania and others	223 (17.1)	449 (22.6)	335 (21.7)	241 (21.0)	
Eastern Europe	373 (28.6)	860 (43.2)	831 (53.8)	586 (51.1)	
Asia	524 (40.1)	322 (16.2)	107 (6.9)	29 (2.5)	
North America	74 (5.7)	132 (6.6)	110 (7.1)	151 (13.2)	
Latin America	112 (8.6)	227 (11.4)	163 (10.5)	139 (12.1)	
Physiological measures					
Systolic blood pressure, mm Hg	125.8 ± 16.2	129.2 ± 15.3	131.1 ± 14.5	131.6 ± 14.7	<0.001
Heart rate, beats/min	71.4 ± 12.2	70.5 ± 11.5	71.8 ± 11.6	72.8 ± 12.0	<0.001
Atrial fibrillation/flutter on ECG	519 (39.9)	766 (38.6)	592 (38.4)	430 (37.7)	0.72
NT-proBNP, pg/mL	1,416 (650-2,645)	1,069 (449-1,988)	936 (402-1,765)	793 (374-1,550)	<0.001
Atrial fibrillation/flutter on ECG	1,998 (1,401-3,398)	1,785 (1,225-2,747)	1,636 (1,109-2,617)	1,406 (958-2,186)	<0.001
No atrial fibrillation/flutter on ECG	878 (432-1,833)	584 (328-1,240)	518 (268-1,075)	473 (250-963)	<0.001
Hemoglobin A1c, %	6.2 ± 1.0	6.3 ± 1.1	6.5 ± 1.3	6.6 ± 1.4	<0.001
Creatinine, μmol/L	97.1 ± 28.9	100.5 ± 30.1	101.3 ± 38.5	99.2 ± 31.1	0.003
eGFR, mL/min/1.73 m²	61.7 ± 19.6	61.9 ± 19.2	62.3 ± 20.1	62.7 ± 20.4	0.59
eGFR,mL/min/1.73 m²					0.84
≥60	675 (51.7)	1,046 (52.6)	789 (51.0)	597 (52.1)	
<60	631 (48.3)	944 (47.4)	757 (49.0)	549 (47.9)	
Urine albumin-to-creatinine ratio, mg/g	139.4 ± 548.2	156.4 ± 595.6	170.8 ± 671.7	183.4 ± 623.5	0.31
Urine albumin-to-creatinine ratio, mg/g					0.027
<30	766 (60.3)	1,181 (61.5)	907 (60.6)	652 (59.3)	
30-299	402 (31.7)	553 (28.8)	439 (29.3)	313 (28.5)	
≥300	102 (8.0)	185 (9.6)	150 (10.0)	135 (12.3)	
Potassium, mmol/L	4.4 ± 0.5	4.4 ± 0.5	4.4 ± 0.5	4.4 ± 0.5	0.17
Sodium, mmol/L	140.4 ± 3.1	140.7 ± 3.0	140.8 ± 3.0	140.8 ± 2.9	0.003
Hemoglobin, g/L	131.6 ± 16.8	134.3 ± 16.1	135.2 ± 16.5	133.9 ± 16.7	<0.001
Alanine aminotransferase, U/L	19.6 ± 14.3	20.4 ± 12.5	21.1 ± 14.4	21.5 ± 13.7	0.003
Bilirubin, mg/dL	0.7 ± 0.4	0.7 ± 0.4	0.6 ± 0.4	0.6 ± 0.4	<0.001
Alkaline phosphatase, U/L	89.3 ± 39.6	84.0 ± 31.7	84.6 ± 31.8	87.6 ± 33.4	<0.001
Blood urea nitrogen, mg/dL	22.7 ± 9.3	22.3 ± 9.1	23.0 ± 10.0	23.1 ± 10.1	0.094
Platelet count, 10^9/L	215.1 ± 70.0	218.5 ± 68.6	218.8 ± 67.6	229.9 ± 67.8	<0.001
White blood cell count, 10^9/L	6.5 ± 3.1	6.8 ± 2.0	7.2 ± 7.2	7.2 ± 2.0	<0.001
Anthropometric measures					
Body mass index, kg/m²	23.0 (21.5-24.1)	27.5 (26.3-28.7)	32.2 (31.1-33.5)	38.5 (36.5-41.3)	N/A
Body weight, kg	61.0 (54.6-67.7)	76.0 (69.7-83.0)	89.1 (81.6-98.0)	105.8 (95.9-117.5)	<0.0001
Waist-to-height ratio	0.53 (0.50-0.57)	0.60 (0.57-0.63)	0.66 (0.63-0.70)	0.74 (0.70-0.79)	<0.001
Waist circumference, cm	87.5 (81.0-94.0)	100.0 (94.0-105.2)	110.0 (103.0-117.0)	122.0 (114.0-130.0)	<0.001
Waist-to-hip ratio	0.92 (0.87-0.97)	0.96 (0.91-1.02)	0.98 (0.93-1.05)	0.98 (0.92-1.05)	<0.001
Relative fat mass	29.4 (25.6-37.9)	32.7 (29.7-42.3)	36.2 (33.2-45.6)	45.9 (37.1-49.6)	<0.001
Body shape index	0.085 (0.081-0.090)	0.085 (0.081-0.089)	0.084 (0.080-0.088)	0.083 (0.078-0.087)	<0.001
Body roundness index	4.0 (3.3-4.7)	5.4 (4.7-6.2)	6.9 (6.0-7.8)	9.0 (7.8-10.4)	<0.001
Weight-adjusted-waist index	11.1 (10.6-11.8)	11.4 (10.9-12.0)	11.6 (11.0-12.2)	11.9 (11.2-12.4)	<0.001

