

# Finerenone and Atrial Fibrillation in Heart Failure

## A Secondary Analysis of the FINEARTS-HF Randomized Clinical Trial

Shingo Matsumoto, MD, PhD; Alasdair D. Henderson, PhD; Pardeep S. Jhund, MBChB, MSc, PhD; Johann Bauersachs, MD; Ovidiu Chioncel, MD; Brian L. Claggett, PhD; Josep Comin-Colet, MD, PhD; Akshay S. Desai, MD, MPH; Gerasimos Filippatos, MD; Carolyn S. P. Lam, MBBS, PhD; Bertram Pitt, MD; Markus Florian Scheerer, PhD; James Lay-Flurrie, MSc; Flaviana Amarante, MD; Meike Brinker, MD; Morten Schou, MD, PhD; Michele Senni, MD; Sanjiv J. Shah, MD; Adriaan A. Voors, MD; Faiez Zannad, MD; Shelley Zieroth, MD; Muthiah Vaduganathan, MD, MPH; Scott D. Solomon, MD; John J. V. McMurray, MD

 [Supplemental content](#)

**IMPORTANCE** Heart failure (HF) with mildly reduced or preserved ejection fraction and atrial fibrillation (AF) are closely intertwined.

**OBJECTIVE** To examine the efficacy and safety of the nonsteroidal mineralocorticoid receptor antagonist finerenone in patients with HF with mildly reduced or preserved ejection fraction according to the absence or presence of AF and the type of AF (paroxysmal vs persistent or permanent).

**DESIGN, SETTING, AND PARTICIPANTS** Prespecified analyses were conducted in the Finerenone Trial to Investigate Efficacy and Safety Superior to Placebo in Patients With Heart Failure (FINEARTS-HF) randomized clinical trial. 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 of 40% or greater, randomized between September 2020 and January 2023. Data analysis was conducted from September 1 to October 1, 2024.

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

**MAIN OUTCOMES AND MEASURES** The primary outcome was the composite of total HF events and cardiovascular death. New-onset AF or atrial flutter (AFL) was a prespecified exploratory outcome.

**RESULTS** Among 5984 patients (mean [SD] age, 72.0 [9.6] years; 2724 [45.5%] female) with known AF status at baseline, 1384 (23.1%) had paroxysmal AF and 1886 (31.5%) had persistent or permanent AF. Patients with both types of AF were older and had worse HF status compared with those without AF (2714 patients [45.4%]). Both types of AF were associated with a higher unadjusted risk of the primary outcome compared with no AF (event rate per 100 person-years of follow-up, 20.3 [95% CI, 17.9-23.1] with paroxysmal AF, 19.8 [95% CI, 17.8-22.0] with persistent or permanent AF, and 11.9 [95% CI, 10.7-13.3] with no AF; rate ratio [RR], 1.62 [95% CI, 1.37-1.92] with paroxysmal AF and 1.66 [95% CI, 1.43-1.93] with persistent or permanent AF vs no AF); however, the associations were attenuated after adjustment for known prognostic variables. The benefit of finerenone on the primary outcome (overall RR, 0.84 [95% CI, 0.74-0.95]) was not modified by baseline AF status (RR, 0.80 [95% CI, 0.65-0.98] with no AF, 0.83 [95% CI, 0.65-1.06] with paroxysmal AF, and 0.85 [95% CI, 0.69-1.05] with persistent or permanent AF; *P* for interaction = .94). New-onset AF or AFL occurred in 6.5% of patients and was associated with a higher subsequent adjusted risk of the primary outcome (rate ratio, 3.65 [95% CI, 2.57-5.18]; *P* < .001). The subdistribution hazard ratio for new-onset AF or AFL among those receiving finerenone vs placebo was 0.77 (95% CI, 0.57-1.04; *P* = .09).

**CONCLUSIONS AND RELEVANCE** The efficacy of finerenone was consistent regardless of AF status. New-onset AF was associated with a substantially higher risk of subsequent outcomes.

**TRIAL REGISTRATION** ClinicalTrials.gov Identifier: [NCT04435626](#)

JAMA Cardiol. doi:10.1001/jamacardio.2025.0848  
Published online March 29, 2025.

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

**Corresponding Author:** John J. V. McMurray, MD, British Heart Foundation Cardiovascular Research Centre, University of Glasgow, 126 University Pl, Glasgow G12 8TA, United Kingdom ([john.mcmurray@glasgow.ac.uk](mailto:john.mcmurray@glasgow.ac.uk)).

**A**trial fibrillation (AF) is a common comorbidity in patients with heart failure (HF), especially in patients with HF and mildly reduced ejection fraction (HFmrEF) or with HF and preserved ejection fraction (HFpEF).<sup>1-3</sup> This arrhythmia often causes hemodynamic deterioration, leading to increases in cardiac filling pressures and natriuretic peptide levels, and is associated with exacerbation of symptoms and worse outcomes.<sup>1-3</sup> In addition, AF is associated with attenuated efficacy of some therapies, such as  $\beta$ -blockers, in patients with HF and reduced ejection fraction (HFrEF).<sup>4-9</sup> Whether AF modifies the effect of mineralocorticoid receptor agonist (MRA) therapy in HFmrEF or HFpEF is uncertain. AF in HF is associated with more advanced disease, more extensive adverse remodeling, and greater neurohumoral activation, all of which might also attenuate the potential benefits of MRA therapy. Additionally, patients with AF usually have worse kidney function, which may make them more susceptible to the adverse effects of MRAs on kidney outcomes and potassium level.<sup>10,11</sup> Moreover, spironolactone was not superior to placebo in the Improved Exercise Tolerance in Heart Failure With Preserved Ejection Fraction by Spironolactone on Myocardial Fibrosis in Atrial Fibrillation (IMPRESS-AF) trial, a dedicated trial in patients with HFpEF and AF.<sup>12</sup> Therefore, it is important to evaluate the efficacy of new treatments according to AF status in patients with HF. Antialdosterone therapies are also of specific interest in relation to AF because aldosterone may play a role in electrical and structural atrial remodeling and contribute to the development of AF.<sup>13-19</sup> This has led to the hypothesis that MRA therapy might reduce the incidence of new-onset AF in patients with HF.<sup>17-21</sup>

In this prespecified subgroup analysis of the Finerenone Trial to Investigate Efficacy and Safety Superior to Placebo in Patients With Heart Failure (FINEARTS-HF) randomized clinical trial, we investigated the efficacy and safety of the non-steroidal MRA finerenone, compared with placebo, according to baseline AF status in patients with HFmrEF or HFpEF. Furthermore, we examined the effect of finerenone on the incidence of new-onset AF or atrial flutter (AFL), which was a prespecified exploratory end point in the FINEARTS-HF trial.

## Methods

The FINEARTS-HF trial was a randomized, double-blind, placebo-controlled, event-driven, clinical trial in patients with HFmrEF or HFpEF. The design, baseline characteristics, and results of the FINEARTS-HF trial have been published.<sup>22,23</sup> Ethics committees for the 653 participating institutions in 37 countries approved the protocol, and all patients gave written informed consent. The trial protocol is available in [Supplement 1](#). The trial followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines. Data analysis was conducted from September 1 to October 1, 2024.

### Trial Population

Briefly, the eligibility criteria were age 40 years or older, symptomatic HF in New York Heart Association (NYHA) functional class II through IV, treatment with a diuretic within 30 days

## Key Points

**Question** Do the efficacy and safety of finerenone differ according to atrial fibrillation (AF) status (absence or presence of AF and type of AF) in patients with heart failure and mildly reduced or preserved ejection fraction?

**Findings** In this secondary analysis of the Finerenone Trial to Investigate Efficacy and Safety Superior to Placebo in Patients With Heart Failure (FINEARTS-HF) randomized clinical trial, AF was common in patients with HF with mildly reduced or preserved ejection fraction. The benefit of finerenone on the primary outcome, composite of total heart failure events and cardiovascular death, was not modified by the presence of AF or its type.

