JAMA Cardiology | Original Investigation

Finerenone in Women and Men With Heart Failure With Mildly Reduced or Preserved Ejection Fraction

A Secondary Analysis of the FINEARTS-HF Randomized Clinical Trial

Misato Chimura, MD, PhD; Xiaowen Wang, MD, MPH; Pardeep S. Jhund, MBChB, MSc, PhD; Alasdair D. Henderson, PhD; Brian L. Claggett, PhD; Akshay S. Desai, MD, MPH; Cândida Fonseca, MD, PhD; Eva Goncalvesova, MD; Tzvetana Katova, MD, PhD; Katharina Mueller, Msc; Andrea Glasauer, PhD; Katja Rohwedder, MD; Prabhakar Viswanathan, MBBS, PhD; Savina Nodari, MD; Carolyn S. P. Lam, MD, PhD; Clara Inés Saldarriaga, MD; Michele Senni, MD; Kavita Sharma, MD; Adriaan A. Voors, MD; Faiez Zannad, MD; Bertram Pitt, MD; Orly Vardeny, PharmD; Muthiah Vaduganathan, MD, MPH; Scott D. Solomon, MD; John J. V. McMurray, MD

IMPORTANCE Sex is associated with the clinical presentation, outcomes, and response to treatment in patients with heart failure (HF). However, little is known about the safety and efficacy of treatment with finerenone according to sex.

OBJECTIVE To estimate the efficacy and safety of finerenone compared with placebo in both women and men.

DESIGN, SETTING, AND PARTICIPANTS Prespecified analyses were conducted in the phase 3 randomized clinical trial Finerenone Trial to Investigate Efficacy and Safety Superior to Placebo in Patients with Heart Failure (FINEARTS-HF). The trial was conducted across 653 sites in 37 countries. Participants were adults aged 40 years and older with symptomatic HF and left ventricular ejection fraction (LVEF) of 40% or greater randomized between September 2020 and January 2023.

INTERVENTION Finerenone (titrated to 20 mg or 40 mg) or placebo.

MAIN OUTCOMES AND MEASURES The primary outcome was a composite of cardiovascular death and total (first and recurrent) HF events (unplanned HF hospitalizations or urgent HF visits).

RESULTS A total of 6001 patients were randomized in FINEARTS-HF, of whom 2732 were women (45.5%), with a mean (SD) age of 73.6 (9.1) years. Women had higher rates of any obesity, higher LVEF (54.6 [7.6%] vs 50.9 [7.6] for men), lower mean (SD) estimated glomerular filtration rate than men (59.7 [19.1] vs 64.1 [20.0] for men; P<.001) , worse New York Heart Association functional class, and lower Kansas City Cardiomyopathy Questionnaire-Total Symptom Scores (KCCQ-TSS) (mean [SD] 62.3 [24.0] vs 71.0 [23.1]). The incident rate of the primary outcome was slightly lower in women (15.7; 95% CI, 14.3-17.3) than in men (16.8; 95% CI, 15.4-18.3) per 100 person-years. Compared with placebo, finerenone reduced the risk of the primary end point similarly in women and men: rate ratio 0.78 (95% CI, 0.65-0.95) in women and 0.88 (95% CI, 0.74-1.04) in men (P = .41 for interaction). Consistent effects were observed for the components of the primary outcome and all-cause mortality. The mean increase (improvement) in KCCQ-TSS from baseline to 12 months was greater with finerenone, regardless of sex (P = .73 for interaction). Finerenone had similar tolerability in women and men.

CONCLUSIONS AND RELEVANCE In FINEARTS-HF, finerenone reduced the risk of the primary end point similarly in women and men with heart failure with mildly reduced or preserved ejection fraction. Finerenone had similar tolerability in women and men.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT04435626

Editor's Note page 70

Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: John J. V. McMurray, MD, Institute of Cardiovascular and Medical Sciences, BHF Glasgow Cardiovascular Research Centre, University of Glasgow, Glasgow G128 TA, United Kingdom (john.mcmurray@glasgow.ac.uk).

JAMA Cardiol. 2025;10(1):59-70. doi:10.1001/jamacardio.2024.4613
Published online November 17, 2024.

Sex-related differences have been reported in heart failure (HF) epidemiology, ejection fraction phenotype, symptoms and presentation, comorbidities, and outcomes.[1-10] More controversially, sex has been reported to modify the response to some treatments in patients with HF. In HF with reduced ejection fraction (HFrEF), women appear to obtain more benefit from cardiac resynchronization therapy.[11] In HF with mildly reduced ejection fraction (HFmrEF) and HF with preserved ejection fraction (HFpEF), sex-specific spline analyses suggested that the benefit of the angiotensin receptor-neprilysin inhibitor (ARNI) sacubitril/valsartan over enalapril, extended to a higher left ventricular ejection fraction (LVEF) in women compared with men in the PARAGON-HF trial (Prospective Comparison of ARNI With ARB Global Outcomes in Heart Failure With Preserved Ejection Fraction).[12] A somewhat similar finding was reported with the steroidal mineralocorticoid receptor antagonist (MRA) spironolactone compared with placebo in the TOPCAT trial (Treatment of Preserved Cardiac Function Heart, Failure With an Aldosterone Antagonist) although the test for interaction between sex, LVEF, and treatment was not statistically significant.[13,14] Recently, semaglutide has been shown to reduce weight more in women than men with HFmrEF/HFpEF and obesity.[15]

These findings underscore the importance of sex-specific evaluation of the effect of treatment in HF as endorsed by leading societies and journals and recently highlighted in HFmrEF/HFpEF.[16-19] For that reason, we prespecified an examination of the efficacy and safety of the nonsteroidal MRA finerenone in women and men with HFmrEF/HFpEF enrolled in the FINEARTS-HF trial (Finerenone Trial to Investigate Efficacy and Safety Superior to Placebo in Patients With Heart Failure).[20-22] Among the 6001 participants analyzed, 45.5% were women. The primary outcome was the composite of cardiovascular death and total (first and recurrent) HF events, including unplanned hospitalization for HF or urgent HF events. Treatment with finerenone reduced the primary end point significantly by 16% compared with placebo (rate ratio, 0.84; 95% CI, 0.74-0.95; $P = .007$).[20]

Key Points

Question Are the effects and safety profile of finerenone in patients with mildly reduced or preserved ejection fraction consistent in women and men?

Findings In this secondary analysis of a randomized clinical trial including 6001 adults with symptomatic heart failure and left ventricular ejection fraction, women and men experienced similar outcomes from finerenone treatment in reducing cardiovascular death and heart failure events, as well as improving symptoms. Adverse events were more common with finerenone but did not differ between the sexes.

Meaning Heart failure with mildly reduced or preserved ejection fraction is relatively more common in women, and results of this study suggest that the consistent efficacy and safety of finerenone is especially relevant for them.

Methods

FINEARTS-HF Study Design and Objectives

FINEARTS-HF was a prospective, randomized, double-blind, placebo-controlled, event-based trial that examined the efficacy and safety of finerenone compared with placebo, in patients with HFmrEF/HFpEF. This study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline. The design, baseline characteristics, and primary results have been published.[20-22] The protocol was approved by the respective ethics committee at each site and all patients gave written consent. The FINEARTS-HF trial protocol is available in Supplement 1, and the statistical analysis plan is available in Supplement 2.

Study Participants and Treatment

Key inclusion criteria were New York Heart Association (NYHA) functional class II-IV, treatment with a diuretic for 30 or more days before randomization, a left ventricular ejection fraction (LVEF) 40% or more with evidence of structural heart disease (either left atrial enlargement or left ventricular hypertrophy), and an elevated natriuretic peptide level (N-terminal pro-B-type natriuretic peptide [NT-proBNP] >300 pg/mL [or BNP >100 pg/mL] for patients in sinus rhythm or NT-proBNP >900 pg/mL [or BNP >300 pg/mL] for patients in atrial fibrillation). Ambulatory and hospitalized patients were eligible for enrolment. Patients with prior LVEF less than 40% with subsequent improvement to 40% or more were also eligible provided that ongoing HF symptoms were present. Key exclusion criteria were estimated glomerular filtration rate (eGFR) less than 25 mL/min/1.73 m^2, serum potassium greater than 5.0 mmol/L at screening or randomization, or symptomatic hypotension with mean systolic blood pressure (SBP) less than 90 mm Hg at screening or randomization. A complete list of exclusion criteria has been pulished.[21]

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

Trial Outcomes

The primary outcome was the composite of total (first and recurrent) HF events (including HF hospitalizations or urgent HF events) and cardiovascular death. Secondary outcomes included total HF events; change from baseline to 6, 9, and 12 months in the Kansas City Cardiomyopathy Questionnaire total symptom score (KCCQ-TSS); improvement in NYHA functional class from baseline to 12 months; time to first occurrence of composite renal end point (sustained decrease in eGFR ≥50% relative to baseline over at least 4 weeks, or sustained eGFR decline in eGFR to <15 mL/min/1.73 m^2, or initiation of dialysis or kidney transplant); and time to all-cause death (tested outside the α control hierarchy for the other secondary outcomes). Due to the small number of events for the composite kidney end point, it was not examined in this subgroup analysis. In sensitivity analyses, we also examined

cardiovascular death, cardiovascular death or a first HF event, and a first HF event. The prespecified safety outcomes included hyperkalemia (serum potassium >5.5 mmol/L or >6.0 mmol/L), hypokalemia (serum potassium <3.5 mmol/L), elevation of serum creatinine (≥2.5 mg/dL or ≥3.0 mg/dL), and hypotension (SBP <100 mm Hg).