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TABLE 1 Continued

	<25.0 kg/m² (n = 1,306)	25.0-29.9 kg/m² (n = 1,990)	30.0-34.9 kg/m² (n = 1,546)	≥35.0 kg/m² (n = 1,146)	*P* Value
Smoking status					0.002
Never	789 (60.4)	1,220 (61.3)	960 (62.1)	719 (62.7)	
Former	368 (28.2)	604 (30.4)	469 (30.3)	349 (30.5)	
Current	149 (11.4)	166 (8.3)	117 (7.6)	78 (6.8)	
LVEF, %	52.1 ± 8.1	52.3 ± 7.8	52.8 ± 7.9	53.2 ± 7.4	0.001
LVEF, %					<0.001
<50	539 (41.3)	755 (38.0)	532 (34.5)	344 (30.1)	
50-59	536 (41.0)	874 (43.9)	697 (45.2)	558 (48.9)	
≥60	231 (17.7)	360 (18.1)	314 (20.3)	240 (21.0)	
NYHA functional class					<0.001
II	999 (76.5)	1,455 (73.1)	1,048 (67.8)	634 (55.3)	
III	302 (23.1)	523 (26.3)	484 (31.3)	502 (43.8)	
IV	5 (0.4)	12 (0.6)	13 (0.8)	10 (0.9)	
KCCQ-TSS	74.6 ± 21.9	69.0 ± 23.3	65.9 ± 22.9	56.5 ± 24.6	<0.001
KCCQ-CSS	72.9 ± 21.4	67.5 ± 21.9	63.9 ± 21.3	55.2 ± 22.3	<0.001
KCCQ-OSS	68.7 ± 21.5	64.7 ± 21.7	61.9 ± 21.4	54.2 ± 22.2	<0.001
Medical history					
Hospitalization for HF	956 (73.2)	1,356 (68.1)	1,070 (69.2)	793 (69.2)	0.017
Time from last HF hospitalization					<0.001
No prior HF hospitalization	455 (34.8)	808 (40.6)	647 (41.8)	466 (40.7)	
0-7 d	196 (15.0)	321 (16.1)	266 (17.2)	219 (19.1)	
8 days-3 mo	465 (35.6)	526 (26.4)	360 (23.3)	267 (23.3)	
3-12 mo	80 (6.1)	129 (6.5)	112 (7.2)	79 (6.9)	
>1 y	110 (8.4)	206 (10.4)	161 (10.4)	115 (10.0)	
Atrial fibrillation/flutter	727 (55.7)	1,098 (55.2)	852 (55.1)	633 (55.2)	0.99
Stroke	226 (17.3)	264 (13.3)	199 (12.9)	140 (12.2)	<0.001
Myocardial infarction	316 (24.2)	583 (29.3)	419 (27.1)	222 (19.4)	<0.001
PCI or CABG	457 (35.0)	744 (37.4)	547 (35.4)	294 (25.7)	<0.001
Peripheral arterial occlusive disease	133 (10.2)	180 (9.0)	130 (8.4)	93 (8.1)	0.26
Hypertension	1,042 (79.8)	1,742 (87.5)	1,438 (93.0)	1,092 (95.3)	<0.001
Type 2 diabetes	384 (29.6)	743 (37.4)	732 (47.4)	575 (50.3)	<0.001
Chronic obstructive pulmonary disease	153 (11.7)	247 (12.4)	187 (12.1)	183 (16.0)	0.006
Sleep apnea	29 (2.2)	88 (4.4)	109 (7.1)	173 (15.1)	<0.001
Treatment					
ACEI	424 (32.5)	727 (36.5)	576 (37.3)	420 (36.6)	0.036
ARB	364 (27.9)	652 (32.8)	616 (39.8)	466 (40.7)	<0.001
ARNI	190 (14.5)	188 (9.4)	86 (5.6)	49 (4.3)	<0.001
Beta-blocker	1,094 (83.8)	1,670 (83.9)	1,330 (86.0)	993 (86.6)	0.069
SGLT2 inhibitors	187 (14.3)	256 (12.9)	212 (13.7)	158 (13.8)	0.67
Loop diuretic	1,134 (86.8)	1,720 (86.4)	1,338 (86.5)	1,034 (90.2)	0.011
Any diuretic	1,292 (98.9)	1,959 (98.4)	1,529 (98.9)	1,137 (99.2)	0.24
Digoxin	117 (9.0)	163 (8.2)	124 (8.0)	66 (5.8)	0.023
Pacemaker/CRT/ICD	77 (5.9)	164 (8.2)	107 (6.9)	64 (5.6)	0.013

Values are mean ± SD, n (%), or median (Q1-Q3).

ACEI = angiotensin-converting enzyme inhibitors; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; CABG = coronary artery bypass graft surgery; CSS = clinical summary score; CRT = cardiac resynchronization therapy; 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; OSS = overall summary score; PCI = percutaneous coronary intervention; SGLT2 = sodium-glucose cotransporter 2; TSS = total symptom score.

risk); and 3,674 patients ≥0.6 (high risk). The baseline characteristics of patients according to their waist-to-height ratio are shown in Supplemental Table 2. Overall, the differences were similar to those described above for BMI (and in **Table 1**), although patients with a higher waist-to-height ratio had a lower eGFR than those with a lower waist-to-height ratio.

CLINICAL OUTCOMES ACCORDING TO ANTHROPOMETRIC MEASURES. BMI. In the minimally adjusted models, compared with underweight/normal weight individuals, only those with obesity class II or III had

TABLE 2 Outcomes According to Body Mass Index Category

	<25.0 kg/m² (n = 1,306)	25.0-29.9 kg/m² (n = 1,990)	30.0-34.9 kg/m² (n = 1,546)	≥35.0 kg/m² (n = 1,146)
Cardiovascular death and total worsening HF events				
No. of events	503	731	598	520
Event rate per 100 person-years (95% CI)	16.5 (14.5-18.9)	15.1 (13.5-17.0)	15.5 (13.6-17.6)	18.8 (16.4-21.7)
RR (95% CI)[a]	Reference	0.96 (0.81-1.15)	1.04 (0.86-1.26)	1.26 (1.03-1.54)
RR (95% CI)[b]	Reference	0.97 (0.81-1.15)	1.04 (0.85-1.26)	1.26 (1.02-1.57)
RR (95% CI)[c]	Reference	1.10 (0.93-1.32)	1.25 (1.03-1.52)	1.59 (1.28-1.99)
Total worsening HF events				
No. of events	393	554	478	427
Event rate per 100 person-years (95% CI)	12.9 (11.1-15.0)	11.5 (10.0-13.2)	12.4 (10.7-14.3)	15.5 (13.2-18.1)
RR (95% CI)[a]	Reference	0.96 (0.78-1.17)	1.11 (0.89-1.38)	1.38 (1.10-1.74)
RR (95% CI)[b]	Reference	0.96 (0.79-1.17)	1.11 (0.89-1.38)	1.37 (1.07-1.74)
RR (95% CI)[c]	Reference	1.09 (0.89-1.33)	1.32 (1.06-1.65)	1.70 (1.32-2.18)
Cardiovascular death or first worsening HF event				
No. of events (%)	295 (22.6)	422 (21.2)	322 (20.8)	298 (26.0)
Event rate per 100 person-years (95% CI)	10.6 (9.5-11.9)	9.5 (8.6-10.4)	9.1 (8.2-10.1)	12.2 (10.9-13.7)
HR (95% CI)[a]	Reference	0.94 (0.80-1.09)	0.95 (0.80-1.12)	1.25 (1.05-1.49)
HR (95% CI)[b]	Reference	0.94 (0.80-1.10)	0.95 (0.80-1.13)	1.27 (1.05-1.52)
HR (95% CI)[c]	Reference	1.07 (0.92-1.26)	1.13 (0.95-1.35)	1.61 (1.33-1.95)
First worsening HF event				
No. of events (%)	234 (17.9)	318 (16.0)	258 (16.7)	236 (20.6)
Event rate per 100 person-years (95% CI)	8.4 (7.4-9.6)	7.2 (6.4-8.0)	7.3 (6.4-8.2)	9.7 (8.5-11.0)
HR (95% CI)[a]	Reference	0.91 (0.77-1.08)	1.00 (0.83-1.20)	1.30 (1.07-1.58)
HR (95% CI)[b]	Reference	0.92 (0.77-1.10)	1.01 (0.83-1.23)	1.33 (1.08-1.64)
HR (95% CI)[c]	Reference	1.04 (0.87-1.25)	1.23 (1.01-1.50)	1.70 (1.37-2.11)
Cardiovascular death				
No. of events (%)	110 (8.4)	177 (8.9)	120 (7.8)	95 (8.3)
Event rate per 100 person-years (95% CI)	3.6 (3.0-4.4)	3.7 (3.2-4.2)	3.1 (2.6-3.7)	3.4 (2.8-4.2)
HR (95% CI)[a]	Reference	0.97 (0.76-1.24)	0.82 (0.62-1.07)	0.91 (0.68-1.21)
HR (95% CI)[b]	Reference	0.98 (0.76-1.26)	0.82 (0.61-1.08)	0.95 (0.69-1.30)
HR (95% CI)[c]	Reference	1.16 (0.90-1.50)	1.00 (0.75-1.34)	1.26 (0.91-1.74)
All-cause death				
No. of events (%)	253 (19.4)	330 (16.6)	236 (15.3)	191 (16.7)
Event rate per 100 person-years (95% CI)	8.3 (7.3-9.4)	6.8 (6.1-7.6)	6.1 (5.3-6.9)	6.9 (6.0-7.9)
HR (95% CI)[a]	Reference	0.77 (0.65-0.91)	0.69 (0.57-0.83)	0.76 (0.62-0.93)
HR (95% CI)[b]	Reference	0.79 (0.66-0.94)	0.71 (0.58-0.86)	0.83 (0.67-1.03)
HR (95% CI)[c]	Reference	0.89 (0.75-1.06)	0.85 (0.69-1.03)	1.05 (0.84-1.31)