**Meaning** In patients with HFmrEF or HFpEF, the efficacy of finerenone was consistent regardless of AF status.

prior to randomization, and a left ventricular ejection fraction (LVEF) of 40% or greater with evidence of structural heart disease (either left atrial enlargement or left ventricular hypertrophy) measured within 12 months of screening. Patients were also required to have elevated natriuretic peptide levels, an N-terminal pro-B-type natriuretic peptide (NT-proBNP) level of 300 pg/mL or greater (or B-type natriuretic peptide [BNP]  $\geq 100$  pg/mL; to convert to nanograms per liter, multiply by 1) for patients in sinus rhythm, or an NT-proBNP level of 900 pg/mL or greater (or BNP  $\geq 300$  pg/mL) for patients with AF. To address the efficacy and safety of finerenone in patients with HF and improved ejection fraction, an area with limited existing evidence, patients with a prior LVEF less than 40% with subsequent improvement to 40% or higher were also eligible for enrollment provided that ongoing HF symptoms were present and all other inclusion criteria were satisfied. Key exclusion criteria at randomization were serum potassium level greater than 5.0 mEq/L (to convert to millimoles per liter, multiply by 1) or estimated glomerular filtration rate (eGFR) less than 25 mL/min/1.73 m<sup>2</sup>. A complete list of exclusion criteria is provided in the article describing the study design.<sup>22</sup>

Eligible participants were randomized in a 1:1 ratio to finerenone or matching placebo, added to usual therapy (eFigure 1 in [Supplement 2](#)). For participants with an eGFR of 60 mL/min/1.73 m<sup>2</sup> or less, the starting dose was 10 mg once daily, with a maximum maintenance dose of 20 mg once daily. For those with an eGFR higher than 60 mL/min/1.73 m<sup>2</sup>, the starting dose was 20 mg once daily, with a maximum maintenance dose of 40 mg once daily.

### AF

In the present study, patients were categorized according to the type of AF (no AF, paroxysmal AF, and persistent or permanent AF). In the FINEARTS-HF trial, the history of AF was collected through the trial case report forms. Also, an electrocardiogram (ECG) at enrollment was recorded, and investigators specified the heart rhythm as sinus rhythm, AF, or other.

Additionally, the type of AF at baseline was reported in patients who had a history of AF: paroxysmal (lasting for  $\leq 7$  days,

including AF cardioverted within 7 days), persistent (lasting >7 days, including AF cardioverted after ≥7 days), or permanent (long-standing AF in which a rhythm control strategy, including cardioversion, cannot sustain sinus rhythm). Among participants without a history of AF, 14 had AF on their baseline ECG. These patients were categorized as having paroxysmal AF in the current analysis (eFigure 2 in [Supplement 2](#)).

### New-Onset AF or AFL After Randomization

New-onset AF or AFL after randomization was adjudicated in the FINEARTS-HF trial as an ECG-recorded event or a physician diagnosis. A diagnosis of new-onset AF or AFL could be made from an ECG (12-lead or single-lead ECG), telemetry, ambulatory monitoring, or an implanted device. In the absence of direct evidence of AF or AFL on an ECG or monitoring device, a physician diagnosis of AF or AFL or a description of the diagnosis with evidence of treatment or referral for treatment of AF or AFL, such as initiation of anticoagulation, cardioversion, or catheter ablation, was used for the adjudication of new-onset AF or AFL.

### Other Clinical Outcomes

The primary trial outcome was the composite of cardiovascular death and total (first and recurrent) HF events (ie, HF hospitalization or urgent HF visit). In this analysis, we also examined the components of the primary outcome, the composite of the first HF event or cardiovascular death (and its components), all-cause death, and the Kansas City Cardiomyopathy Questionnaire total symptom scores (KCCQ-TSS). Prespecified safety outcomes were also evaluated. Because of its known association with AF, we also did a post hoc analysis of fatal or nonfatal stroke during follow-up.

### Statistical Analysis

Patient characteristics and outcomes were compared according to the types of AF at baseline (no AF, paroxysmal AF, and persistent or permanent AF). Baseline characteristics are summarized as frequencies with percentages for categorical variables and means with SDs or medians with IQRs for continuous variables. For continuous variables, differences between the 3 groups were assessed using a 1-way analysis of variance and the Kruskal-Wallis test. Differences in categorical variables were compared using the  $\chi^2$  test.

Incidence rates for each outcome of interest are presented per 100 person-years of follow-up, calculated using Poisson regression with robust SEs. The cumulative incidence curves were plotted using the Nelson-Aalen method for total (first and recurrent) outcomes and the Kaplan-Meier method for time-to-first-event outcomes. The association between the types of AF and clinical outcomes was evaluated using semiparametric proportional rates models for total (first and recurrent) events and Cox proportional hazards models for time-to-first-event data, stratified according to geographic region and baseline LVEF (<60% or ≥60%).<sup>24</sup> Further adjustment was performed for study treatment, age, sex, body mass index, eGFR, NYHA functional classification, heart rate, systolic blood pressure, type 2 diabetes, prior hospitalization for HF, myocardial infarction, and log-transformed NT-proBNP level.

The effect of finerenone compared with placebo by AF status at baseline was calculated as a rate ratio (RR) and 95% CI derived from semiparametric proportional rates models for total (first and recurrent) events or as a hazard ratio and 95% CI from Cox proportional hazards models for time-to-first events within baseline AF categories.<sup>24</sup> All models were stratified by geographic region and baseline LVEF (<60% or ≥60%) as prespecified in the statistical analysis plan for the main trial.<sup>23</sup> Change in KCCQ-TSS from baseline to 12 months according to treatment assignment was examined using analysis of covariance, adjusted for baseline value, geographic region, and LVEF (<60% or ≥60%). Interactions between the effect of finerenone and baseline AF category were tested by the Wald test. Safety outcomes are reported as counts and percentages according to randomized treatment, and the treatment effect was analyzed with logistic regression, adjusted for geographic region and baseline LVEF (<60% or ≥60%).

The association between new-onset AF or AFL and subsequent outcomes was examined using new-onset AF or AFL as a time-updated covariate in the subset of participants without AF at baseline. Patients without any AF or AFL (ie, no history of AF or AFL and no AF or AFL on their baseline ECG) were considered not exposed at baseline and became exposed if they developed new-onset AF. The effects of finerenone compared with placebo on new-onset AF or AFL, with competing risks of death, were analyzed using the Fine-Gray proportional subhazards model, adjusted for region and LVEF (<60% or ≥60%). We tested the proportional hazards assumption using Schoenfeld residuals, which showed that the proportional hazards assumption was not violated in the analyses of new-onset AF or AFL (eFigure 3 in [Supplement 2](#)). Cause-specific cumulative incidence functions using time-dependent weights were used for visualizing the cumulative incidence of new-onset AF or AFL.

Two-tailed  $P < .05$  was considered statistically significant. All analyses were performed using Stata version 18.0 statistical software (StataCorp LLC).

## Results

Among 5984 patients (mean [SD] age, 72.0 [9.6] years; 2724 [45.5%] female) with known AF status at baseline, 1384 (23.1%) had paroxysmal AF, 1886 (31.5%) had persistent or permanent AF, and 2714 (45.4%) had no AF (eFigure 2 in [Supplement 2](#)). Overall, the median (IQR) duration of follow-up was 32 (23-37) months.