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 χ^2 test for categorical variables and the Wilcoxon rank sum test for nonnormally distributed variables and *t* test for normally distributed continuous variables. A Poisson model with robust SEs was used to analyze the incidence rate of events by sex with total follow-up time included as an offset in the model. To compare the effects of finerenone vs placebo according to sex, time-to-event data were evaluated using Kaplan-Meier curves and Cox proportional hazards regression models, with treatment assignment as a fixed effect and region and baseline LVEF (<60% or ≥60%) as stratification factors, with hazard ratios (HR) and 95% CIs reported. Total (first and recurrent) events were evaluated using Nelson-Aalen cumulative hazard curves and rate ratios (RRs) with 95% CIs from semiparametric proportional rates models from the approach of Lin et al,[23] with adjustments and stratification for the variables mentioned previously. Models were also adjusted for baseline variables (age, heart rate, SBP, body mass index, eGFR, NYHA functional class III/IV, LVEF, myocardial infarction, NT-proBNP [log], diabetes, history of atrial fibrillation, and history of HF hospitalization). The effect of finerenone vs placebo across the range of LVEF as a continuous variable was modeled using a restricted cubic spline with 3 knots. The proportion of patients with improvement in NYHA functional class from baseline to 12 months was evaluated using logistic regression models, adjusted for treatment assignment and stratification factors, and odds ratios (OR) with 95% CIs reported, with these models also being adjusted for the variables mentioned previously.

Changes from baseline to 12 months in creatinine, serum potassium, SBP, and KCCQ-TSS between treatment groups were analyzed using mixed-effects models for repeated measurements, adjusted for baseline values, follow-up visits, treatment assignment, interaction between treatment and visit, and stratification factors. Missing values were excluded from the analysis. Least squares mean differences between treatment groups at each visit were reported. Responder analyses were conducted to compare the proportions of patients experiencing a deterioration (defined as a deterioration of ≥5 points) and those showing clinically significant improvements, categorized as small (≥5 points), moderate (≥10 points), or large (≥20 points) changes in KCCQ-TSS at 12 months, as described previously.[24] These comparisons were analyzed using logistic regression models adjusted for baseline KCCQ score, stratification factors region, and baseline LVEF (<60%, ≥60%). The incidence of safety end points was estimated using logistic regression models adjusted for stratification factors and treatment effect with an interaction by sex, which was tested using a likelihood ratio test. All statistical analyses were conducted using STATA version 18 (StataCorp LLC), and a $P < .05$ was considered statistically significant.

Results

Patient Characteristics: Women vs Men

Overall, 2732 women (45.5%) and 3269 men (54.5%) were analyzed (eFigure 1 in Supplement 3). Baseline characteristics by sex are presented in **Table 1**. Women were older than men (mean [SD] age, 73.6 [9.1] years vs 70.6 [9.9] years for men) and had lower mean (SD) eGFR than men (59.7 [19.1] vs 64.1 [20.0] for men; $P < .001$) and higher rates of BMI class II-II obesity than men (654 of 2732 [24.0%] vs 492 of 3269 [15.1%]). The median NT-proBNP levels were similar in women and men (with and without atrial fibrillation). The mean (SD) LVEF was 54.6% (7.6%) in women vs 50.9% (7.6%) in men. The distribution of LVEF by sex is shown in eFigure 2 in Supplement 3; the proportion of women with a LVEF 60% or more was 24.9% vs 14.3% of men. Women also had a worse NYHA functional class distribution (35.0% NYHA class III/IV vs 27.5% in men) and much worse self-reported health status (KCCQ-TSS, KCCQ-overall summary score, and KCCQ-clinical summary score—all approximately 10 points lower in women compared with men). Women had worse scores across all KCCQ domains, with lower values in the physical limitation, social limitations, symptom frequency, symptom burden, and quality-of-life domains compared with men (eTable 1 and eFigure 3 in Supplement 3). Women were much less likely than men to be current or former smokers and had lower rates of chronic obstructive pulmonary disease. Women had lower rates of diabetes (despite a higher rate of obesity), coronary heart disease, and peripheral arterial disease but higher rates of hypertension and atrial fibrillation.

Background Treatment at Baseline: Women vs Men

Women were more often treated with angiotensin receptor blockers than angiotensin-converting enzyme inhibitors compared with men but treated less frequently with sodium-glucose cotransporter 2 inhibitors. The use of β-blockers and loop diuretics was similar in both women and men although thiazide diuretics were used more frequently in women.

Trial Treatment Dose Achieved: Women vs Men

In patients assigned to the 10 mg, increasing to 20 mg, dosing strategy, the mean (SD) achieved dose in the placebo arm for the duration of the trial was 16.8 (4.0) mg in women and 16.6 (4.1) in men; for finerenone, the mean (SD) dose was 15.8 (4.3) mg in women and 15.5 (4.4) mg in men. In patients assigned to the 20 mg, increasing to 40 mg, dosing strategy, the mean (SD) achieved dose in the placebo arm was 34.5 (7.8) mg in women and 34.5 (7.7) in men; for finerenone the mean (SD) dose was 32.0 (9.2) mg in women and 32.5 (9.1) mg in men.

Clinical Outcomes: Women vs Men

Women had slightly lower event rates than men (eTable 2 in Supplement 3). The incidence rate of the primary outcome was slightly lower in women (15.7; 95% CI, 14.3-17.3) than in men

Table 1. Baseline Characteristics of Women and Men

Characteristic	Women (n = 2732)	Men (n = 3269)	*P* value
Participants			
Age, mean (SD), y	73.6 (9.1)	70.6 (9.9)	<.001
Age >70 y, No. (%)	1867 (68.4)	1739 (53.2)	<.001
Region, No. (%)			
Asia	354 (13.0)	629 (19.2)	<.001
Eastern Europe	1228 (45.0)	1422 (43.5)	
Latin America	328 (12.0)	313 (9.6)	
North America	188 (6.9)	283 (8.7)	
Western Europe, Oceania, other	634 (23.2)	622 (19.0)	
Race, No. (%)[a]			
Asian	360 (13.2)	636 (19.5)	<.001
Black	52 (1.9)	36 (1.1)	
White	2224 (81.4)	2511 (76.8)	
Other	96 (3.5)	86 (2.6)	
Heart failure characteristics			
NYHA functional class, No. (%)			
II	1776 (65.0)	2370 (72.5)	<.001
III	935 (34.2)	878 (26.9)	
IV	21 (0.8)	20 (0.6)	
Any prior hospitalization for HF, No. (%)	1623 (59.4)	1996 (61.1)	.19
LVEF, % mean (SD)	54.6 (7.6)	50.9 (7.6)	<.001
Improved LVEF ≥40%, No. (%)	68 (2.5)	205 (6.3)	<.001
LVEF ≥60%, No. (%)	679 (24.9)	468 (14.3)	<.001
KCCQ total symptom score, mean (SD)	62.3 (24.0)	71.0 (23.1)	<.001
KCCQ overall summary score, mean (SD)	57.7 (22.2)	67.0 (21.3)	<.001
KCCQ clinical summary score, mean (SD)	59.9 (22.5)	69.9 (21.5)	<.001
Physiological and laboratory measurements			
SBP, mean (SD), mm Hg	130.1 (15.3)	128.8 (15.3)	.001
Heart rate, mean (SD), bpm	72.1 (12.0)	70.9 (11.6)	<.001
BMI, mean (SD)	30.6 (6.7)	29.4 (5.6)	<.001
BMI group, No. (%)			
<18.5 (Underweight)	41 (1.5)	24 (0.7)	<.001
18.5 to <25 (Normal weight)	537 (19.7)	704 (21.6)	
25 to <30 (Overweight)	803 (29.5)	1187 (36.4)	
30 to <35 (Class I obesity)	692 (25.4)	854 (26.2)	
≥35 (Class II-III obesity)	654 (24.0)	492 (15.1)	
Waist circumference, mean (SD), cm	101.7 (16.3)	105.8 (16.0)	<.001
Increased waist circumference[b]	2183 (79.9)	1822 (55.7)	<.001
Waist/hip ratio, mean (SD)	0.93 (0.10)	1.00 (0.10)	<.001
eGFR, mean (SD), mL/min/1.73 m^2	59.7 (19.1)	64.1 (20.0)	<.001
eGFR <60, No. (%), mL/min/1.73 m^2	1452 (53.1)	1436 (43.9)	<.001
eGFR <45, No. (%), mL/min/1.73 m^2	677 (24.8)	655 (20.0)	<.001
eGFR <30, No. (%), mL/min/1.73 m^2	118 (4.3)	103 (3.2)	<.001
NT-proBNP level, median (IQR), pg/mL	1074 (443-1984)	1014 (452-1911)	.41
In patients with AF, median (IQR), pg/mL	1769 (1212-2808)	1683 (1108-2802)	.16
In patients without AF, median (IQR), pg/mL	568 (307-1247)	608 (316-1270)	.30
Hemoglobin, mean (SD), g/dL	12.8 (1.5)	13.8 (1.7)	<.001
Potassium, mean (SD), mmol/L	4.3 (0.5)	4.4 (0.5)	<.001
HbA_{1c}, median (IQR), %	6.0 (5.7-6.7)	6.1 (5.7-6.8)	.03
UACR, mean (SD), mg/g	133 (487)	185 (697)	.001
UACR category, No. (%), mg/g[c]			
< 30	1625 (61.8)	1886 (59.6)	.002
30 to <300	785 (29.9)	927 (29.3)	
≥300	220 (8.4)	354 (11.2)	