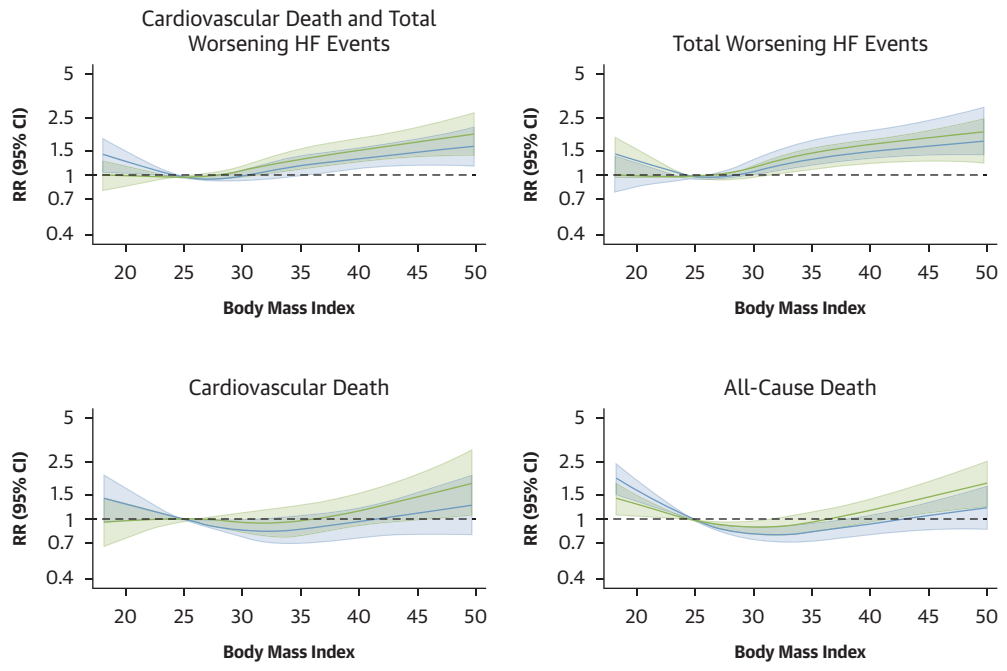
[a]Models were stratified by geographic region and left ventricular ejection fraction stratification and adjusted for treatment assignment. [b]Models were stratified by geographic region and left ventricular ejection fraction stratification and adjusted for treatment assignment, age, sex, systolic blood pressure, heart rate, estimated glomerular filtration rate, left ventricular ejection fraction, NYHA functional class, prior heart failure hospitalization, type 2 diabetes, myocardial infarction or coronary revascularization, and atrial fibrillation/flutter. [c]Models were stratified by geographic region and left ventricular ejection fraction stratification and adjusted for log of N-terminal pro-B-type natriuretic peptides, in addition to the variables mentioned above.

RR = rate ratio; other abbreviations as in Table 1.

a significantly higher risk of the primary composite outcome, total worsening HF events, and first worsening HF event (Table 2). Conversely, patients with overweight and obesity had a significantly lower risk of all-cause death, in the minimally adjusted models, compared with underweight/normal-weight individuals. In the fully adjusted models, patients with obesity class I and II or III still had a significantly higher risk of the primary composite outcome, total worsening HF events, and first worsening HF event, but higher BMI was no longer associated with a lower risk of all-cause death (Table 2).

When examined as a continuous variable, a BMI of >25 kg/m² was associated with a higher risk of the primary composite outcome and total worsening HF events, but not cardiovascular or all-cause death, in the minimally adjusted models. A BMI of <25 kg/m² was associated with a higher risk of all these outcomes (Figure 1). In the fully adjusted models, a BMI of >25 kg/m² was associated with a higher risk of all outcomes examined (including cardiovascular and

FIGURE 1 **Outcomes According to Continuous Body Mass Index: Blue Spline Minimally Adjusted Analysis/Green Spline Fully Adjusted Analysis**



The blue spline is stratified for geographic region and left ventricular ejection fraction stratification and adjusted for treatment assignment. The green spline is stratified by geographic region and baseline left ventricular ejection fraction and adjusted for treatment assignment, age, sex, systolic blood pressure, heart rate, estimated glomerular filtration rate, left ventricular ejection fraction, NYHA functional class, prior heart failure hospitalization, type 2 diabetes, myocardial infarction or coronary revascularization, atrial fibrillation/flutter, and log of N-terminal pro-B-type natriuretic peptide. HF = heart failure; RR = rate ratio.

all-cause death), whereas a BMI of <25 kg/m^2 was now only significantly associated with a higher risk of all-cause death (**Figure 1**).

Waist-to-height ratio. In the minimally adjusted models, compared with patients in the lowest waist-to-height ratio category, those in the highest category had a higher risk of the primary composite outcome and total worsening HF events. Patients in the highest category did not have a significantly different risk of cardiovascular or all-cause death compared with those in the lowest category (Supplemental Table 3). Patients in the intermediate category did not have a significantly different risk of any of the outcomes examined compared with those in the lowest category. None of these associations were altered in the fully adjusted models (Supplemental Table 3).