### Baseline Characteristics According to AF Status

Baseline characteristics according to type of AF are shown in [Table 1](#). Patients with both types of AF at baseline were older and had more severe HF (including a higher proportion in NYHA functional class III or IV and lower KCCQ-TSS) with substantially higher NT-proBNP levels compared with those without AF. Heart rate-limiting and antiarrhythmic drugs, such as amiodarone, sotalol, diltiazem, flecainide, and digoxin, were more often used in patients with AF. Of these, amiodarone, sotalol, and flecainide were more often used in patients with par-

Table 1. Baseline Characteristics According to Atrial Fibrillation (AF) Status at Baseline

Characteristic	No AF (n = 2714)	Paroxysmal AF (n = 1384)	Persistent or permanent AF (n = 1886)	P value
Age, y				
Mean (SD)	69.5 (10.2)	73.9 (8.8)	74.1 (8.6)	<.001
>70, No. (%)	1353 (49.9)	923 (66.7)	1316 (69.8)	<.001
Sex, No. (%)				
Female	1188 (43.8)	684 (49.4)	852 (45.2)	<.001
Male	1526 (56.2)	700 (50.6)	1034 (54.8)	
Region, No. (%)				
Western Europe, Oceania, and others <sup>a</sup>	398 (14.7)	388 (28.0)	463 (24.5)	<.001
Eastern Europe	1227 (45.2)	544 (39.3)	879 (46.6)	
Asia	468 (17.2)	195 (14.1)	315 (16.7)	
North America	206 (7.6)	180 (13.0)	84 (4.5)	
Latin America	415 (15.3)	77 (5.6)	145 (7.7)	
Race, No. (%) <sup>b</sup>				
Asian	474 (17.5)	198 (14.3)	319 (16.9)	<.001
Black	62 (2.3)	15 (1.1)	10 (0.5)	
White	2078 (76.6)	1130 (81.6)	1518 (80.5)	
Other	100 (3.7)	41 (3.0)	39 (2.1)	
NYHA functional class III or IV, No. (%)	723 (26.6)	440 (31.8)	689 (36.5)	<.001
KCCQ score, mean (SD)				
OSS	64.6 (22.0)	62.1 (22.2)	60.7 (22.3)	<.001
CSS	67.4 (22.4)	64.6 (22.6)	63.0 (22.4)	<.001
TSS	68.6 (23.7)	66.5 (23.9)	65.2 (24.1)	<.001
BMI				
Mean (SD)	30.0 (6.0)	30.0 (6.3)	29.8 (6.2)	.70
Category, No. (%)				
<18.5	22 (0.8)	12 (0.9)	31 (1.6)	.24
18.5–24.9	563 (20.8)	293 (21.2)	378 (20.1)	
25.0–29.9	904 (33.4)	448 (32.5)	636 (33.8)	
30.0–34.4	704 (26.0)	347 (25.2)	489 (26.0)	
≥35.0	517 (19.1)	279 (20.2)	348 (18.5)	
Heart rate, mean (SD), bpm	69.0 (10.0)	69.4 (12.3)	76.5 (12.2)	<.001
Blood pressure, mm Hg				
Systolic				
Mean (SD)	130.9 (15.1)	129.3 (15.8)	127.5 (15.1)	<.001
>140, No. (%)	690 (25.4)	334 (24.1)	366 (19.4)	<.001
Diastolic, mean (SD)	75.0 (9.9)	74.2 (10.6)	77.0 (10.5)	<.001
LVEF, %				
Mean (SD)	52.3 (8.1)	52.9 (7.5)	52.7 (7.6)	.03
Category				
<50	1094 (40.3)	421 (30.5)	650 (34.5)	<.001
50 to <60	1097 (40.4)	686 (49.7)	883 (46.8)	
≥60	521 (19.2)	272 (19.7)	352 (18.7)	
History of <40, No. (%)	139 (5.1)	70 (5.1)	63 (3.3)	.01
Left atrial measure, mean (SD)				
Diameter, cm	4.4 (0.7)	4.6 (0.9)	4.9 (0.8)	<.001
Area, cm <sup>2</sup>	24.5 (6.6)	26.7 (6.6)	29.7 (8.3)	<.001
Volume index, mL/m <sup>2</sup>	40.9 (14.8)	48.7 (17.1)	57.1 (22.6)	<.001
eGFR, mL/min/1.73 m <sup>2</sup>				
Mean (SD)	65.6 (20.6)	59.1 (19.1)	59.3 (18.1)	<.001
<60, No. (%)	1111 (40.9)	746 (53.9)	1019 (54.0)	<.001
<45, No. (%)	500 (18.4)	378 (27.3)	451 (23.9)	<.001

(continued)

Table 1. Baseline Characteristics According to Atrial Fibrillation (AF) Status at Baseline (continued)

Characteristic	No AF (n = 2714)	Paroxysmal AF (n = 1384)	Persistent or permanent AF (n = 1886)	P value
Baseline UACR, median (IQR), mg/g	15.0 (6.0-57.5)	19.0 (7.0-62.0)	24.0 (9.0-85.0)	<.001
Potassium, median (IQR), mEq/L	4.4 (4.1-4.7)	4.3 (4.0-4.6)	4.3 (4.0-4.6)	<.001
Hemoglobin, median (IQR), g/dL	13.4 (12.3-14.5)	13.2 (12.1-14.2)	13.5 (12.4-14.7)	<.001
Anemia, No. (%)	697 (27.3)	417 (31.9)	465 (25.9)	<.001
NT-proBNP, median (IQR), pg/mL	540 (286-1185)	1033 (480-1927)	1712 (1144-2809)	<.001
AF on ECG, No. (%)	NA	390 (28.2)	1886 (100.0)	<.001
History of AFL, No. (%)	38 (1.4)	62 (4.5)	31 (1.6)	<.001
AFL on ECG, No. (%)	5 (0.2)	32 (2.3)	29 (1.5)	<.001
Medical history, No. (%)				
Prior hospitalization for HF	1490 (54.9)	903 (65.2)	1213 (64.3)	<.001
Recency of hospitalization for HF				
≤7 d	371 (24.9)	266 (29.5)	364 (30.0)	<.001
>7 d to 6 mo	786 (52.8)	458 (50.7)	570 (47.0)	
>6 to 12 mo	83 (5.6)	59 (6.5)	58 (4.8)	
>12 mo	250 (16.8)	120 (13.3)	221 (18.2)	
Type 2 diabetes	1230 (45.5)	535 (38.7)	667 (35.4)	<.001
Hypertension	2423 (89.3)	1231 (88.9)	1656 (87.8)	.29
Myocardial infarction	983 (36.2)	299 (21.6)	258 (13.7)	<.001
CABG	510 (18.8)	209 (15.1)	196 (10.4)	<.001
PCI	891 (32.8)	307 (22.2)	273 (14.5)	<.001
Peripheral arterial disease	294 (10.8)	102 (7.4)	139 (7.4)	<.001
COPD	319 (11.8)	200 (14.5)	248 (13.1)	.04
Stroke	327 (12.0)	204 (14.7)	297 (15.7)	<.001
CHA <sub>2</sub> DS <sub>2</sub> -VASc score ≥2	2684 (99.3)	1369 (99.1)	1868 (99.2)	.88
Treatment, No. (%)				
ACEI	1020 (37.6)	478 (34.5)	654 (34.7)	.06
ACEI or ARB	1998 (73.6)	931 (67.3)	1306 (69.2)	<.001
ARNI	272 (10.0)	112 (8.1)	126 (6.7)	<.001
β-Blocker	2254 (83.1)	1166 (84.2)	1660 (88.0)	<.001
SGLT2 inhibitor	374 (13.8)	194 (14.0)	241 (12.8)	.51
Loop diuretic	2252 (83.0)	1253 (90.5)	1718 (91.1)	<.001
Thiazide	446 (16.4)	167 (12.1)	215 (11.4)	<.001
Digoxin	23 (0.8)	98 (7.1)	347 (18.4)	<.001
Amiodarone	72 (2.7)	316 (22.8)	94 (5.0)	<.001
Sotalol	10 (0.4)	35 (2.5)	7 (0.4)	<.001
Calcium channel blocker	978 (36.0)	440 (31.8)	546 (29.0)	<.001
Verapamil	17 (0.6)	14 (1.0)	17 (0.9)	.36
Diltiazem	7 (0.3)	14 (1.0)	26 (1.4)	<.001
Flecainide	3 (0.1)	20 (1.4)	3 (0.2)	<.001
Anticoagulant	173 (6.4)	1096 (79.2)	1595 (84.6)	<.001
Antiplatelet	635 (23.4)	112 (8.1)	79 (4.2)	<.001
Pacemaker	91 (3.4)	134 (9.7)	106 (5.6)	<.001

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AFL, atrial flutter; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor blocker and neprilysin inhibitor; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CABG, coronary artery bypass grafting; CHA<sub>2</sub>DS<sub>2</sub>-VASc, congestive heart failure, hypertension, age 75 years or older, diabetes, stroke, vascular disease, age 65 to 74 years, and female sex; COPD, chronic obstructive pulmonary disease; CSS, clinical summary score; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; HF, heart failure; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; NA, not applicable; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; OSS, overall summary score; PCI, percutaneous coronary intervention; SGLT2, sodium-glucose

cotransporter 2; TSS, total symptom score; UACR, urine albumin-creatinine ratio.