(continued)

Table 1. Baseline Characteristics of Women and Men (continued)

Characteristic	Women (n = 2732)	Men (n = 3269)	*P* value
Medical history, No. (%)			
Hypertension	2452 (89.8)	2873 (87.9)	.02
Diabetes	1036 (37.9)	1403 (42.8)	<.001
Myocardial infarction	449 (16.4)	1092 (33.4)	<.001
Peripheral arterial disease	171 (6.3)	366 (11.2)	<.001
AF history	1538 (56.3)	1735 (53.1)	.01
Chronic obstructive pulmonary disease	288 (10.5)	485 (14.8)	<.001
Smoking status			
Current	112 (4.1)	399 (12.2)	<.001
Former	433 (15.9)	1360 (41.6)	
Never	2187 (80.0)	1510 (46.2)	
Stroke	376 (13.8)	455 (13.9)	.86
Anemia	674 (26.2)	910 (29.4)	.008
Treatments, No. (%)			
β-Blocker	2309 (84.5)	2786 (85.2)	.45
ACEi	879 (32.2)	1276 (39.0)	<.001
ARB	1084 (39.7)	1017 (31.1)	<.001
ARNI	153 (5.6)	360 (11.0)	<.001
SGLT2i	320 (11.7)	497 (15.2)	<.001
Loop diuretics	2362 (86.5)	2877 (88.0)	.07
Thiazide/thiazide-like diuretics	443 (16.2)	388 (11.9)	<.001
Digoxin	266 (9.7)	205 (6.3)	<.001
Anticoagulant	1352 (49.5)	1525 (46.7)	.03
Pacemaker	155 (5.7)	177 (5.4)	.66
ICD	5 (0.2)	43 (1.3)	<.001

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); eGFR, estimated glomerular filtration rate; HbA_{1c}, glycated hemoglobin; HF, heart failure; ICD, implantable cardiac 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; SBP, systolic blood pressure; SGLT2i, sodium–glucose cotransporter 2 inhibitor; UACR, urine albumin-to-creatinine ratio.

SI conversion factors: To convert HbA_{1c} to proportion of total hemoglobin, multiply by 0.01; hemoglobin from g/dL to g/L, multiply by 10; potassium from mmol/L to mEq/L, divide by 1.0.

[a] Race (as chosen by participants) was captured on a dedicated demographics case report form 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. In the table "other" includes American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, and not reported.

[b] Defined as >88 cm in women and >102 cm in men.

[c] Baseline UACR unavailable in 204 patients, hence percentages are expressed as the number of participants of 5797. Also, BMI is unavailable for 13 patients, SBP is unavailable for 2 patients, KCCQ is unavailable for 15 patients, LVEF is unavailable for 8 patients, NT-proBNP is unavailable for 158 patients, and HbA1c is unavailable for 113 patients.

(16.8; 95% CI, 15.4-18.3) per 100 person-years. The difference between women and men increased after adjustment for baseline variables associated with prognosis (eTable 2 in Supplement 3). Although women had a lower (worse) baseline KCCQ-TSS than men and baseline KCCQ-TSS was associated with incidence of the primary outcome, women had a lower incidence of the primary outcome than men across the range of KCCQ-TSS (eFigure 4 in Supplement 3). The incidence of different causes of death varied between women and men (eFigure 5 in Supplement 3).

Effect of Finerenone: Women vs Men

There was no evidence that sex modified the effect of finerenone compared with placebo on the primary end point, with an RR of 0.78 (95% CI, 0.65-0.95) in women and 0.88 (95% CI, 0.74-1.04) in men (*P* = .41 for interaction) (**Table 2** and **Figure 1**). Adjusting for established variables did not change this result (Table 2). The reduction in risk of the primary composite end point was observed across the range of LVEF in both women and men (Figure 1). Consistent benefits were observed for the components of the primary outcome, ie, total HF events (RR, 0.76; 95% CI, 0.62-0.94 in women vs RR, 0.86; 95% CI, 0.70-1.04 in men; *P* = .45 for interaction), and cardiovascular death (HR, 0.87; 95% CI, 0.66-1.15 in women vs HR, 0.96; 95% CI, 0.76-1.20 in men; *P* = .62 for interaction) (Table 2, **Figure 2**; eFigure 6 in Supplement 3). A similar pattern was seen for cardiovascular death or first HF event (*P* = .62 for interaction), first HF event (*P* = .98 for interaction), and all-cause death (*P* = .82 for interaction) (Table 2, Figure 2; eFigure 6 in Supplement 3).

The improvement in NYHA functional class from baseline to 12 months did not differ significantly with finerenone compared with placebo and did not differ between sexes (*P* = .16 for interaction) (eTable 3 in Supplement 3). The mean increase (improvement) in KCCQ-TSS from baseline to 12 months was greater with finerenone compared with placebo

Table 2. Effect of Randomized Treatment on Outcomes According to Sex in FINEARTS-HF

Outcome	Women (n = 2732)				Men (n = 3269)				Finerenone results: women vs men					
	Placebo (n = 1377)		Finerenone (n = 1355)		Placebo (n = 1621)		Finerenone (n = 1648)		RR or HR (95% CI)[a]			RR or HR (95% CI)[b]		
	Total No. of events or No. of events, (%)	Event rate (95% CI)[c]	Total No. of events or No. of events, (%)	Event rate (95% CI)[c]	Total No. of events or No. of events, (%)	Event rate (95% CI)[c]	Total No. of events or No. of events, (%)	Event rate (95% CI)[c]	Women	Men	*P* value for interaction	Women	Men	*P* value for interaction
Primary composite outcome[d]	592	17.6 (15.4-20.0)	451	13.8 (12.0-15.9)	691	17.8 (15.8-20.0)	632	15.8 (13.8-18.0)	RR: 0.78 (0.65-0.95)	RR: 0.88 (0.74-1.04)	.41	RR: 0.75 (0.62-0.90)	RR: 0.85 (0.71-1.01)	.40
Total HF events	483	14.3 (12.4-16.6)	358	11.0 (9.4-12.8)	541	13.9 (12.2-15.9)	484	12.1 (10.4-14.1)	RR: 0.76 (0.62-0.94)	RR: 0.86 (0.70-1.04)	.45	RR: 0.73 (0.59-0.90)	RR: 0.83 (0.69-1.01)	.38
Cardiovascular death or first HF event	327 (23.7)	10.8 (9.6-12.0)	266 (19.6)	8.8 (7.8-10.0)	392 (24.2)	11.2 (10.1-12.4)	358 (21.7)	9.7 (8.8-10.8)	HR: 0.81 (0.69-0.96)	HR: 0.86 (0.75-0.99)	.62	HR: 0.79 (0.67-0.93)	HR: 0.81 (0.70-0.94)	.81
Cardiovascular death	110 (8.0)	3.3 (2.7-3.9)	93 (6.9)	2.8 (2.3-3.5)	150 (9.3)	3.9 (3.3-4.5)	149 (9.0)	3.7 (3.2-4.4)	HR: 0.87 (0.66-1.15)	HR: 0.96 (0.76-1.20)	.62	HR: 0.84 (0.63-1.11)	HR: 0.90 (0.71-1.13)	.81
First HF event	262 (19.0)	8.6 (7.6-9.8)	211 (15.6)	7.0 (6.1-8.0)	311 (19.2)	8.9 (7.9-1.0)	268 (16.3)	7.3 (6.4-8.2)	HR: 0.81 (0.67-0.97)	HR: 0.81 (0.69-0.95)	.98	HR: 0.78 (0.65-0.95)	HR: 0.77 (0.65-0.91)	.88
All-cause death	218 (15.8)	6.4 (5.7-7.4)	201 (14.8)	6.1 (5.3-7.0)	304 (18.8)	7.8 (7.0-8.7)	290 (17.6)	7.2 (6.4-8.1)	HR: 0.94 (0.78-1.14)	HR: 0.92 (0.78-1.08)	.82	HR: 0.94 (0.78-1.15)	HR: 0.90 (0.76-1.06)	.63

Abbreviations: FINEARTS-HF, Finerenone Trial to Investigate Efficacy and Safety Superior to Placebo in Patients with Heart Failure; HF, heart failure; HR, hazard ratio; RR, rate ratio.