When examined as a continuous variable, a waist-to-height ratio >0.62 (ie, the median) was associated with a higher risk of the primary composite outcome, total worsening HF events, and all-cause death, but not cardiovascular death (Supplemental Figure 1). There was a trend toward a lower risk of the primary composite outcome and total worsening HF events, but a higher risk of all-cause death, in patients with a waist-to-height ratio <0.62 (Supplemental Figure 1).

Other anthropometric measures. After adjustment for prognostic variables, greater adiposity was associated with a higher risk of the primary composite outcome and total worsening HF events, although this association was less pronounced for waist-to-hip ratio (Supplemental Figure 1). None of these anthropometric measures, except for relative mass, were associated clearly with cardiovascular death.

EFFECTS OF FINERENONE ON CLINICAL OUTCOMES ACCORDING TO ANTHROPOMETRIC MEASURES.

BMI. Compared with placebo, finerenone reduced the risk of total (first and recurrent) worsening HF events and cardiovascular death across BMI categories

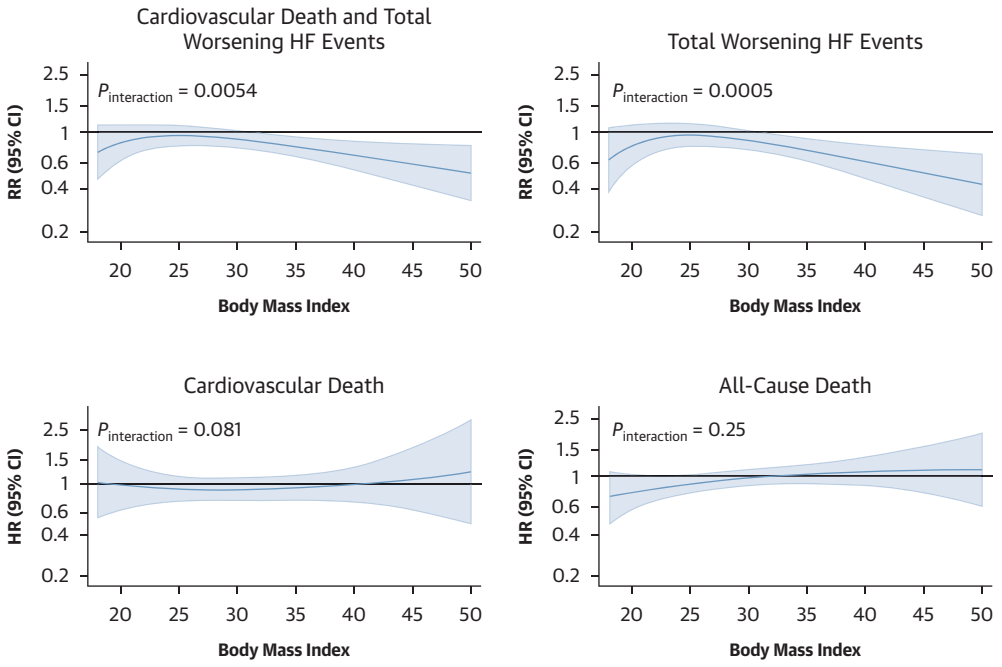
TABLE 3 Effects of Finerenone Compared With Placebo on Outcomes According to Body Mass Index Category

	<25.0 kg/m² (N = 1,306)		25.0-29.9 kg/m² (N = 1,990)		30.0-34.9 kg/m² (N = 1,546)		≥35.0 kg/m² (N = 1,146)		*P* Value for interaction
	Finerenone (n = 662)	Placebo (n = 644)	Finerenone (n = 996)	Placebo (n = 994)	Finerenone (n = 767)	Placebo (n = 779)	Finerenone (n = 571)	Placebo (n = 575)	
Cardiovascular death and total worsening HF events									0.32
No. of events	237	266	349	382	277	321	209	311	
Event rate per 100 person-years (95% CI)	15.2 (12.5-18.4)	17.9 (14.9-21.5)	14.5 (12.0-17.4)	15.8 (13.6-18.4)	14.5 (12.1-17.4)	16.4 (13.7-19.7)	15.2 (12.3-18.6)	22.5 (18.6-27.2)	
RR (95% CI)[a]	0.80 (0.62-1.04)		0.91 (0.72-1.15)		0.92 (0.72-1.19)		0.67 (0.50-0.89)		
Total worsening HF events									0.27
No. of events	185	208	264	290	217	261	165	262	
Event rate per 100 person-years (95% CI)	11.9 (9.5-14.8)	14.0 (11.4-17.2)	10.9 (8.8-13.6)	12.0 (10.1-14.3)	11.4 (9.2-13.9)	13.3 (10.8-16.4)	12.0 (9.4-15.2)	19.0 (15.4-23.4)	
RR (95% CI)[a]	0.80 (0.59-1.07)		0.91 (0.69-1.20)		0.90 (0.68-1.20)		0.63 (0.46-0.86)		
Cardiovascular death or worsening HF event									0.14
No. of events (%)	140 (21.1)	155 (24.1)	198 (19.9)	224 (22.5)	156 (20.3)	166 (21.3)	126 (22.1)	172 (29.9)	
Event rate per 100 person-years (95% CI)	9.8 (8.3-11.6)	11.4 (9.7-13.3)	8.8 (7.7-10.2)	10.2 (8.9-11.6)	8.9 (7.6-10.4)	9.3 (8.0-10.8)	10.0 (8.4-11.9)	14.6 (12.5-16.9)	
HR (95% CI)[a]	0.82 (0.65-1.03)		0.85 (0.70-1.03)		0.99 (0.79-1.23)		0.68 (0.54-0.85)		
First worsening HF event									0.10
No. of events (%)	111 (16.8)	123 (19.1)	146 (14.7)	172 (17.3)	123 (16.0)	135 (17.3)	95 (16.6)	141 (24.5)	
Event rate per 100 person-years (95% CI)	7.8 (6.5-9.4)	9.0 (7.6-10.8)	6.5 (5.5-7.7)	7.8 (6.7-9.1)	7.0 (5.9-8.3)	7.6 (6.4-9.0)	7.5 (6.1-9.2)	11.9 (10.1-14.1)	
HR (95% CI)[a]	0.81 (0.63-1.05)		0.82 (0.66-1.03)		0.96 (0.75-1.23)		0.62 (0.47-0.80)		
Cardiovascular death									0.90
No. of events (%)	52 (7.9)	58 (9.0)	85 (8.5)	92 (9.3)	60 (7.8)	60 (7.7)	45 (7.9)	50 (8.7)	
Event rate per 100 person-years (95% CI)	3.3 (2.5-4.4)	3.9 (3.0-5.1)	3.5 (2.9-4.4)	3.8 (3.1-4.7)	3.1 (2.4-4.0)	3.1 (2.4-3.9)	3.3 (2.4-4.4)	3.6 (2.7-4.8)	
HR (95% CI)[a]	0.83 (0.57-1.21)		0.91 (0.67-1.22)		1.03 (0.72-1.47)		0.89 (0.59-1.33)		
All-cause death									0.28
No. of events (%)	113 (17.1)	140 (21.7)	163 (16.4)	167 (16.8)	115 (15.0)	121 (15.5)	99 (17.3)	92 (16.0)	
Event rate per 100 person-years (95% CI)	7.2 (6.0-8.7)	9.4 (7.9-11.1)	6.7 (5.8-7.8)	6.9 (5.9-8.0)	6.0 (5.0-7.2)	6.2 (5.2-7.4)	7.1 (5.9-8.7)	6.6 (5.4-8.1)	
HR (95% CI)[a]	0.75 (0.59-0.96)		0.96 (0.78-1.20)		0.97 (0.75-1.25)		1.11 (0.83-1.47)		
Improvement in NYHA functional class from baseline to 12 months									0.56
No. (%)	116 (17.5)	102 (15.8)	188 (18.9)	184 (18.5)	137 (17.9)	157 (20.2)	115 (20.1)	110 (19.1)	
OR (95% CI)[b]	1.15 (0.86-1.54)		1.02 (0.81-1.28)		0.88 (0.68-1.14)		1.08 (0.81-1.46)		
Change in KCCQ-TSS from baseline to 12 months									0.16
Mean change ± SD	6.30 ± 19.50	4.55 ± 20.22	7.88 ± 20.54	8.61 ± 20.63	9.50 ± 21.54	6.86 ± 21.03	12.47 ± 23.28	11.20 ± 23.13	
Difference in mean (95% CI)[c]	2.10 (0.15-4.05)		0.15 (−1.45 to 1.76)		2.11 (0.24-3.98)		3.06 (0.64-5.49)		
Change in KCCQ-OSS from baseline to 12 months									0.17
Mean change ± SD	5.86 ± 17.83	4.58 ± 19.08	6.52 ± 17.86	7.04 ± 19.34	7.33 ± 19.12	5.78 ± 19.11	9.73 ± 19.83	8.69 ± 19.80	
Difference in mean (95% CI)[c]	1.71 (−0.23 to 3.65)		−0.16 (−1.71 to 1.39)		0.83 (−0.96 to 2.62)		2.64 (0.46-4.83)		
Change in KCCQ-CSS from baseline to 12 months									0.23
Mean change ± SD	4.34 ± 17.10	3.00 ± 18.57	5.85 ± 18.03	6.11 ± 18.67	6.33 ± 18.79	5.16 ± 18.91	9.19 ± 19.83	8.00 ± 19.62	
Difference in mean (95% CI)[c]	1.82 (−0.08 to 3.72)		0.15 (−1.36 to 1.67)		0.79 (−0.98 to 2.56)		2.62 (0.43-4.80)		