SI conversion factors: To convert potassium to millimoles per liter, multiply by 1; hemoglobin to grams per liter, multiply by 10.

<sup>a</sup> Includes Australia, Austria, Germany, Denmark, Spain, United Kingdom, Israel, Italy, Netherlands, New Zealand, and Portugal.

<sup>b</sup> 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. Other includes American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, and not reported.



oxysmal AF compared with those with persistent or permanent AF, but the opposite was seen for digoxin.

### Outcomes According to AF Status

eFigure 4 and eTable 1 in Supplement 2 show the associations between AF type (vs no AF) and outcomes. Regardless of the type, patients with AF at baseline had a higher risk of the primary outcome compared with patients without AF (event rate per 100 person-years of follow-up, 20.3 [95% CI, 17.9-23.1] for paroxysmal AF, 19.8 [95% CI, 17.8-22.0] for persistent or permanent AF, and 11.9 [95% CI, 10.7-13.3] for no AF; rate ratio [RR], 1.62 [95% CI, 1.37-1.92] for paroxysmal AF and 1.66 [95% CI, 1.43-1.93] for persistent or permanent AF vs no AF), and a similar pattern was observed for the other outcomes except for cardiovascular death and fatal or nonfatal stroke (eFigure 4 and eTable 1 in Supplement 2). By contrast, after adjustment for baseline prognostic variables, AF at baseline was not associated with worse outcomes, and this was similar for paroxysmal and persistent or permanent AF (adjusted RR, 1.18 [95% CI, 0.99-1.39] for paroxysmal AF and 0.92 [95% CI, 0.77-1.10] for persistent or permanent AF vs no AF) (eTable 1 in Supplement 2).

### Effects of Finerenone Compared With Placebo

#### According to AF Status

For the primary outcome, the benefits of finerenone were consistent in patients with and without AF at baseline, regardless of AF type (Table 2 and Figure 1). The overall RR for the primary outcome was 0.84 (95% CI, 0.74-0.95); it was 0.80 (95% CI 0.65-0.98) for the group with no AF, 0.83 (95% CI, 0.65-1.06) for the paroxysmal AF group, and 0.85 (95% CI 0.69-1.05) for the persistent or permanent AF group ( $P$  for interaction = .94) (Table 2 and Figure 1). For the other outcomes examined, including changes in the KCCQ-TSS, the effects of finerenone were not modified by AF status at baseline (Table 2 and Figure 1).

### New-Onset AF or AFL, Subsequent Outcomes, and the Effects of Finerenone Compared With Placebo

New-onset AF or AFL was confirmed by adjudication in 175 patients during the study follow-up, ie, 6.5% in those without any AF or AFL at baseline, resulting in the overall event rate (per 100 person-years) of 2.7 (95% CI, 2.4-3.2), with an event rate of 2.4 (95% CI, 1.9-3.0) per 100 person-years in the finerenone group and 3.1 (95% CI, 2.5-3.7) per 100 person-years in the placebo group (estimated cumulative incidence at 3 years was 7.8% with finerenone and 8.9% with placebo) (Figure 2). The occurrence of AF or AFL after randomization was associated with a higher risk of all subsequent outcomes, eg, the RR for the primary outcome was 3.67 (95% CI, 2.64-5.10) in patients experiencing new-onset AF compared with those without any AF or AFL at baseline and during follow-up (eTable 2 in Supplement 2). The association between new-onset AF or AFL and worse subsequent outcomes was still significant after adjustment for prognostic variables (adjusted RR, 3.65 [95% CI, 2.57-5.18];  $P < .001$ ) (eTable 2 in Supplement 2).

Figure 2 shows the association between randomized treatment assignment and the occurrence of new-onset AF or AFL

during follow-up in patients without AF or AFL at baseline, accounting for competing risks of death. Patients assigned to receive finerenone were less likely to experience new-onset AF or AFL compared with those assigned to placebo, although the between-treatment difference was not statistically significant (subdistribution hazard ratio, 0.77 [95% CI, 0.57-1.04];  $P = .09$ ).

### Safety of Finerenone Compared With Placebo

#### According to AF Status

Compared with those without AF at baseline, patients with persistent or permanent AF more frequently experienced hypokalemia (potassium level  $<3.5$  mEq/L): 160 (6.1%) in the group with no AF, 84 (6.4%) in the paroxysmal AF group, and 162 (8.9%) in the persistent or permanent AF group ( $P = .001$  for no AF vs persistent or permanent AF). Hypotension (systolic blood pressure  $<100$  mm Hg) was observed more frequently in those with AF, regardless of its type, compared with those without AF: 347 (13.1%) in the group with no AF, 231 (17.3%) in the paroxysmal AF group, and 314 (17.2%) in the persistent or permanent AF group ( $P = .006$  for paroxysmal AF vs no AF and  $P < .001$  for persistent or permanent AF vs no AF). The safety of finerenone, compared with placebo, was not modified by the presence of AF at baseline (Table 3).

## Discussion

The key findings in this prespecified analysis of the FINEARTS-HF trial were that the effects of finerenone, compared with placebo, were consistent in patients with and without AF and by type of AF. We also described the adjudicated incidence of clinically reported new-onset AF or AFL in patients with HFmrEF or HFpEF and outcomes related to this. In addition, we showed that there was a numerical reduction in new-onset AF or AFL with finerenone compared with placebo. We also provided further information on the controversial question of whether AF is associated with worse outcomes in HF (and how outcomes vary by type of AF).<sup>11,25-28</sup>

Previous analyses of trials in HFmrEF have suggested that the benefits of certain treatments may be attenuated in the presence of AF. Such an interaction between heart rhythm and efficacy has been reported for  $\beta$ -blockers, cardiac resynchronization therapy, and omecamtiv mecarbil.<sup>6-9,29</sup> Less is known about whether an interaction of this type might occur in patients with HFmrEF or HFpEF, as only 1 prior therapy, sodium-glucose cotransporter 2 inhibitors, has shown convincing benefit in such patients,<sup>30</sup> and no such interaction was identified for this treatment.<sup>28</sup> We found that the effects of finerenone, compared with placebo, were also consistent irrespective of the presence of AF or type of AF in patients with HFmrEF or HFpEF. This finding is in keeping with analyses of prior trials testing the steroidal MRAs spironolactone and eplerenone in HFmrEF where there was no suggestion of attenuated benefit in patients with AF at baseline.<sup>31,32</sup>

Of more potential interest is the role that aldosterone may play in the electrical and structural remodeling of the atria and therefore the occurrence of new AF.<sup>13-19</sup> Because of this puta-