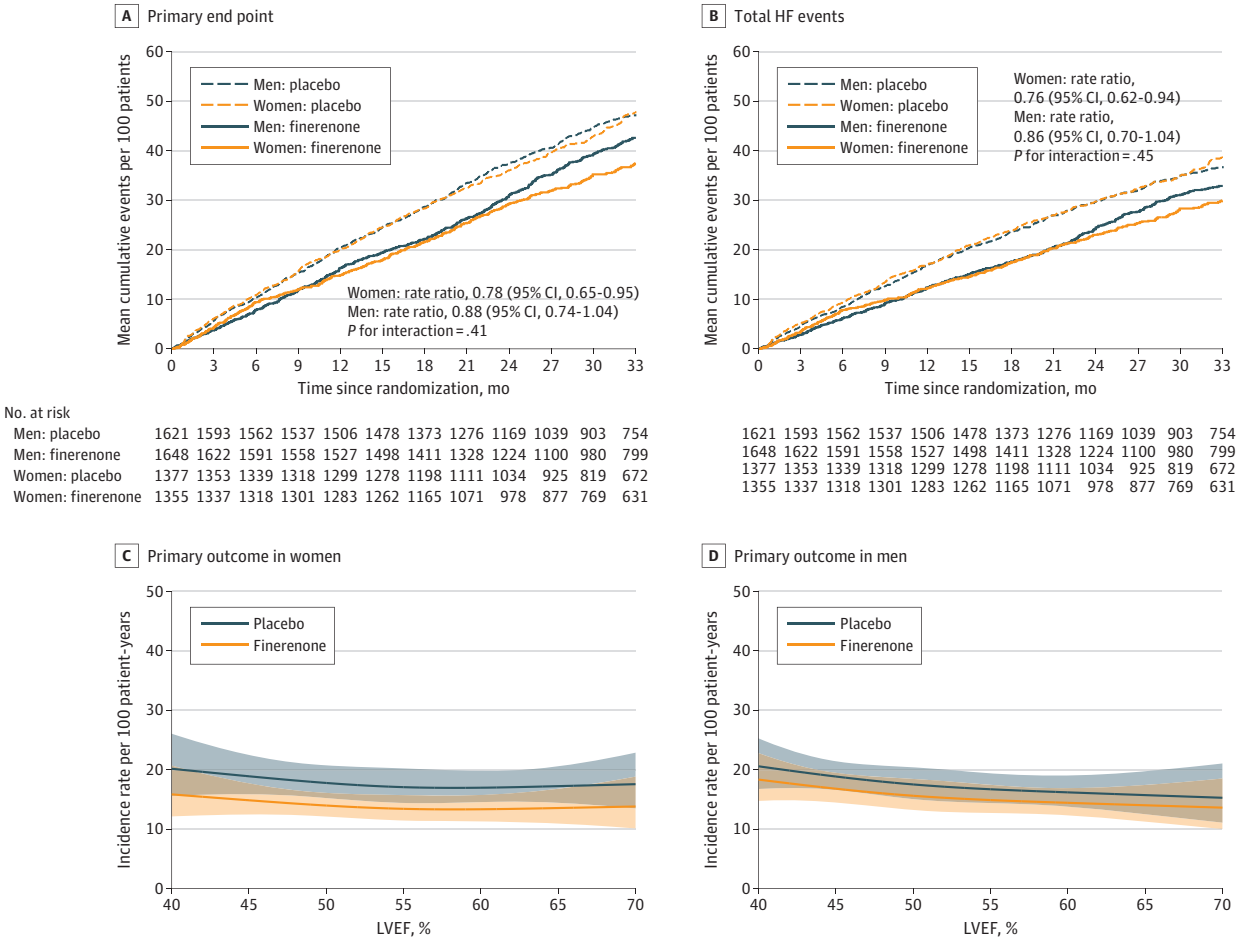
[a] Models were stratified by region and baseline left ventricular ejection fraction (<60% or ≥60%), and adjusted for treatment assignment.

[b] Models were stratified by region and baseline left ventricular ejection fraction (<60% or ≥60%), and adjusted for treatment assignment, age, heart rate, systolic blood pressure, body mass index, estimated glomerular filtration rate, NYHA functional class III/IV, left ventricular ejection fraction, myocardial infarction, N-terminal pro-B-type natriuretic peptide [log], diabetes, history of atrial fibrillation, and history of HF hospitalization.

[c] Event rate is the number of events per 100 person-years.

[d] Cardiovascular death and total HF events.

Figure 1. Key Trial Outcomes According to Sex and Treatment Assignment in Finerenone Trial to Investigate Efficacy and Safety Superior to Placebo in Patients With Heart Failure (FINEARTS-HF)



A and B, The Nelson-Aalen estimate of the cumulative hazard for the primary composite end point and total HF events. C and D, The association between LVEF and the incidence rate for the primary outcome, by sex and treatment. The shaded area represents the 95% CI. HF indicates heart failure; LVEF, left ventricular ejection fraction.

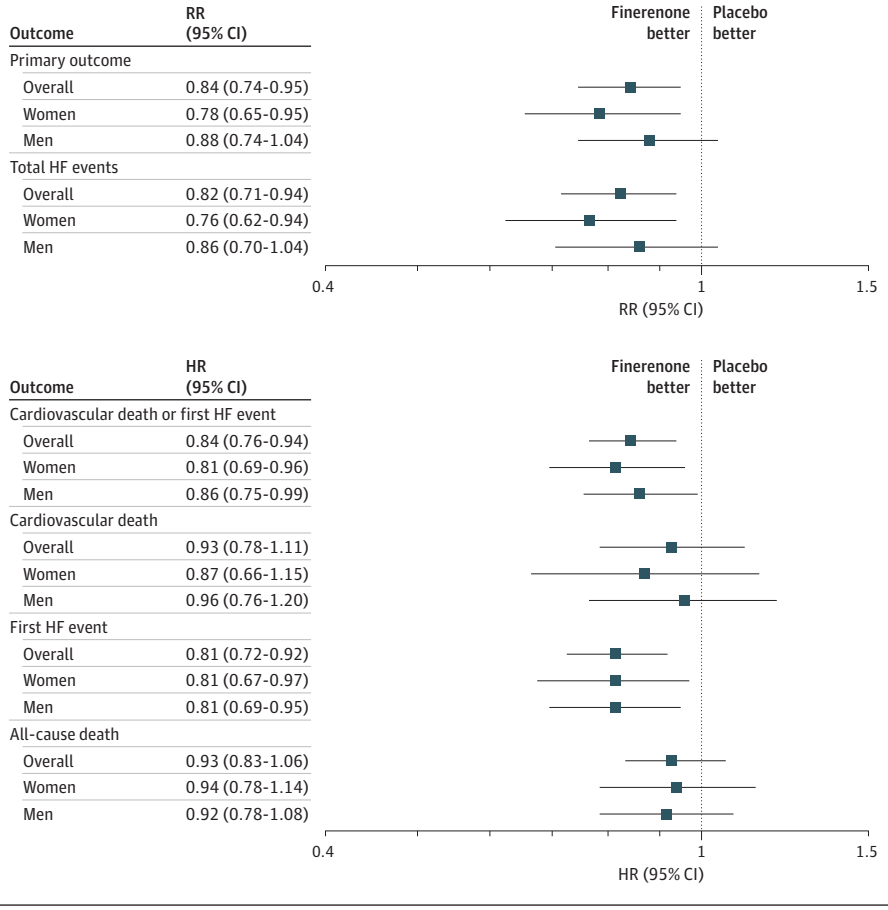
irrespective of sex (P = .73 for interaction) (eTable 3 and eFigure 7 in Supplement 3). The proportion of patients with an improvement in KCCQ-TSS of at least 5 points, 10 points, and 20 points tended to be greater with finerenone compared with placebo (but only statistically significant, overall, for ≥20 points), with consistent effects observed in both women and men (P = .24 for interaction at 5 points; P = .16 for interaction at 10 points; and P = .65 for interaction at 20 points) (eTable 3 and eFigure 8 in Supplement 3). Although not statistically significant, the proportion of patients with a decrease in KCCQ-TSS of at least 5 points tended to be smaller in those treated with finerenone compared with placebo in both women and men (P = .58 for interaction) (Table 2; eFigure 8 in Supplement 3).