[a]Models were stratified for geographic region and left ventricular ejection fraction stratification. [b]Models were adjusted for geographic region and left ventricular ejection fraction stratification. [c]Models were adjusted for baseline value, geographic region, and left ventricular ejection fraction stratification.

Abbreviations as in Tables 1 and 2.

FIGURE 2 **Effects of Finerenone Compared With Placebo on Outcomes According to Continuous Body Mass Index**



Models were stratified for geographic region and left ventricular ejection fraction stratification. Abbreviations as in Figure 1.

(underweight/normal weight, RR: 0.80 [95% CI: 0.62-1.04]; overweight: 0.91 [95% CI: 0.72-1.15]; obesity class I: 0.92 [95% CI: 0.72-1.19]; and obesity class II-III: 0.67 [95% CI: 0.50-0.89]), and, although the relative risk reduction appeared greatest in people with marked obesity, the interaction between baseline BMI category and the effect of treatment was not significant ($P_{interaction}$ = 0.32) (Table 3). The effects of finerenone on secondary clinical outcomes did not differ significantly across BMI categories (Table 3). Findings were similar when the effect of finerenone was examined according to the following BMI categories: underweight/normal weight (<24.9 kg/m^2), overweight (25.0-29.9 kg/m^2), and obesity (≥30.0 kg/m^2) (Supplemental Table 4).

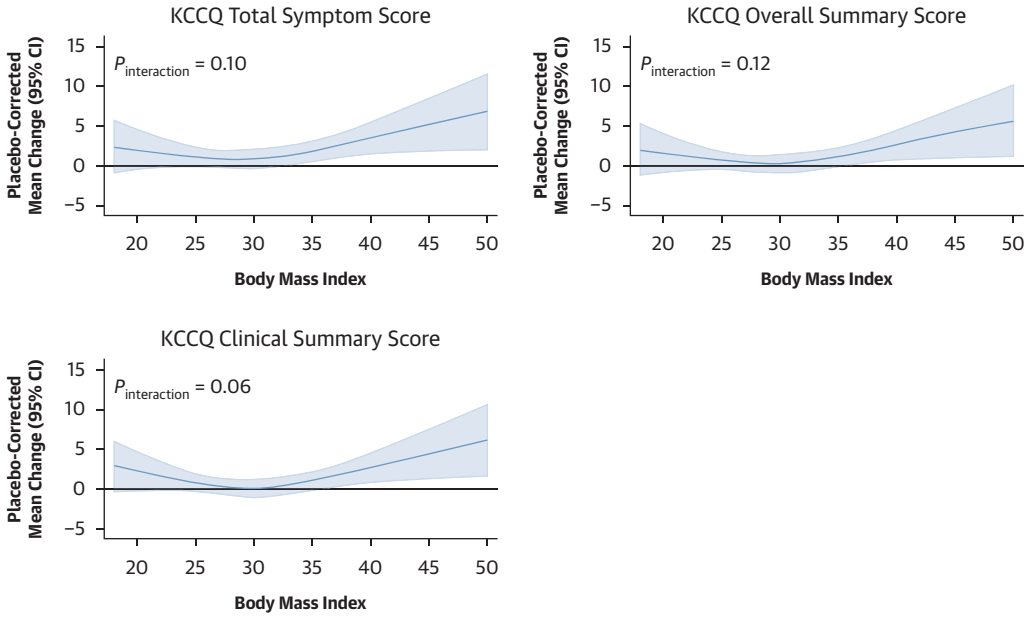
When BMI was examined as a continuous variable, the beneficial effect of finerenone on the primary composite outcome and total worsening HF events was evident across the range of BMI, but seemed to be greater in those with higher BMI ($P_{interaction}$ = 0.005 and <0.001, respectively) (Figure 2). The effect of finerenone on cardiovascular or all-cause death was not modified by continuous BMI (Figure 2).

The mean increase in KCCQ scores from baseline to 12 months was greater with finerenone compared with placebo, with a consistent effect across BMI categories ($P_{interaction}$ = 0.16, 0.17, and 0.23 for the KCCQ-TSS, KCCQ-OSS, and KCCQ-CSS, respectively) (Table 3). The effect of finerenone on improvement in NYHA functional class from baseline to 12 months was not modified by BMI ($P_{interaction}$ = 0.56). When BMI was examined as a continuous variable, the beneficial effect of finerenone on the improvement in KCCQ scores was evident across the range of BMI but appeared to be greater in those with higher BMI ($P_{interaction}$ = 0.10, 0.12, and 0.06 for KCCQ-TSS, KCCQ-OSS, and KCCQ-CSS, respectively) (Figure 3).