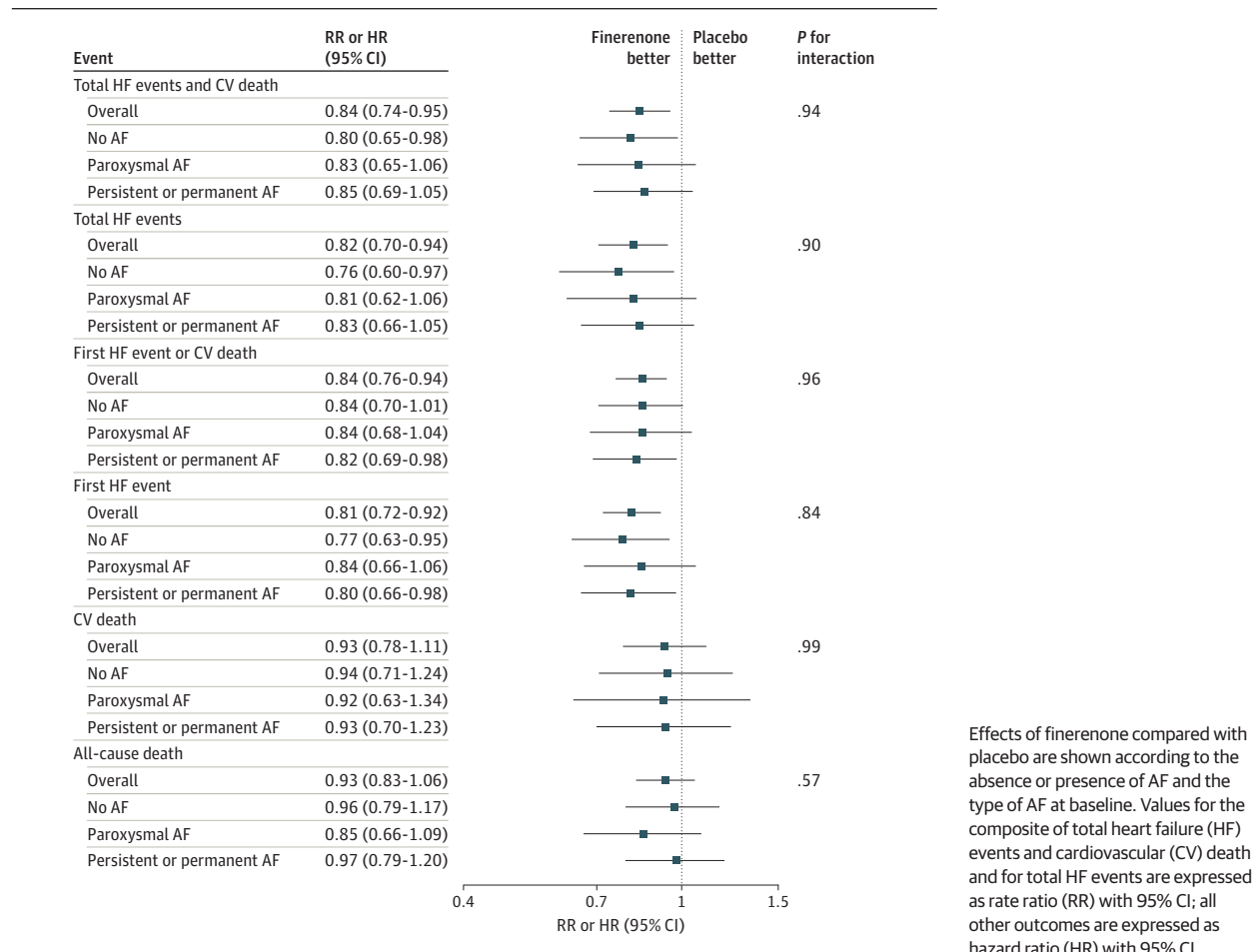
Table 2. Effects of Finerenone Compared With Placebo According to Atrial Fibrillation (AF) Status at Baseline

Outcome	No AF		Paroxysmal AF		Persistent or permanent AF		P value
	Placebo (n = 1367)	Finerenone (n = 1347)	Placebo (n = 685)	Finerenone (n = 699)	Placebo (n = 940)	Finerenone (n = 946)	
Total HF events and CV death							
Events, No.	447	352	354	311	480	415	
Event rate, No./100 person-years (95% CI)	13.2 (11.4-15.3)	10.6 (9.1-12.4)	22.2 (18.6-26.5)	18.5 (15.5-22.3)	21.3 (18.5-24.4)	18.3 (15.6-21.5)	
RR (95% CI) <sup>a</sup>	1 [Reference]	0.80 (0.65-0.98)	1 [Reference]	0.83 (0.65-1.06)	1 [Reference]	0.85 (0.69-1.05)	.94
Total HF events							
Events, No.	344	259	297	256	381	322	
Event rate, No./100 person-years (95% CI)	10.2 (8.6-12.0)	7.8 (6.5-9.4)	18.6 (15.3-22.6)	15.3 (12.5-18.7)	16.9 (14.4-19.7)	14.2 (11.8-17.1)	
RR (95% CI) <sup>a</sup>	1 [Reference]	0.76 (0.60-0.97)	1 [Reference]	0.81 (0.62-1.06)	1 [Reference]	0.83 (0.66-1.05)	.90
First HF event or CV death							
Events, No. (%)	268 (19.6)	225 (16.7)	179 (26.1)	164 (23.5)	271 (28.8)	232 (24.5)	
Event rate, No./100 person-years (95% CI)	8.5 (7.6-9.6)	7.2 (6.3-8.2)	12.8 (11.0-14.9)	10.9 (9.3-12.7)	13.7 (12.1-15.5)	11.3 (9.9-12.9)	
HR (95% CI) <sup>a</sup>	1 [Reference]	0.84 (0.70-1.01)	1 [Reference]	0.84 (0.68-1.04)	1 [Reference]	0.82 (0.69-0.98)	.96
First HF event							
Events, No. (%)	209 (15.3)	162 (12.0)	149 (21.8)	136 (19.5)	214 (22.8)	178 (18.8)	
Event rate, No./100 person-years (95% CI)	6.7 (5.8-7.6)	5.2 (4.5-6.1)	10.6 (9.0-12.6)	9.0 (7.6-10.7)	10.8 (9.4-12.4)	8.7 (7.4-10.1)	
HR (95% CI) <sup>a</sup>	1 [Reference]	0.77 (0.63-0.95)	1 [Reference]	0.84 (0.66-1.06)	1 [Reference]	0.80 (0.66-0.98)	.84
CV death							
Events, No. (%)	103 (7.5)	93 (6.9)	57 (8.3)	55 (7.9)	100 (10.6)	94 (9.9)	
Event rate, No./100 person-years (95% CI)	3.0 (2.5-3.7)	2.8 (2.3-3.4)	3.6 (2.8-4.6)	3.3 (2.5-4.3)	4.4 (3.6-5.4)	4.1 (3.4-5.1)	
HR (95% CI) <sup>a</sup>	1 [Reference]	0.94 (0.71-1.24)	1 [Reference]	0.92 (0.63-1.34)	1 [Reference]	0.93 (0.70-1.23)	.99
All-cause death							
Events, No.	206 (15.1)	192 (14.3)	135 (19.7)	120 (17.2)	180 (19.1)	177 (18.7)	
Event rate, No./100 person-years (95% CI)	6.1 (5.3-7.0)	5.8 (5.0-6.7)	8.4 (7.1-10.0)	7.1 (5.9-8.5)	7.9 (6.9-9.2)	7.8 (6.7-9.0)	
HR (95% CI) <sup>a</sup>	1 [Reference]	0.96 (0.79-1.17)	1 [Reference]	0.85 (0.66-1.09)	1 [Reference]	0.97 (0.79-1.20)	.57
Change at 12 mo in KCCQ-TSS							
Change, mean (95% CI)	6.3 (5.1-7.4)	7.6 (6.4-8.7)	7.7 (6.0-9.4)	8.7 (7.1-10.3)	7.4 (5.9-8.9)	9.9 (8.4-11.4)	
Treatment difference in means at 12 mo (95% CI) <sup>a</sup>	Reference	1.3 (-0.1 to 2.7)	Reference	1.0 (-1.0 to 3.1)	Reference	2.5 (0.7 to 4.3)	.43

Abbreviations: CV, cardiovascular; HF, heart failure; HR, hazard ratio; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire total symptom score; RR, rate ratio.

<sup>a</sup> Stratified by region and left ventricular ejection fraction.

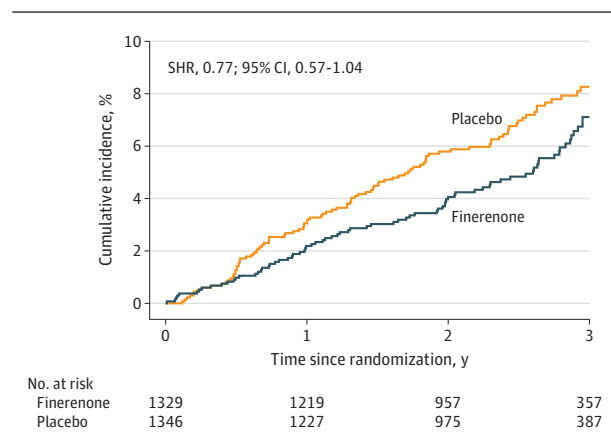
**Figure 1. Effects of Finerenone Compared With Placebo According to Atrial Fibrillation (AF) Status at Baseline**



tive role of aldosterone, it has been postulated that MRAs might reduce the incidence of new-onset AF.<sup>21,31</sup> This may have been the case with finerenone in the FINEARTS-HF trial, where the subdistribution hazard ratio for finerenone compared with placebo was 0.77 (95% CI, 0.57-1.04;  $P = .09$ ). Normally, such a trend, even with borderline statistical significance, should be treated with caution or even skepticism. However, the steroidal MRA eplerenone significantly reduced new-onset AF and AFL compared with placebo in patients with HFrEF in the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) trial.<sup>21,31</sup> Finerenone also significantly reduced the risk of new-onset AF in patients with type 2 diabetes and chronic kidney disease enrolled in the Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD) trial.<sup>20</sup> Recently, a meta-analysis using pooled data from 20 trials (including EMPHASIS-HF and FIDELIO-DKD) with nearly 22 000 participants with cardiovascular or kidney disease showed that MRAs reduced AF events (risk ratio, 0.76; 95% CI, 0.67-0.87) in patients both with and without prior AF.<sup>21</sup> Thus, the totality of evidence suggests that MRAs may indeed reduce the risk of new-onset AF in predisposed populations.