Potassium levels showed a slight increase in the finerenone group at 1 month, with minimal change thereafter (eFigure 9 in Supplement 3). At 12 months, the placebo-corrected increase in potassium was 0.19 mmol/L (95% CI, 0.15-0.22 mmol/L) in women and 0.20 mmol/L (95% CI, 0.16-0.23 mmol/L) in men (to convert potassium from millimoles per liter to milliequivalents per liter, divide by 1.0). Similarly, creatinine levels increased by a small amount in the finerenone group at 1 month, followed by minimal change thereafter (eFigure 9 in Supplement 3). At 12 months, the placebo-corrected increase in creatinine was 0.07 mg/dL (95% CI, 0.04-0.09 mg/dL) in women and 0.08 mg/dL (95% CI, 0.05-0.10 mg/dL) in men (to convert creatinine from milligrams per deciliter to micromoles per liter, multiply by 88.4). SBP decreased modestly at 1 month in the finerenone group, with little change thereafter (eFigure 9 in Supplement 3). At 12 months, the placebo-corrected reduction in SBP was −2.68 mm Hg (95% CI, −3.93 to −1.43 mm Hg) in women and −3.52 mm Hg (95% CI, −4.60 to −2.45 mm Hg) in men.

Tolerability and Safety: Women vs Men

Comparing placebo groups, hypokalemia was more common and elevated creatinine was less common in women compared with men (**Table 3**). Finerenone increased the incidence of hyperkalemia and hypotension, and reduced the risk of hy-

Figure 2. Effects of Finerenone on Key Outcomes According to Sex in Finerenone Trial to Investigate Efficacy and Safety Superior to Placebo in Patients With Heart Failure (FINEARTS-HF)



The Lin et al[23] proportional rates approach (recurrent events) and Cox proportional hazards regression (time to first event) models are stratified by region and baseline left ventricular ejection fraction (<60% or ≥60%) and adjusted for treatment assignment. HF indicates heart failure; HR, hazard ratio; RR, rate ratio.

Table 3. Tolerability According to Sex in FINEARTS-HF

	Women (n = 2732)		Men (n = 3269)		Tolerability: women vs men		
					Odds ratio (95% CI)[a]		
Safety profile	Placebo	Finerenone	Placebo	Finerenone	Women	Men	*P* value for interaction
Hypotension, No. (%)							
SBP <100 mm Hg	154 (11.6)	209 (16.1)	207 (13.1)	329 (20.4)	1.57 (1.24-1.98)	1.76 (1.44-2.16)	.50
Elevated serum creatinine, No. (%)							
≥ 2.5 mg/dL	20 (1.5)	31 (2.4)	69 (4.4)	110 (6.9)	1.58 (0.89-2.79)	1.60 (1.17-2.18)	.99
≥ 3.0 mg/dL	9 (0.7)	12 (0.9)	25 (1.6)	45 (2.8)	1.31 (0.55-3.13)	1.80 (1.10-2.95)	.56
Elevated serum potassium, No. (%)							
>5.5 mmol/L	79 (6.0)	170 (13.2)	120 (7.6)	243 (15.1)	2.36 (1.78-3.13)	2.21 (1.75-2.79)	.72
>6.0 mmol/L	14 (1.1)	37 (2.9)	27 (1.7)	49 (3.1)	2.74 (1.47-5.11)	1.83 (1.14-2.96)	.31
Decreased serum potassium, No. (%)							
< 3.5 mmol/L	148 (11.2)	61 (4.7)	133 (8.5)	66 (4.1)	0.39 (0.29-0.54)	0.45 (0.33-0.61)	.56

Abbreviations: FINEARTS-HF, Finerenone Trial to Investigate Efficacy and Safety Superior to Placebo in Patients with Heart Failure; SBP, systolic blood pressure.

SI conversion factors: To convert creatinine from mg/dL to µmoL, multiply by 88.4; potassium from mmoL/L to mEq/L, divide by 1.0.

[a] Models were adjusted for region and baseline left ventricular ejection fraction (<60% or ≥60%), and treatment assignment.

pokalemia compared with placebo, and these differences were similar in both women and men (Table 3). The proportion of women experiencing a potassium level >5.5 mmol/L was 13.2% in the finerenone group vs 6.0% in the placebo group (odds ratio, 2.36; 95% CI, 1.78-3.13). In men, these proportions were 15.1% in the finerenone group and 7.6% in the placebo group (odds ratio, 2.21; 95% CI, 1.75-2.79; P = .72 for interaction). Potential antiandrogen adverse effects were infrequent in both treatment groups, with no evidence of a difference between finerenone and placebo (eTable 4 in Supplement 3).

Discussion

It is important to evaluate the efficacy and safety of new treatments for HF in both women and men, considering their different clinical and pharmacokinetic profiles.[25-31] Notably, approximately half of the patients in the FINEARTS-HF trial were women, making it one of the few cardiovascular trials with a substantial representation of women. In the present prespecified subgroup analysis, finerenone reduced the risk of the primary composite end point of total (first and recurrent) HF events (including HF hospitalizations and urgent HF events) and cardiovascular death, to a similar extent in both women and men. Additionally, finerenone improved symptoms, as evidenced by the KCCQ-TSS, in both women and men. Furthermore, sex did not modify the tolerability of finerenone.

As expected, there were notable differences between women and men that were consistent with previous reports.[13,32-35] Women were older than men, more often had a history of hypertension and poor renal function and often had obesity yet were less likely to have diabetes. Comorbidities were less prevalent in women compared with men, with marked differences in the prevalence of coronary artery disease and chronic obstructive pulmonary disease (potentially related to big differences in smoking). Conversely, women were assessed by physicians to have worse NYHA functional class, and correspondingly lower self-reported KCCQ scores than men, despite having a higher LVEF and similar NT-proBNP levels compared with men. Indeed, there was a notably higher proportion of women with LVEF 60% or more compared with men (24.9% of women vs 14.3% of men).

The use of loop diuretics was similar between women and men, although more women received a thiazide diuretic. However, despite evidence suggesting that women respond more favorably to sacubitril/valsartan in patients with LVEF 45% or more, as demonstrated in PARAGON-HF,[12] the proportion of women receiving an ARNI was lower than men, as was the use of SGLT2 inhibitors.

Despite their worse KCCQ-TSS and NYHA functional class, women had a lower risk of the outcomes of interest, especially mortality, and particularly after adjustment compared with men. This has also been reported,[34] although the difference between women and men is not as large as in HFrEF. The explanation for this is uncertain but may be related to the lower prevalence of ischemic heart disease among women.[34]

The most important finding in the FINEARTS-HF trial is that finerenone reduced the incidence of the primary end point and total HF events similarly in women and men, which was notable given the higher LVEF in women. While comparing different clinical trials is difficult, two separate analyses of TOPCAT suggested that spironolactone had a greater benefit in women compared with men, particularly at a higher LVEF.[14] However, these reports from TOPCAT differ from not just FINEARTS-HF but also previous trials in HFrEF where the benefit of MRA therapy was similar in women and men.[35]

Improving symptoms and health-related quality of life in HF patients is important and this may be especially true for women who have much worse KCCQ scores than men (almost 10 points lower). Therefore, it was notable that finerenone treatment led to statistically significant improvements in KCCQ scores, in both women and men. Although these overall mean changes appeared small, they were very similar to those observed with SGLT2 inhibitors and sacubitril/valsartan in patients with HFmrEF/HFpEF.[36-38]

HF treatments must also be safe. The excess incidences of elevated potassium, creatinine, and low blood pressure with finerenone compared with placebo showed no significant difference between women and men. Notably, the average increases in creatinine levels were small in both sexes, which may address concerns that elevated creatinine is often seen as a barrier to the use of this treatment. Nevertheless, the doubling in incidence of hyperkalemia with finerenone compared with placebo underscores the need for careful monitoring of potassium levels when using finerenone in clinical practice.

Limitations

As with any study of this type, there are several potential limitations. Most importantly, the participants analyzed were enrolled in a randomized clinical trial with specific inclusion and exclusion criteria, which may limit the generalizability of these findings to all patients with HFmrEF or HFpEF. For some analyses (eg, laboratory variables), there were missing data although these were not extensive. It was difficult to assess the effect of treatment on the risk of death from cardiovascular causes due to the relatively low rate of this event and the relatively short follow-up period. In the adjusted analyses, there may have been unknown confounders.

Conclusions

In this secondary analysis of the FINEHART-HF randomized clinical trial, finerenone reduced the risk of the primary composite outcome of total (first and recurrent) HF events and cardiovascular death, while also improving symptoms, in both women and men. Additionally, finerenone had similar tolerability in women and men. Heart failure with mildly reduced or preserved ejection fraction is relatively more common in women, and results of this study suggest that the consistent efficacy and safety of finerenone is especially relevant for them.

ARTICLE INFORMATION

Accepted for Publication: October 21, 2024.