Patients with a higher BMI were less likely to experience increases in potassium levels and a decrease in systolic blood pressure (to <100 mm Hg) than those with a lower BMI. The effects of finerenone, compared with placebo, on the incidence of abnormal laboratory measurements and vital signs were generally consistent, regardless of BMI category (Supplemental Table 5).

Waist-to-height ratio. Finerenone, compared with placebo, reduced the risk of total worsening HF events and cardiovascular death, irrespective of waist-to-height ratio, with no interaction between waist-to-height ratio category and the effect of

FIGURE 3 Effects of Finerenone Compared With Placebo on KCCQ Scores From Baseline to 12 Months According to Continuous Body Mass Index



Models were adjusted for baseline value, geographic region, and left ventricular ejection fraction stratification. KCCQ, Kansas City Cardiomyopathy Questionnaire.

treatment ($P_{interaction}$ = 0.87) (Supplemental Table 6). The effects of finerenone on secondary outcomes were also consistent across waist-to-height ratio categories (Supplemental Table 6). Consistent effects were observed for the primary composite outcome, each of its components, and all-cause death when waist-to-height ratio was examined as a continuous variable (**Figure 4**).

The effects of finerenone, compared with placebo, on the incidence of abnormal laboratory measurements and vital signs were generally consistent, regardless of waist-to-height ratio category (Supplemental Table 7).

Other anthropometric measures. The effect of finerenone, compared with placebo, on the primary composite outcome according to continuous anthropometric indices are shown in Supplemental Figure 2. The beneficial effect of finerenone on the primary composite outcome was not modified by any of these anthropometric indices, except for body shape index; there was a nominally significant interaction between body shape index and the effect of finerenone, such that the beneficial effect of finerenone seemed to be greater in patients with lower body shape index values (Supplemental Figure 2).

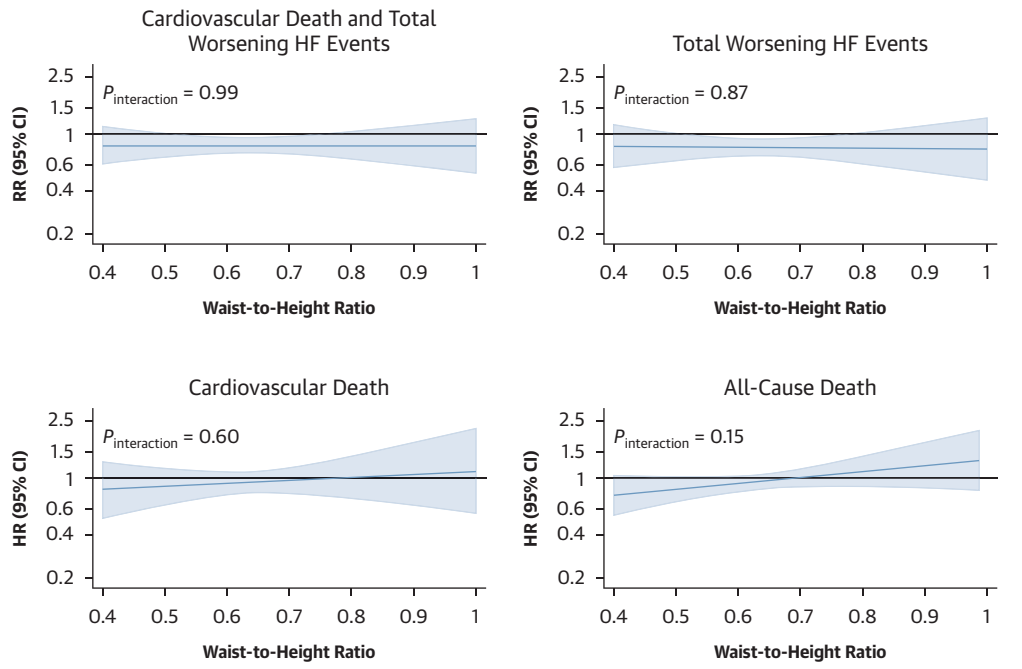
Effect of finerenone on weight and BMI during follow-up. Body weight decreased during follow-up in both treatment groups. Although the decrease in body weight was greater with finerenone than placebo early during follow-up, there were no significant difference between treatment groups at 12 months (placebo-corrected absolute mean change at 12 months: −0.16 kg [95% CI: −0.41 to 0.10]; placebo-corrected relative mean change at 12 months: −0.22% [95% CI: −0.54% to 0.10%]) (Supplemental Figure 3).

DISCUSSION

In this prespecified analysis of FINEARTS-HF, the beneficial effects of finerenone on clinical events and symptoms were observed across the range of BMI (and other anthropometric indices), although the effect on the primary composite outcome and worsening HF events seemed to be greatest in patients with higher BMIs.

EFFECT OF FINERENONE ACCORDING TO ANTHROPOMETRIC MEASURES. There is some evidence to suggest that treatment with MRAs is more effective in patients with obesity compared with individuals without

FIGURE 4 Effects of Finerenone Compared With Placebo on Outcomes According to Continuous Waist-to-Height Ratio



Models were stratified for geographic region and left ventricular ejection fraction stratification. Abbreviations as in Figure 1.

obesity. As mentioned in the Introduction, data from 2 separate trials of participants with HFrEF (RALES and EMPHASIS-HF) with 2 different steroidal MRAs (spironolactone and eplerenone) using a range of anthropometric indices have suggested that the benefit of steroidal MRA treatment may be greater in individuals with greater adiposity.[6] If these findings are true, they are all the more important in patients with HFpEF, where obesity is more prevalent than in HFrEF. Although a similar borderline interaction between adiposity and the effect of treatment was observed among patients in the TOPCAT patients enrolled in the Americas, this trial did not show a significant benefit of spironolactone overall.[9] Consequently, before FINEARTS-HF, the benefits of MRAs in HFmrEF/HFpEF were unproven and their effects according to BMI in these patients were uncertain. In the present analysis of approximately 6,000 patients with HFmrEF/HFpEF, the nonsteroidal MRA finerenone decreased the risk of cardiovascular death and total worsening HF events, as well as total worsening HF events across the full spectrum of BMI (and other anthropometric indices). There seemed to be a greater decrease in worsening HF events in participants with the highest BMIs, and this observation, coupled with the findings from prior trials using MRAs in HFrEF, supports the hypothesis that adipose tissue secretes aldosterone and that obesity leads to excessive aldosterone production.[1,2] This suggestion that greater adiposity may modify the effect of MRA treatment is not confined to patients with HF. In patients with type 2 diabetes and chronic kidney disease enrolled in FIDELIO-DKD (Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease) and FIGARO-DKD (Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease), the beneficial effects of finerenone, compared with placebo, on cardiovascular events and kidney failure progression were numerically greater in individuals with a higher waist circumference (Asian and non-Asian women: ≥80 cm; Asian men: ≥90 cm; non-Asian men: ≥94 cm), although neither waist circumference nor BMI showed a statistically significant interaction with the effects of finerenone.[25]

What is not clear, however, is why the interaction between adiposity and treatment was only observed in FINEARTS-HF for BMI and not for waist-to-height ratio or any of the other anthropometric indices examined. This finding is especially puzzling given that some of these other indices are considered better measurements of adiposity than BMI.