The low incidence of clinically recognized new-onset AF or AFL confirmed by adjudication, 3.1 (95% CI, 2.5-3.7) cases

**Figure 2. Cumulative Incidence of New-Onset Atrial Fibrillation or Atrial Flutter in Patients Randomized to Receive Finerenone or Placebo**



This figure shows cumulative incidence functions with a competing risk of death. This analysis included only patients without atrial fibrillation or atrial flutter at baseline. SHR indicates subdistribution hazard ratio.

per 100 person-years (cumulative incidence of approximately 8% at 3 years) likely underestimates the frequency of



Table 3. Safety of Finerenone Compared With Placebo According to Atrial Fibrillation (AF) Status at Baseline<sup>a</sup>

Safety outcome	No. (%)						P value for interaction
	No AF		Paroxysmal AF		Persistent or permanent AF		
	Placebo	Finerenone	Placebo	Finerenone	Placebo	Finerenone	
Potassium, mEq/L							
Hyperkalemia							
>5.5	92 (7.0)	199 (15.2)	50 (7.7)	87 (13.0)	57 (6.3)	127 (14.0)	.38
>6.0	17 (1.3)	50 (3.8)	8 (1.2)	13 (1.9)	16 (1.8)	23 (2.5)	.20
Hypokalemia, <3.5	110 (8.3)	50 (3.8)	54 (8.3)	30 (4.5)	117 (12.9)	45 (5.0)	.40
Elevated serum creatinine, mg/dL							
≥2.5	40 (3.0)	66 (5.1)	22 (3.4)	32 (4.8)	27 (3.0)	43 (4.7)	.90
≥3.0	15 (1.1)	25 (1.9)	8 (1.2)	14 (2.1)	11 (1.2)	18 (2.0)	.99
Systolic blood pressure <100 mm Hg	138 (10.4)	209 (15.9)	95 (14.4)	136 (20.2)	124 (13.6)	190 (20.8)	.72

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

the safety analysis. All analyses were adjusted for region and left ventricular ejection fraction.

<sup>a</sup> Patients who had received at least 1 dose of the study drug were included in

AF and AFL that would be documented by ambulatory monitoring. However, this is similar to the incidence of clinically recognized AF and AFL reported in TOPCAT-Americas (incidence rate, 3.0/100 person-years; 8.5% over a median follow-up of 2.9 years), EMPEROR-Preserved (incidence rate, 4.0/100 person-years; 8% over a median follow-up of 2.2 years), and PARAGON-HF (incidence rate, 4.3/100 person-years; 12% over a median follow-up of 2.9 years) and slightly higher than in prior HFrEF trials.<sup>9,11,26,31,33-35</sup> Despite its relatively low incidence, having new-onset AF or AFL was associated with substantially worse subsequent outcomes, consistent with prior findings in patients with HFrEF.<sup>35</sup> Whether this indicates that new-onset AF or AFL destabilizes HF or the occurrence of AF or AFL is a consequence of HF that is already deteriorating is impossible to tell from analyses like these, but in either case, new-onset AF or AFL merits urgent clinical attention given the poor subsequent course of such patients.

Finally, we examined outcomes related to a preexisting diagnosis of AF, whether the paroxysmal type or the persistent or permanent type. As noted in several prior trials, history of AF was associated with worse outcomes in the FINEARTS-HF trial.<sup>28,31,33-35</sup> However, in many of these trials, including FINEARTS-HF, this association was confounded by the requirement for patients with AF to have higher natriuretic peptide levels at enrollment. In the present study, the association between AF and a higher risk of HF outcomes was no longer significant after adjustment for key prognostic variables, including NT-proBNP level, as was also reported in the DELIVER trial.<sup>28</sup> At first sight, this finding may appear difficult to reconcile with the poor outcomes following new-onset AF and might support the view that incident AF is a marker of more severe or deteriorating HF

rather than a mediator of the poor subsequent outcomes. However, patients with preexisting AF were more often treated with heart rate-controlling and antiarrhythmic therapies, whereas patients with new-onset AF might not be protected against a sudden increase in ventricular rate and the hemodynamic consequences of that.

### Limitations

As with other studies like this, there are some limitations. Since we studied patients enrolled in a randomized clinical trial with specific inclusion and exclusion criteria, our results may not be generalizable to all patients with HFmrEF or HFpEF in the general population. The association between incident AF and subsequent cardiovascular outcomes may be confounded by variables beyond those we adjusted for in our models.

### Conclusions

AF was common in patients with HFmrEF or HFpEF included in the FINEARTS-HF trial. Although AF was associated with a higher unadjusted risk of HF outcomes, this association was attenuated after adjustment for known prognostic variables, including NT-proBNP level. The effects of finerenone compared with placebo were consistent, regardless of the presence of AF and type of AF at baseline. While new-onset AF or AFL was not frequently observed even in patients with established HFmrEF or HFpEF, it was associated with much worse subsequent outcomes. Finerenone numerically appeared to reduce the incidence of new-onset AF or AFL, although this effect was not statistically significant.

#### ARTICLE INFORMATION

**Accepted for Publication:** March 5, 2025.

**Published Online:** March 29, 2025.  
doi:10.1001/jamacardio.2025.0848

**Open Access:** This is an open access article distributed under the terms of the [CC-BY-NC-ND](#)

[License](#), which does not permit alteration or commercial use, including those for text and data mining, AI training, and similar technologies. © 2025 Matsumoto S et al. *JAMA Cardiology*.

**Author Affiliations:** British Heart Foundation Cardiovascular Research Centre, University of Glasgow, Glasgow, United Kingdom (Matsumoto,

Henderson, Jhund, McMurray); Division of Cardiovascular Medicine, Department of Internal Medicine, Toho University Faculty of Medicine, Tokyo, Japan (Matsumoto); Department of Cardiology and Angiology, Hannover Medical School, Hanover, Germany (Bauersachs); Emergency Institute for Cardiovascular Diseases

"Prof. Dr. C.C. Iliescu," University of Medicine Carol Davila, Bucharest, Romania (Chioncel); Cardiovascular Division, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts (Claggett, Desai, Vaduganathan, Solomon); Department of Cardiology, Bellvitge University Hospital, and Bellvitge Biomedical Research Institute, Centro de Investigación Biomédica En Red Enfermedades Cardiovasculares, University of Barcelona, L'Hospitalet de Llobregat, Barcelona, Spain (Comin-Colet); Department of Cardiology, Attikon University Hospital, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece (Filippatos); National Heart Centre Singapore and Duke-National University of Singapore, Singapore, Singapore (Lam); Department of Medicine, University of Michigan School of Medicine, Ann Arbor (Pitt); Medical Affairs & Pharmacovigilance, Pharmaceuticals, Bayer AG, Berlin, Germany (Scheerer); Research & Development, Pharmaceuticals, Bayer plc, Reading, United Kingdom (Lay-Flurrie); Cardiology and Nephrology Clinical Development, Bayer SA, São Paulo, Brazil (Amarante); Research & Development, Pharmaceuticals, Bayer AG, Wuppertal, Germany (Brinker); Department of Cardiology, Herlev-Gentofte University Hospital, Hellerup, Denmark (Schou); Cardiovascular Department, University of Milano-Bicocca, Papa Giovanni XXIII Hospital, Bergamo, Italy (Senni); Division of Cardiology, Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, Illinois (Shah); Department of Cardiology, University of Groningen, Groningen, the Netherlands (Voors); Université de Lorraine, Inserm Clinical Investigation Center at Institut Lorrain du Cœur et des Vaisseaux, University Hospital of Nancy, Nancy, France (Zannad); Section of Cardiology, Max Rady College of Medicine, University of Manitoba, Winnipeg, Manitoba, Canada (Zieroth).