Published Online: November 17, 2024. doi:10.1001/jamacardio.2024.4613

Author Affiliations: British Heart Foundation Cardiovascular Research Centre, University of Glasgow, Glasgow, United Kingdom (Chimura, Jhund, Henderson, McMurray); Cardiovascular Division, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts (Wang, Claggett, Desai, Vaduganathan, Solomon); Department of Internal Medicine, Hospital São Francisco Xavier, Lisbon, Portugal (Fonseca); Faculty of Medicine, Comenius University, Bratislava, Slovakia (Goncalvesova); Department of Noninvasive Cardiology, National Cardiology Hospital, Sofia, Bulgaria (Katova); Bayer AG, Berlin, Germany (Mueller, Glasauer, Rohwedder, Viswanathan); Department of Cardiology, University of Brescia, Brescia, Italy (Nodari);

National Heart Centre Singapore (Lam); Centro Cardiovascular Colombiano, Clínica Santa María, Medellin, Colombia (Saldarriaga); University of Milano-Bicocca, Papa Giovanni XXIII Hospital, Bergamo, Italy (Senni); Division of Cardiology, Johns Hopkins University School of Medicine, Baltimore (Sharma); Department of Cardiology, University Medical Center Groningen, Groningen, The Netherlands (Voors); Université de Lorraine, Inserm Clinical Investigation Centre, CHU, Nancy, France (Zannad); University of Michigan, School of Medicine, Ann Arbor (Pitt); Department of Medicine, University of Minnesota, Minneapolis (Vardeny); NOVA Medical School, Universidade Nova de Lisboa, Lisbon, Portugal (Fonseca); ASST "Spedali Civili" Hospital, Brescia, Italy (Nodari); Duke-National University of Singapore, Singapore (Lam); Minneapolis VA Health Care System, Minneapolis, Minnesota (Vardeny).

Author Contributions: Drs Henderson and McMurray had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Wang, Glasauer, Viswanathan, Lam, Sharma, Voors, Zannad, Solomon.
Acquisition, analysis, or interpretation of data: Chimura, Jhund, Henderson, Claggett, Desai, Fonseca, Goncalvesova, Katova, Mueller, Glasauer, Rohwedder, Viswanathan, Nodari, Saldarriaga, Senni, Sharma, Voors, Zannad, Pitt, Vardeny, Vaduganathan, McMurray.
Drafting of the manuscript: Chimura, Sharma.
Critical review of the manuscript for important intellectual content: Wang, Jhund, Henderson, Claggett, Desai, Fonseca, Goncalvesova, Katova, Mueller, Glasauer, Rohwedder, Viswanathan, Nodari, Lam, Saldarriaga, Senni, Sharma, Voors, Zannad, Pitt, Vardeny, Vaduganathan, Solomon, McMurray.
Statistical analysis: Chimura, Wang, Jhund, Henderson, Mueller.
Obtained funding: Katova, Solomon.
Administrative, technical, or material support: Glasauer, Sharma.
Supervision: Claggett, Mueller, Rohwedder, Nodari, Saldarriaga, Voors, Zannad, Solomon.

Conflict of Interest Disclosures: Dr Chimura reported receiving grants from the Daiwa Foundation and the Japan Research Foundation for Clinical Pharmacology during the conduct of the study and personal fees from Otsuka Pharma outside the submitted work. Dr Jhund reported that his employer the University of Glasgow has been remunerated for working on clinical trials from Bayer AG, Novartis, AstraZeneca, and Novo Nordisk outside the submitted work; Dr Jhund reported receiving grants from Analog Devices Inc, AstraZeneca, and Roche Diagnostics, receiving personal fees from ProAdWise Communications; and being Director GCTP Ltd. Dr Claggett reported receiving statistical consulting fees from Alnylam, Cardior, Cardurion, Cytokinetics, CVRx, Intellia, and Eli Lilly outside the submitted work. Dr Desai reported receiving institutional research grants to Brigham and Women's Hospital (BWH) from Bayer and personal consulting fees from Bayer during the conduct of the study; institutional research grants to BWH from Abbott, Alnylam, AstraZeneca, DevPro Biopharma, Novartis, and Pfizer, personal consulting fees from Abbott, Alnylam, AstraZeneca, Avidity Biopharma, Axon Therapeutics, Biofourmis, Boston Scientific, Endotronix, GlaxoSmithKline, Merck, Medtronic, Medpace, Icon, Novartis, New Amsterdam, Parexel, Porter Health, Regeneron, Roche, River2Renal, scPharmaceuticals, Veristat, Verily, and Zydus outside the submitted work. Dr Fonseca reported receiving personal fees as national coordinator of the FINEARTS-HF study from Bayer during the conduct of the study; personal speaker fees (financial support to congresses participation) from AstraZeneca, medical writing support from Boehringer Ingelheim, personal speaker and consulting fees from BIAL and Novo Nordisk, travelling and congresses inscription, investigation fees, speaker and consulting fees from Novartis and Pfizer, and personal fees (traveling and congresses inscription, medical writing support, speaker and consulting fees, and grants for investigations) from CSL VIFOR, outside the submitted work. Dr Goncalvesova reported receiving personal fees from Bayer, grants from Novartis, personal fees from Boehringer-Ingelheim, Pfizer, Servier, Amgen, and Merck outside the submitted work. Dr Mueller reported being an employee of and holding stock in Bayer AG. Dr Glasauer reported being an employee of Bayer AG. Dr Rohwedder reported being an employee of Bayer AG during the conduct of the study. Dr Viswanathan reported being an employee of Bayer Pharmaceuticals, the sponsor of the FINEARTS-HF study. Dr Lam reported receiving grants from the National Medical Research Council of Singapore; receiving support by a Clinician Scientist Award from the National Medical Research Council of Singapore, research support from Novo Nordisk and Roche Diagnostics, serving as consultant or on the Advisory Board/ Steering Committee/ Executive Committee of Alnylam Pharma, AnaCardio AB, Applied Therapeutics, AstraZeneca, Bayer, Biopeutics, Boehringer Ingelheim, Boston Scientific, Bristol-Myers Squibb, Corteria, CPC Clinical Research, Eli Lilly , other from Others - Impulse Dynamics, Intellia Therapeutics, Ionis Pharmaceutical, Janssen Research & Development LLC, Medscape/WebMD Global LLC, Merck, Novartis, Novo Nordisk, Quidel Corporation, Radcliffe Group Ltd., Roche, and Us2.outside the submitted work; in addition, Dr Lam had a patent for PCT/SG2016/050217 pending Method for diagnosis and prognosis of chronic heart failure and a patent for US Patent No. 10,702, 247 issued Automated clinical workflow that recognizes and analyses 2-dimensional and Doppler echo images for cardiac measurements and the diagnosis, prediction and prognosis of heart disease. Dr Saldarriaga reported receiving research grants from Bayer during the conduct of the study; personal advisory fees from Merck, Novo Nordisk, speaker fees from Novartis, AstraZeneca, Boehringer Ingelheim, Ely Lilly, Sanofi, and Pfizer outside the submitted work. Dr Senni reported receiving personal fees from Novartis, Bayer, MSD, Abbott, Vifor, Merck, AstraZeneca, Boehringer Ingelheim, Novo Nordisk, and Cardurion outside the submitted work. Dr Sharma reported receiving personal advisory board and consulting fees from Bayer during the conduct of the study, Alleviant, grants from Amgen, and personal advisory board and consulting fees from Bristol-Myers Squibb, Boehringer-Ingelheim, Cytokinetics, Edwards LifeSciences, Novartis, Novo Nordisk, and Rivus outside the submitted work. Dr Voors reported receiving consultant reimbursement to employer (Universitair Medisch Centrum Groningen) from Bayer outside the submitted work. Dr Zannad reported receiving personal fees (steering committees, DMCs, advisory board) from 89bio, Applied Therapeutics, Bayer, Betagenon, Biopeutics, Boehringer, CVRx, Cardior, Cambrian, Cereno pharmaceutical, Cellprothera, CVCT, Lupin, Merck, Northsea, Otsuka, Owkin, Salubris, and Viatris both during the conduct of the study and outside the submitted work. Dr Pitt reported receiving personal consultant fees from Bayer outside the submitted work; in addition, Dr Pitt had a patent issued for US 9931412 (site-specific delivery of eplereone to the myocardium); and consultant fees from AstraZeneca, Boehringer Ingelheim, Lexicon, and consultant fees and owning stock/stock options for Vifor , ScPharmaceuticals, SQinnovations, G3 Pharmaceuticals, KBP Biosciences, Sarfez Pharmaceuticals, Cereno scientific, Sea Star medical, Anacardio, Protonintel, brainstorm, and medical US Patent pending 63/045,783 (histone modulating agents for the preventions and treatment of organ damage). Dr Vardeny reported receiving grants from AstraZeneca, research support to institution from Bayer and Cardurion, and personal fees from Cardior outside the submitted work. Dr Vaduganathan reported receiving research grant support from 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, serving on advisory boards, clinical trial committees, or having speaker engagements from AstraZeneca, Galmed, Novartis, Bayer AG, Occlutech, and Impulse Dynamics outside the submitted work. Dr Solomon reported research support to institution from Bayer; grants from Alexion, Alnylam, Applied Therapeutics, AstraZeneca, Bellerophon, Bayer, BMS, Boston Scientific, Cytokinetics, Edgewise, Eidos/BridgeBio, Gossamer, GSK, Ionis, Lilly, NIH/NHLBI, Novartis, Novo Nordisk, Respicardia, Sanofi Pasteur, Tenaya, Theracos, and US2; AI Grant to Institution and personal consulting fees from Abbott, Action, Akros, Alexion, Alnylam, Amgen, Arena, AstraZeneca, Bayer, BMS, Cardior, Cardurion, Corvia, Cytokinetics, GSK, Intellia, Lilly, Novartis, Roche, Theracos, Quantum Genomics, Tenaya, Sanofi-Pasteur, Dinaqor, Tremeau, CellProThera, Moderna, American Regent, Sarepta, Lexicon, Anacardio, Akros, and Valon outside the submitted work. Dr McMurray reported payment from Bayer to Glasgow University during the conduct of the study; personal lecture fees from Abbott, Alkem Metabolics, AstraZeneca, 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; personal lecture fees from Alynylam Pharmaceuticals, Amgen, AnaCardio, AstraZeneca, Bayer, Berlin Cures, BMS, Cardurion, Cytokinetics, Ionis Pharmaceuticals, Novartis, Regeneron Pharmaceuticals, River 2 Renal Corp; personal consultancy fees from Novartis, Cytokinetics, Amgen, GSK, Cardurion, and payment to Glasgow University from AstraZeneca, personal fees from Global Clinical Trial Partners Ltd. Director, other from British Heart Foundation, National Institute for Health- National Heart Lung, and Blood Institute (NIH-NHLBI), Boehringer Ingelheim, SQ Innovations;