A key goal in the treatment of patients with HF is to improve health status, and this goal is all the more important in patients with obesity, who have a much greater symptom burden and worse physical function and quality of life than individuals without obesity, as confirmed by the KCCQ scores recorded at baseline in the present analysis. It is, therefore, important that finerenone, compared with placebo, increased (improved) the mean KCCQ scores from baseline to 12 months across BMI categories. Consistent with prior findings from HFpEF trials testing the effects of sodium-glucose cotransporter 2 inhibitors and the glucagon-like peptide-1 receptor agonist semaglutide,[26-29] there was a trend toward a greater improvement in KCCQ scores with finerenone in individuals with a higher BMI, although the average effect with semaglutide was much larger than with finerenone.

As anticipated, and in line with previous findings, finerenone did not decrease or increase body weight at 12 months compared with placebo,[6,25,30] and the modest and transient decrease in body weight observed with finerenone is most likely due to an early diuretic and natriuretic effect of this treatment.[31]

Hypotension (defined as a systolic blood pressure of <100 mm Hg) was less common in patients with the highest BMI, compared with a lower BMI, probably because those with a high BMI had higher baseline blood pressure. Patients with the highest BMI also had a lower incidence of hyperkalemia, compared with participants with lower BMI, for uncertain reasons (although diuretic use was slightly greater in people with the highest BMI). Increases in potassium and creatinine levels and a decrease in systolic blood pressure were more common with finerenone compared with placebo. Conversely, finerenone decreased the risk of hypokalemia compared with placebo. These effects were generally consistent across BMI categories.

ASSOCIATION BETWEEN ANTHROPOMETRIC MEASURES AND OUTCOMES. The present analyses also provided an opportunity to investigate the association between anthropometric measures and outcomes in patients with HFmrEF/HFpEF. Recent analyses from PARADIGM-HF (Prospective Comparison of ARNI with ACE inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure trial) and DANISH (Danish Study to Assess the Efficacy of ICDs in Patients With Nonischemic Systolic Heart Failure on Mortality) have challenged the counterintuitive epidemiologic observation of a lower risk of death in patients with HFrEF and greater adiposity, sometimes referred to as the obesity-survival paradox.[10,11] Indeed, DANISH showed a clear association between greater adiposity and higher mortality during a median duration of follow-up of 9.5 years.[11,12] The present analysis of FINEARTS-HF confirms and extends these findings to HFmrEF/HFpEF. In unadjusted analyses, a higher BMI (compared with normal/underweight) was associated with lower mortality, and the opposite association was observed for BMI and worsening HF events. However, after comprehensive adjustment for potential confounders, the association between BMI and lower mortality was attenuated (and eliminated when adiposity was assessed by the other anthropometric indices). Overall, the association of worse quality of life, greater symptom and comorbidity burden, and higher risk of HF hospitalization with greater adiposity in the present and prior reports provides a strong rationale for promoting weight loss in patients with obesity and HFmrEF/HFpEF. Indeed, recent randomized clinical trials have demonstrated the beneficial effects of pharmacologically induced weight loss in these patients with the glucagon-like peptide 1 receptor agonist semaglutide and the glucose-dependent insulinotropic polypeptide/glucagon-like peptide 1 receptor agonist, tirzepatide.[32-36] These results provide a strong rationale for future dedicated morbidity and mortality trials of incretin-based therapies in patients with HFmrEF/HFpEF and obesity.

STUDY LIMITATIONS. First, patients enrolled in clinical trials are selected according to specific inclusion and exclusion criteria, and our results may not be generalizable to all patients with HFmrEF/HFpEF in the general population. Second, although this analysis was prespecified, the results reported in this study are based on subgroup analysis. The statistical power to assess the treatment effect within each of the 4 prespecified BMI categories was limited. However, we also analyzed the treatment effect using BMI as a continuous variable, and this analysis provides greater statistical power than the analysis of BMI as a categorical variable. Third, the possibility of measurement error when measuring, for example, hip and waist circumference cannot be excluded, especially when these measurements are performed by different individuals. Fourth, only 65 patients had a BMI of <18.5 kg/m^2, and our findings cannot be extrapolated to patients with a very low BMI. Fifth, owing to the observational nature of the analyses on the association between anthropometric measures and outcomes, the possibility of unmeasured

confounding, despite adjustment for known prognostic variables, remains. For example, data on the level of cardiorespiratory fitness, which may modify the obesity-survival paradox observed in HF, were not available. Finally, data on aldosterone levels were not available.

CONCLUSIONS

In patients with HFmrEF/HFpEF enrolled in FINEARTS-HF, there was no consistent evidence of an obesity-survival paradox when comparing BMI with other anthropometric measures, after comprehensive adjustment for potential confounders. The beneficial effects of finerenone on clinical events and symptoms were observed across the range of BMI (and other anthropometric indices), with a possibly greater effect in patients with higher BMI.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