**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:** Matsumoto, Jhund, Filippatos, Lam, Scheerer, Amarante, Zannad, Solomon.

**Acquisition, analysis, or interpretation of data:** Matsumoto, Henderson, Jhund, Bauersachs, Chioncel, Claggett, Comin-Colet, Desai, Filippatos, Pitt, Scheerer, Lay-Flurrie, Amarante, Brinker, Schou, Senni, Shah, Voors, Zannad, Zieroth, Vaduganathan, McMurray.

**Drafting of the manuscript:** Matsumoto, Chioncel, Amarante.

**Critical review of the manuscript for important intellectual content:** Henderson, Jhund, Bauersachs, Chioncel, Claggett, Comin-Colet, Desai, Filippatos, Lam, Pitt, Scheerer, Lay-Flurrie, Amarante, Brinker, Schou, Senni, Shah, Voors, Zannad, Zieroth, Vaduganathan, Solomon, McMurray.

**Statistical analysis:** Matsumoto, Henderson, Jhund, Lay-Flurrie.

**Obtained funding:** Scheerer, Amarante, Solomon.

**Administrative, technical, or material support:**

Bauersachs, Lam, Amarante, Brinker, Schou.

**Supervision:** Jhund, Chioncel, Claggett, Comin-Colet, Lam, Scheerer, Amarante, Solomon.

**Conflict of Interest Disclosures:** Dr Matsumoto reported receiving grants and personal fees from Abbott, Bayer Pharma, Boehringer Ingelheim, Daiichi-Sankyo, Medtronic, Novartis, Ono Pharma, Orbus Neich, Otsuka Pharma, and the Uehara Memorial Foundation outside the submitted work.

Dr Henderson reported receiving personal fees from Bayer AG outside the submitted work. Dr Jhund reported that his employer, the University of Glasgow, was remunerated for clinical trial work from AstraZeneca during the conduct of the study; and reported that his employer, the University of Glasgow, was remunerated for clinical trial work from AstraZeneca, Novartis, and Novo Nordisk, that he received speakers' fees from AstraZeneca, Novartis, Alkerm Metabolics, ProAdWise Communications, and Sun Pharmaceuticals, that he received advisory board fees from AstraZeneca, Boehringer Ingelheim, and Novartis, that he received grants from AstraZeneca, Boehringer Ingelheim, Analog Devices Inc, Roche Diagnostics, Bayer AG, Novartis, and Novo Nordisk, and that he served as a director of GCTP Ltd outside the submitted work. Dr Bauersachs reported receiving grants from Abiomed, CVRx, Norgine, Roche, and Zoll and receiving personal fees from Abbott, Novartis, Bayer, Pfizer, Boehringer Ingelheim, AstraZeneca, Cardior, CVRx, Bristol Myers Squibb, Amgen, Corvia, Norgine, Edwards, Roche, Vifor, and Zoll outside the submitted work. Dr Claggett reported receiving personal fees from Alnylam, Bristol Myers Squibb, Cardior, Cardurion, Corvia, Cytokinetics, CVRx, Intellia, Rocket, and Eli Lilly and serving on a data safety monitoring board for Novo Nordisk outside the submitted work. Dr Desai reported receiving grants and personal fees from Bayer during the conduct of the study; and receiving grants from Abbott, Alnylam, AstraZeneca, Bayer, Novartis, and Pfizer and personal fees from Abbott, Alnylam, AstraZeneca, Avidity Biopharma, Axon Therapeutics, Bayer, Biofourmis, Boston Scientific, Endotronix, GlaxoSmithKline, Medpace, Medtronic, Merck, New Amsterdam, Novartis, Parexel, Porter Health, Regeneron, River2Renal, Roche, scPharmaceuticals, Veristat, Verily, and Zydyus outside the submitted work. Dr Filippatos reported receiving personal fees from Bayer during the conduct of the study; and receiving personal fees from Bayer, Boehringer Ingelheim, Servier, Novartis, Impulse Dynamics, Vifor, Medtronic, Cardior, and Novo Nordisk, receiving grants from the European Union, and serving as a committee member for Impulse Dynamics and Novo Nordisk outside the submitted work. Dr Lam reported receiving grants or research support from the National Medical Research Council of Singapore, Novo Nordisk, and Roche Diagnostics, serving as a consultant or on a committee for Alleviant Medical, Allysta Pharma, Alnylam Pharma, AnaCardio AB, Applied Therapeutics, AstraZeneca, Bayer, Biopeutics, Boehringer Ingelheim, Boston Scientific, Bristol Myers Squibb, CardioRenal, Corteria, CPC Clinical Research, Eli Lilly, Impulse Dynamics, Intellia Therapeutics, Ionis Pharmaceuticals, Janssen Research & Development LLC, Medscape/WebMD Global LLC, Merck, Novartis, Novo Nordisk, Prosciento Inc, Quidel Corp, Radcliffe Group Ltd, Recardio Inc, ReCor Medical, Roche, Sanofi, Siemens Healthcare Diagnostics, and Us2.ai, being cofounder and nonexecutive director of Us2.ai, having patent PCT/SG2016/050217 pending, and having US patent 10,702,247 issued outside the submitted work. Dr Pitt reported receiving personal fees from AstraZeneca, Bayer, Boehringer Ingelheim, Brainstorm Medical, Bristol Myers Squibb, Lexicon, scPharmaceuticals, SQ Innovation, G3 Pharmaceuticals, Sarfez Pharmaceuticals, KBP Biosciences, Cereno, Prointel, Anacardio, SeaStar

Medical, Vifor, and Minneralis, having US patent 9931412 issued, having US patent 63/045,783 pending, and having stock or stock options in scPharmaceuticals, SQ Innovation, G3 Pharmaceuticals, Sarfez Pharmaceuticals, KBP Biosciences, Cereno, Prointel, SeaStar Medical, Vifor, and Brainstorm Medical outside the submitted work. Dr Scheerer reported being a shareholder of Bayer AG during the conduct of the study; and being a shareholder of AstraZeneca, Novo Nordisk, and Eli Lilly outside the submitted work. Dr Brinker reported being a shareholder of Bayer AG outside the submitted work. Dr Schou reported receiving personal fees from Boehringer Ingelheim, Novo Nordisk, Novartis, and AstraZeneca and a grant from Bayer outside the submitted work. Dr Senni reported receiving personal fees from Novartis, Merck, Vifor, Bayer, Novo Nordisk, AstraZeneca, Boehringer Ingelheim, Cardurion, Amgen, Abbott, and MSD outside the submitted work. Dr Shah reported receiving personal fees from Bayer during the conduct of the study; and receiving research grants from the National Institutes of Health, American Heart Association, AstraZeneca, Corvia, and Pfizer and consulting fees from Abbott, Alleviant, AstraZeneca, Amgen, Aria CV, Axon Therapies, Bayer, Boehringer Ingelheim, Boston Scientific, Bristol Myers Squibb, Cycleron, Cytokinetics, Edwards Lifesciences, Eidos, Imara, Impulse Dynamics, Intellia, Ionis, Lilly, Merck, MyoKardia, Novartis, Novo Nordisk, Pfizer, Prothema, Regeneron, Rivus, Sardocor, Shifamed, Tenax, Tenaya, and Ultromics outside the submitted work. Dr Voors reported that his employer received nonfinancial support and/or consultancy fees from Adrenomed, Anacardio, AstraZeneca, Bayer AG, Bristol Myers Squibb, Boehringer Ingelheim, Corteria, Eli Lilly, Merck, Moderna, Novartis, Novo Nordisk, Roche Diagnostics, and Salubris Bio outside the submitted work. Dr Zannad reported receiving personal fees from Bayer during the conduct of the study; and receiving personal fees from 89bio, Abbott, Acceleron, Applied Therapeutics, Bayer, Betagenon, Biopeutics, Boehringer Ingelheim, Bristol Myers Squibb, Cambrian, Cardior, Cellprothera, Cereno, CEVA, Corteria, CVRx, CVCT, Inventiva, KBP Biosciences, Lupin, Merck, Northsea, Novo Nordisk, Otsuka, Owkin, Ribocure, Roche Diagnostics, Salubris, Us2.ai, and Viatrix, having stock options for G3 Therapeutics, having equities at Cereno, Cardiorenal, and Eshmoun, and being the founder of Cardiovascular Clinical Trialists outside the submitted work. Dr Zieroth reported receiving personal fees from Abbott, AstraZeneca, Bayer, Bristol Myers Squibb, Boehringer Ingelheim, CSL Vifor, Cytokinetics, Edwards, Eli Lilly, GSK, Medtronic, Merck, Novo Nordisk, Pfizer, and Salubris Bio and serving on a clinical trial committee or as a national lead for studies sponsored by AstraZeneca, Boehringer Ingelheim, Merck, Novartis, Pfizer, and Salubris Bio outside the submitted work. Dr Vaduganathan reported receiving personal fees from American Regent, Amgen, AstraZeneca, Bayer AG, Baxter Healthcare, Bristol Myers Squibb, 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 serving on clinical trial committees for Amgen, AstraZeneca, Galmed,