payment to Glasgow University from Catalyze Group, and personal fees from data safety monitoring g board from WIRB-Copernicus Group Clinical Inc outside the submitted work. No other disclosures were reported.

Funding/Support: FINEARTS-HF was funded by Bayer AG. Misato Chimura was funded by Daiwa Foundation and the Japan Research Foundation for Clinical Pharmacology.

Role of the Funder/Sponsor: The funder (Bayer AG) designed and conducted the FINEARTS-HF trial in conjunction with the Steering Committee; the funder was responsible for data collection and management during the trial. The analysis, and interpretation of the data for this manuscript were conducted independently at the University of Glasgow and the preparation, review, and approval of the manuscript, along with the decision to submit the manuscript for publication, was made solely by the authors.

Meeting Presentation: This paper was presented at the American Heart Association's Scientific Sessions 2024; November 17, 2024; Chicago, Illinois.

Data Sharing Statement: See Supplement 4.

REFERENCES

1. Eaton CB, Pettinger M, Rossouw J, et al. Risk factors for incident hospitalized heart failure with preserved versus reduced ejection fraction in a multiracial cohort of postmenopausal women. *Circ Heart Fail*. 2016;9(10):e002883. doi:10.1161/CIRCHEARTFAILURE.115.002883

2. Savji N, Meijers WC, Bartz TM, et al. The association of obesity and cardiometabolic traits with incident HFpEF and HFrEF. *JACC Heart Fail*. 2018;6(8):701-709. doi:10.1016/j.jchf.2018.05.018

3. Kannel WB, Hjortland M, Castelli WP. Role of diabetes in congestive heart failure: the Framingham study. *Am J Cardiol*. 1974;34(1):29-34. doi:10.1016/0002-9149(74)90089-7

4. Levy D, Larson MG, Vasan RS, Kannel WB, Ho KK. The progression from hypertension to congestive heart failure. *JAMA*. 1996;275(20):1557-1562. doi. doi:10.1001/jama.1996.03530440037034

5. Samad Z, Boyle S, Ersboll M, et al; REMIT Investigators. Sex differences in platelet reactivity and cardiovascular and psychological response to mental stress in patients with stable ischemic heart disease: insights from the REMIT study. *J Am Coll Cardiol*. 2014;64(16):1669-1678. doi:10.1016/j.jacc.2014.04.087

6. Pimple P, Lima BB, Hammadah M, et al. Psychological distress and subsequent cardiovascular events in individuals with coronary artery disease. *J Am Heart Assoc*. 2019;8(9):e011866. doi:10.1161/JAHA.118.011866

7. Stolfo D, Uijl A, Vedin O, et al. Sex-based differences in heart failure across the ejection fraction spectrum: phenotyping, and prognostic and therapeutic implications. *JACC Heart Fail*. 2019;7(6):505-515. doi:10.1016/j.jchf.2019.03.011

8. Beale AL, Nanayakkara S, Segan L, et al. Sex differences in heart failure with preserved ejection fraction pathophysiology: a detailed invasive hemodynamic and echocardiographic analysis. *JACC Heart Fail*. 2019;7(3):239-249. doi:10.1016/j.jchf.2019.01.004

9. Beale AL, Meyer P, Marwick TH, Lam CSP, Kaye DM. Sex differences in cardiovascular pathophysiology: why women are overrepresented in heart failure with preserved ejection fraction. *Circulation*. 2018;138(2):198-205. doi:10.1161/CIRCULATIONAHA.118.034271

10. Dewan P, Jackson A, Lam CSP, et al. Interactions between left ventricular ejection fraction, sex and effect of neurohumoral modulators in heart failure. *Eur J Heart Fail*. 2020;22(5):898-901. doi:10.1002/ejhf.1776

11. Linde C, Cleland JGF, Gold MR, et al. The interaction of sex, height, and QRS duration on the effects of cardiac resynchronization therapy on morbidity and mortality: an individual-patient data meta-analysis. *Eur J Heart Fail*. 2018;20(4):780-791. doi:10.1002/ejhf.1133

12. McMurray JJV, Jackson AM, Lam CSP, et al. Effects of sacubitril-valsartan versus valsartan in women compared with men with heart failure and preserved ejection fraction: insights from PARAGON-HF. *Circulation*. 2020;141(5):338-351. doi:10.1161/CIRCULATIONAHA.119.044491

13. Merrill M, Sweitzer NK, Lindenfeld J, Kao DP. Sex differences in outcomes and responses to spironolactone in heart failure with preserved ejection fraction: a secondary analysis of TOPCAT trial. *JACC Heart Fail*. 2019;7(3):228-238. doi:10.1016/j.jchf.2019.01.003

14. Solomon SD, Claggett B, Lewis EF, et al; TOPCAT Investigators. Influence of ejection fraction on outcomes and efficacy of spironolactone in patients with heart failure with preserved ejection fraction. *Eur Heart J*. 2016;37(5):455-462. doi:10.1093/eurheartj/ehv464

15. Verma S, Butler J, Borlaug BA, et al; STEP-HFpEF Trial Committees and Investigators. Efficacy of semaglutide by sex in obesity-related heart failure with preserved ejection fraction: STEP-HFpEF trials. *J Am Coll Cardiol*. 2024;84(9):773-785. doi:10.1016/j.jacc.2024.06.001

16. National Institutes of Health. NIH policy and guidelines on the inclusion of women and minorities as subjects in clinical research. Accessed September 24, 2024. https://grants.nih.gov/policy/inclusion/women-and-minorities/guidelines.htm

17. European Medicines Agency. Gender considerations in the conduct of clinical trials. Accessed September 24, 2024. https://www.ema.europa.eu/en/documents/scientific-guideline/ich-gender-considerations-conduct-clinical-trials-step-5_en.pdf

18. Health Canada. Guidance document: considerations for inclusion of women in clinical trials and analysis of sex differences. Accessed September 24, 2024. https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/clinical-trials/considerations-inclusion-women-clinical-trials-analysis-data-sex-differences.html

19. Kittleson MM, Panjrath GS, Amancherla K, et al. 2023 ACC expert consensus decision pathway on management of heart failure with preserved ejection fraction: a report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol*. 2023;81(18):1835-1878. doi:10.1016/j.jacc.2023.03.393

20. Solomon SD, McMurray JJV, Vaduganathan M, et al; FINEARTS-HF Committees and Investigators. Finerenone in heart failure with mildly reduced or preserved ejection fraction. *N Engl J Med*. 2024;391(16):1475-1485. doi:10.1056/NEJMoa2407107

21. Vaduganathan M, Claggett BL, Lam CSP, et al. Finerenone in patients with heart failure with mildly reduced or preserved ejection fraction: Rationale and design of the FINEARTS-HF trial. *Eur J Heart Fail*. 2024;26(6):1324-1333. doi:10.1002/ejhf.3253

22. Solomon SD, Ostrominski JW, Vaduganathan M, et al. Baseline characteristics of patients with heart failure with mildly reduced or preserved ejection fraction: The FINEARTS-HF trial. *Eur J Heart Fail*. 2024;26(6):1334-1346. doi:10.1002/ejhf.3266

23. Lin DY, Wei LJ, Yang I, Ying Z. Semiparametric regression for the mean and rate functions of recurrent events. *J R Stat Soc Series B Stat Methodol*. 2000;62:711-730. doi:10.1111/1467-9868.00259