FINEARTS-HF was funded by Bayer AG. The Steering Committees of the trial designed and oversaw their conduct in collaboration with the Sponsor. The primary analyses, interpretation of the data, and initial manuscript drafting were conducted independently by the academic team. Dr Butt has received advisory board honoraria from AstraZeneca and Bayer; has received consultant honoraria from Novartis and AstraZeneca; and has received travel grants from AstraZeneca. Dr Jhund has received speakers' fees from AstraZeneca, Novartis, Alkem Metabolics, ProAdWise Communications, Sun Pharmaceuticals; has received advisory board fees from AstraZeneca, Boehringer Ingelheim, and Novartis; has received research funding from AstraZeneca, Boehringer Ingelheim, Analog Devices Inc, Roche Diagnostics; his employer the University of Glasgow has been remunerated for clinical trial work from AstraZeneca, Bayer AG, Novartis, and Novo Nordisk; and he is a director at GCTP Ltd. Dr Claggett has received personal consulting fees from Alnylam, Bristol Myers Squibb, Cardior, Cardurion, Corvia, CVRx, Eli Lilly, Intellia, and Rocket; and has served on a data safety monitoring board for Novo Nordisk. Dr Desai has received institutional research grants (to Brigham and Women's Hospital) from Abbott, Alnylam, AstraZeneca, Bayer, Novartis, and Pfizer; and has received personal consulting fees from Abbott, Alnylam, AstraZeneca, Bayer, Biofourmis, Boston Scientific, Medpace, Medtronic, Merck, Novartis, Parexel, Porter Health, Regeneron, River2Renal, Roche, Veristat, Verily, and Zydus. Drs Viswanathan, Lage, Scheerer, and Lay-Flurrie are full-time employees of Bayer. Dr Lam has received research support from Novo Nordisk and Roche Diagnostics; has received consulting fees from Alleviant Medical, Allysta Pharma, AnaCardio AB, Applied Therapeutics, AstraZeneca, Bayer, Biopeutics, Boehringer Ingelheim, Boston Scientific, Bristol Myers Squibb, CardioRenal, CPC Clinical Research, Eli Lilly, Impulse Dynamics, Intellia Therapeutics, Ionis Pharmaceutical, Janssen Research & Development LLC, Medscape/WebMD Global LLC, Merck, Novartis, Novo Nordisk, Prosciento Inc, Quidel Corporation, Radcliffe Group Ltd., Recardio Inc, ReCor Medical, Roche Diagnostics, Sanofi, Siemens Healthcare Diagnostics and, Us2.ai; and is a co-founder and nonexecutive director of Us2.ai. Dr Senni has served on advisory boards for, as a consultant for, and has received honoraria from Novartis, Abbott, Merck, MSD, Vifor, AstraZeneca, Cardurion, Novo Nordisk, Bayer, and Boehringer Ingelheim. Dr Shah has received research grants from the NIH (U54 HL160273, X01 HL169712, R01 HL140731, R01 HL149423), AHA (24SFRNPCN1291224), AstraZeneca, Corvia, and Pfizer; and has received consulting fees from Abbott, Alleviant, AstraZeneca, Amgen, Aria CV, Axon Therapies, Bayer, Boehringer Ingelheim, Boston Scientific, Bristol Myers Squibb, Cyclerion, Cytokinetics, Edwards Lifesciences, Eidos, Imara, Impulse Dynamics, Intellia, Ionis, Lilly, Merck, MyoKardia, Novartis, Novo Nordisk, Pfizer, Prothena, Regeneron, Rivus, Sardocor, Shifamed, Tenax, Tenaya, and Ultromics. Dr Voors' employer received consultancy fees and/or research support from Adrenomed, Anacardio, AstraZeneca, Bayer AG, BMS, Boehringer Ingelheim, Corteria, EliLilly, Merck, Moderna, Novartis, Novo Nordisk, Roche diagnostics, and SalubrisBio. Dr Bauersachs received honoraria for lectures/consulting from Novartis, Vifor, Bayer, Pfizer, Boehringer Ingelheim, AstraZeneca, Cardior, CVRx, BMS, Amgen, Corvia, Norgine, Edwards, and Roche not related to this paper; and has received research support for the department from Zoll, CVRx, Abiomed, Norgine, and Roche, not related to this paper. Dr Zannad has received personal fees from 89Bio, Abbott, Acceleron, Applied Therapeutics, Bayer, Betagenon, Boehringer, BMS, CVRx, Cambrian, Cardior, Cereno pharmaceutical, Cellprothera, CEVA, Inventiva, KBP, Merck, NovoNordisk, Owkin, Otsuka, Roche Diagnostics, Northsea, USa2; has stock options at G3Pharmaceutical; has equity in Cereno, Cardiorenal, and Eshmoun Clinical research; and is the founder of Cardiovascular Clinical Trialists. Dr Pitt is a consultant for Bayer, AstraZeneca, Boehringer Ingelheim, Lexicon, Bristol Myers Squibb, KBP Biosciences*, Sarfez Pharmaceuticals*, Pharmaceuticals*, SQinnovations*, G3 Pharmaceuticals, Sea Star medical*, Vifor* Prointel*, and Brainstorm Medical; has stock options in KBP Biosciences, Sarfez Pharmaceuticals, Pharmaceuticals, SQinnovations, Sea Star medical, Vifor, Prointel, and Brainstorm Medical; and has U.S. Patent 9931412-site specific delivery of eplerenone to the myocardium, and U.S. Patent pending 63/045,783 Histone modulating agents for the prevention and treatment of organ failure. Dr Vaduganathan has received research grant support, served on advisory boards, or had speaker engagements with American Regent, Amgen, AstraZeneca, Bayer AG, Baxter Healthcare, BMS, Boehringer Ingelheim, Chiesi, Cytokinetics, Fresenius Medical Care, Idorsia Pharmaceuticals, Lexicon Pharmaceuticals, Merck, Milestone Pharmaceuticals, Novartis, Novo Nordisk, Pharmacosmos, Relypsa, Roche Diagnostics, Sanofi, and Tricog Health; and participates on clinical trial committees for studies sponsored by AstraZeneca, Galmed, Novartis, Bayer AG, Occlutech, and Impulse Dynamics. Dr Solomon has received research grants from Alexion, Alnylam, AstraZeneca, Bellerophon, Bayer, BMS, Boston Scientific, Cytokinetics, Edgewise, Eidos, Gossamer, GSK, Ionis, Lilly, MyoKardia, NIH/NHLBI, Novartis, Novo Nordisk, Respicardia, Sanofi Pasteur, Theracos, US2.AI; and has consulted for Abbott, Action, Akros, Alexion, Alnylam, Amgen, Arena, AstraZeneca, Bayer, Boehringer Ingelheim, BMS, Cardior, Cardurion, Corvia, Cytokinetics, Daiichi-Sankyo, GSK, Lilly, Merck, Myokardia, Novartis, Roche, Theracos, Quantum Genomics, Janssen, Cardiac Dimensions, Tenaya, Sanofi-Pasteur, Dinaqor, Tremeau, CellProThera, Moderna, American Regent, Sarepta, Lexicon, Anacardio, Akros, and Valo. Dr McMurray has received payments through Glasgow University from work on clinical trials; has receviedconsulting and grants from Amgen, AstraZeneca, Bayer, Cardurion, Cytokinetics, GSK and Novartis, British Heart Foundation, National Institute for Health - National Heart, Lung, and Blood Institute (NIH-NHLBI), Boehringer Ingelheim, SQ Innovations, and Catalyze Group; has receivedpersonal consultancy fees from Alynylam Pharmaceuticals, Amgen, AnaCardio, AstraZeneca, Bayer, Berlin Cures, BMS, Cardurion, Cytokinetics, Ionis

Pharmaceuticals, Novartis, Regeneron Pharmaceuticals, and River 2 Renal Corp; has received personal lecture fees from Abbott, Alkem Metabolics, Astra Zeneca, Blue Ocean Scientific Solutions Ltd., Boehringer Ingelheim, Canadian Medical and Surgical Knowledge, Emcure Pharmaceuticals Ltd., Eris Lifesciences, European Academy of CME, Hikma Pharmaceuticals, Imagica Health, Intas Pharmaceuticals, J.B. Chemicals & Pharmaceuticals Ltd, Lupin Pharmaceuticals, Medscape/Heart.Org., ProAdWise Communications, Radcliffe Cardiology, Sun Pharmaceuticals, The Corpus, Translation Research Group, and Translational Medicine Academy; and data safety monitoring board membership for WIRB-Copernicus Group Clinical Inc; andis a director of Global Clinical Trial Partners Ltd.All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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KEY WORDS body mass index, heart failure with preserved ejection fraction, mineralocorticoid receptor antagonist, obesity, waist-to-height ratio

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