24. Yang M, Henderson A, Talebi A, et al. Effect of finerenone on the KCCQ in patients with HFmrEF/HFpEF: A prespecified analysis of FINEARTS-HF. *J Am Coll Cardiol*. Published online September 29, 2024. doi:10.1016/j.jacc.2024.09.023

25. Rosano GM, Lewis B, Agewall S, et al. Gender differences in the effect of cardiovascular drugs: a position document of the Working Group on Pharmacology and Drug Therapy of the ESC. *Eur Heart J*. 2015;36(40):2677-2680. doi:10.1093/eurheartj/ehv161

26. Soldin OP, Mattison DR. Sex differences in pharmacokinetics and pharmacodynamics. *Clin Pharmacokinet*. 2009;48(3):143-157. doi:10.2165/00003088-200948030-00001

27. Regitz-Zagrosek V. Therapeutic implications of the gender-specific aspects of cardiovascular disease. *Nat Rev Drug Discov*. 2006;5(5):425-438. doi:10.1038/nrd2032

28. Pandey A, Omar W, Ayers C, et al. Sex and race differences in lifetime risk of heart failure with preserved ejection fraction and heart failure with reduced ejection fraction. *Circulation*. 2018;137(17):1814-1823. doi:10.1161/CIRCULATIONAHA.117.031622

29. Gori M, Lam CS, Gupta DK, et al; PARAMOUNT Investigators. Sex-specific cardiovascular structure and function in heart failure with preserved ejection fraction. *Eur J Heart Fail*. 2014;16(5):535-542. doi:10.1002/ejhf.67

30. Lam CSP, Arnott C, Beale AL, et al. Sex differences in heart failure. *Eur Heart J*. 2019;40(47):3859-3868c. doi:10.1093/eurheartj/ehz835

31. Vaduganathan M, Tahhan AS, Alrohaibani A, et al. Do women and men respond similarly to therapies in contemporary heart failure clinical trials? *JACC Heart Fail*. 2019;7(3):267-271. doi:10.1016/j.jchf.2018.12.016

32. Rossello X, Ferreira JP, Pocock SJ, et al. Sex differences in mineralocorticoid receptor antagonist trials: a pooled analysis of three large clinical trials. *Eur J Heart Fail*. 2020;22(5):834-844. doi:10.1002/ejhf.1740

33. O'Meara E, Clayton T, McEntegart MB, et al; CHARM Investigators. Sex differences in clinical characteristics and prognosis in a broad spectrum of patients with heart failure: results of the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) program. *Circulation*. 2007;115(24):3111-3120. doi:10.1161/CIRCULATIONAHA.106.673442

34. Dewan P, Rørth R, Raparelli V, et al. Sex-related differences in heart failure with preserved ejection fraction. *Circ Heart Fail*. 2019;12(12):e006539. doi:10.1161/CIRCHEARTFAILURE.119.006539

35. Jhund PS, Talebi A, Henderson AD, et al. Mineralocorticoid receptor antagonists in heart failure: an individual patient level meta-analysis. *Lancet*. 2024;404(10458):1119-1131. doi:10.1016/S0140-6736(24)01733-1

36. Butler J, Filippatos G, Jamal Siddiqi T, et al. Empagliflozin, health status, and quality of life in patients with heart failure and preserved ejection fraction: The EMPEROR-Preserved Trial. *Circulation*.

2022;145(3):184-193. doi:10.1161/CIRCULATIONAHA.121.057812

37. Chandra A, Polanczyk CA, Claggett BL, et al. Health-related quality of life outcomes in PARAGON-HF. *Eur J Heart Fail*. 2022;24(12):2264-2274. doi:10.1002/ejhf.2738

38. Kosiborod MN, Bhatt AS, Claggett BL, et al. Effect of dapagliflozin on health status in patients with preserved or mildly reduced ejection fraction. *J Am Coll Cardiol*. 2023;81(5):460-473. doi:10.1016/j.jacc.2022.11.006

Editor's Note

Sex-Specific Efficacy and Safety in HF Trials
Inclusion Is Only the First Step

Sadiya Khan, MD, MSc; Clyde W. Yancy, MD, MSc; Gregg C. Fonarow, MD

Heart failure is one of the major health threats to women and men, with both sexes facing similarly high lifetime risks of developing heart failure and dismal outcomes following diagnosis. Yet, important sex-related differences are observed in the age at presentation, symptoms, comorbid conditions, ejection fraction phenotype, health-related quality of life, and clinical outcomes for heart failure.[1] Given that biological sex assigned at birth may modify the efficacy or safety of therapies, sex-specific evaluations of randomized clinical trials of efficacy, safety, and tolerability of evidence-based heart failure therapies are essential. While sex-specific analyses are mandated by regulatory and funding agencies, randomized clinical trials in heart failure still do not reliably have sufficient representation of women to rigorously evaluate meaningful sex differences. Therefore, both representative inclusion of women in clinical trials and reporting of sex-specific analyses remain important priorities.

Related article page 59

Women represent well over 50% of the patients who present with heart failure with mildly reduced ejection fraction (HFmrEF) or preserved ejection fraction (HFpEF), often with left ventricular ejection fraction greater than 0.60.[1] Yet, in contrast with heart failure with reduced ejection fraction (HFrEF), where multiple therapies have been demonstrated to improve clinical outcome, until recently there was an absence of evidence-based therapies for HFmrEF and HFpEF.[1] Clinical trials have established clinical benefits of sodium glucose cotransporter inhibitors and incretin mimetics in patients with HFmrEF or HFpEF.[1] Similar efficacy, safety, and tolerability were found for women and men with these agents. While there were definitive data for mineralocorticoid receptor antagonists (MRA) in HFrEF, data in HFrEF and HFpEF were inadequate.[1] The Finerenone Trial to Investigate Efficacy and Safety Superior to Placebo in Patients With Heart Failure (FINEARTS-HF) convincingly demonstrated that the nonsteroidal MRA finerenone reduced the primary composite risk of cardiovascular death and total worsening heart failure events in patients with heart failure and ejection fraction 40% or more.[2]

Chimura and colleagues[3] have provided a detailed prespecified secondary sex-based analysis of FINEARTS-HF. The trial enrolled 2732 women (45.5%) of the total population. Compared with placebo, finerenone similarly reduced the risk of the primary composite end point with a rate ratio of 0.78 (95% CI, 0.65-0.95) in women and 0.88 (95% CI, 0.77-1.04) in men, (P = .41 for interaction).[3] Improvements in health status indexed by KCCQ score were also similar by sex. While adverse events, particularly hyperkalemia, were more frequent with finerenone vs placebo, tolerability and safety were similar in women and men.

The findings of this trial and the demonstration of consistent benefit of finerenone represents an important therapeutic advance in women and men with HFmrEF/HFpEF and is a definitive declaration of MRA efficacy for heart failure across the entire EF spectrum and for all heart failure phenotypes. Future trials should mimic sex-specific analyses as was done in Chimura and colleagues[3] along with equitable implementation by sex.

In practice, careful attention to dosing and close monitoring for hyperkalemia for both women and men will be obligatory. This work sets the stage for translating these findings by ensuring there is effective, safe, and equitable implementation regardless of sex and avoiding the all-too-common undertreatment of women with heart failure even when evidence of benefit is available.

Author Affiliations: Division of Cardiology, Northwestern University Feinberg School of Medicine, Chicago, Illinois (Khan, Yancy); Associate Editor, *JAMA Cardiology* (Khan); Deputy Editor, *JAMA Cardiology* (Yancy); Ahmanson-UCLA Cardiomyopathy Center, David Geffen School of Medicine, University of California, Los Angeles (Fonarow); Section Editor, *JAMA Cardiology* (Fonarow).

Corresponding Author: Gregg C. Fonarow, MD, UCLA Division of Cardiology, 10833 LeConte Ave, Los Angeles, CA 90095-1679 (gfonarow@mednet.ucla.edu).

Published Online: November 17, 2024. doi:10.1001/jamacardio.2024.4624

Conflict of Interest Disclosures: Dr Khan reported grants from the National Heart, Lung, and Blood Institute and the American Heart Association outside the submitted work. Dr Fonarow reported receiving personal fees from Abbott, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Cytokinetics, Edwards, Eli Lilly, Janssen, Johnson & Johnson, Medtronic, Merck, Novartis, and Pfizer outside the submitted work. No other disclosures were reported.

1. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2022;145(18):e895-e1032. doi:10.1161/CIR.0000000000001063

2. Solomon SD, McMurray JJV, Vaduganathan M, et al; FINEARTS-HF Committees and Investigators. Finerenone in heart failure with mildly reduced or preserved ejection fraction. *N Engl J Med*. 2024;391(16):1475-1485. doi:10.1056/NEJMoa2407107

3. Chimura M, Wang X, Jhund PS, et al. Finerenone in women and men with heart failure with mildly reduced or preserved ejection fraction: a secondary analysis of the FINEARTS-HF randomized clinical trial. *JAMA Cardiol*. Published online November 17, 2024. doi:10.1001/jamacardio.2024.4613