Novartis, Bayer AG, Occlutech, and Impulse Dynamics outside the submitted work. Dr Solomon reported receiving grants to his institution from Bayer during the conduct of the study; and receiving grants from Alexion, Alnylam, Applied Therapeutics, AstraZeneca, Bellerophon, Bayer, Bristol Myers Squibb, Boston Scientific, Cytokinetics, Edgewise, Eidos/BridgeBio, Gossamer, GSK, Ionis, Lilly, National Heart, Lung, and Blood Institute of the National Institutes of Health, Novartis, Novo Nordisk, Respicardia, Sanofi Pasteur, Tenaya, Theracos, and Us2.ai and receiving personal fees from Abbott, Action, Akros, Alexion, Alnylam, Amgen, Arena, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Cardiac Dimensions, Cardior, Cardurion, Corvia, Cytokinetics, Daiichi Sankyo, GSK, Intellia, Eli Lilly and Co, Janssen, Merck, Myokardia, Novartis, Roche, Theracos, Quantum Genomics, Tenaya, Sanofi-Pasteur, Dinacor, Trembeau, CellProthera, Moderna, American Regent, Sarepta, Lexicon, Anacardio, Akros, and Valo outside the submitted work. Dr McMurray reported receiving research support to his institution from Bayer during the conduct of the study; and receiving research support to his institution from Amgen, British Heart Foundation, National Heart, Lung, and Blood Institute of the National Institutes of Health, Alnylam Pharmaceuticals, AstraZeneca, Bayer, Cardurion, Cytokinetics, Novartis, and Roche and receiving personal fees from Abbott, Alkerm Metabolics, Alnylam Pharmaceuticals, Amgen, AnaCardio, AstraZeneca, Bayer, Berlin Cures, Blue Ocean Scientific Solutions Ltd, Boehringer Ingelheim, Bristol Myers Squibb, Canadian Medical and Surgical Knowledge, Cardurion, Catalyze Group, Cytokinetics, European Academy of CME, GSK, Ionis Pharmaceuticals, Novartis, River BioMedics, Biohaven Pharmaceuticals, Chugai Pharmaceuticals, Protherics Medicine Developments Ltd, DalCor Pharmaceuticals, Alkerm Metabolics, Canadian Medical and Surgical Knowledge, Centrix Healthcare, Emcure Pharmaceuticals, Eris Lifesciences, Hikma Pharmaceuticals, Imagica Health, Intas Pharmaceuticals, J.B. Chemicals & Pharmaceuticals, Lupin Pharmaceuticals, Medscape/Heart.org, ProAdWise Communications, Radcliffe Cardiology, Regeneron Pharmaceuticals, River 2 Renal Corp, SQ Innovations, Sun Pharmaceuticals, The Corpus, Translational Medicine Academy, Translational Research Group, Regeneron, MCI India, Hilton Pharmaceuticals, IMEDIC Pharmaceuticals Micro Labs Ltd, At the Limits Ltd, ARMGO Pharmaceuticals, WCG Clinical Services, WIRB-Copernicus Group Clinical Inc, and Global Clinical Trial Partners Ltd, and being a director of Global Clinical Trial Partners Ltd outside the submitted work. No other disclosures were reported.

**Funding/Support:** The FINEARTS-HF trial was sponsored by Bayer AG.

**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 the 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, were performed solely by the authors.

**Meeting Presentation:** This paper was presented at ACC.25; March 29, 2025; Chicago, Illinois.

**Data Sharing Statement:** See [Supplement 3](#).

## REFERENCES

- Kotecha D, Lam CS, Van Veldhuisen DJ, Van Gelder IC, Voors AA, Rienstra M. Heart failure with preserved ejection fraction and atrial fibrillation: vicious twins. *J Am Coll Cardiol*. 2016;68(20):2217-2228. doi:10.1016/j.jacc.2016.08.048
- Reddy YNV, Obokata M, Verbrugge FH, Lin G, Borlaug BA. Atrial dysfunction in patients with heart failure with preserved ejection fraction and atrial fibrillation. *J Am Coll Cardiol*. 2020;76(9):1051-1064. doi:10.1016/j.jacc.2020.07.009
- Reddy YNV, Borlaug BA, Gersh BJ. Management of atrial fibrillation across the spectrum of heart failure with preserved and reduced ejection fraction. *Circulation*. 2022;146(4):339-357. doi:10.1161/CIRCULATIONAHA.122.057444
- Newman JD, O'Meara E, Böhm M, et al. Implications of atrial fibrillation for guideline-directed therapy in patients with heart failure: JACC state-of-the-art review. *J Am Coll Cardiol*. 2024;83(9):932-950. doi:10.1016/j.jacc.2023.12.033
- Rienstra M, Damman K, Mulder BA, Van Gelder IC, McMurray JJ, Van Veldhuisen DJ. Beta-blockers and outcome in heart failure and atrial fibrillation: a meta-analysis. *JACC Heart Fail*. 2013;1(1):21-28. doi:10.1016/j.jchf.2012.09.002
- McDonagh TA, Metra M, Adamo M, et al; ESC Scientific Document Group. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2021;42(36):3599-3726. doi:10.1093/eurheartj/ehab368
- Heidenreich PA, Bozkurt B, Aguilar D, et al; ACC/AHA Joint Committee Members. 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
- Kotecha D, Holmes J, Krum H, et al; Beta-Blockers in Heart Failure Collaborative Group. Efficacy of  $\beta$  blockers in patients with heart failure plus atrial fibrillation: an individual-patient data meta-analysis. *Lancet*. 2014;384(9961):2235-2243. doi:10.1016/S0140-6736(14)61373-8
- Solomon SD, Claggett BL, Miao ZM, et al. Influence of atrial fibrillation on efficacy and safety of omecamtiv mecarbil in heart failure: the GALACTIC-HF trial. *Eur Heart J*. 2022;43(23):2212-2220. doi:10.1093/eurheartj/ehac144
- O'Meara E, Khairy P, Blanchet MC, et al; AF-CHF Investigators. Mineralocorticoid receptor antagonists and cardiovascular mortality in patients with atrial fibrillation and left ventricular dysfunction: insights from the Atrial Fibrillation and Congestive Heart Failure trial. *Circ Heart Fail*. 2012;5(5):586-593. doi:10.1161/CIRCHEARTFAILURE.111.965160
- Cikes M, Claggett B, Shah AM, et al. Atrial fibrillation in heart failure with preserved ejection fraction: the TOPCAT trial. *JACC Heart Fail*. 2018;6(8):689-697. doi:10.1016/j.jchf.2018.05.005
- Shantsila E, Shahid F, Sun Y, et al. Spironolactone in atrial fibrillation with preserved cardiac fraction: the IMPRESS-AF trial. *J Am Heart Assoc*. 2020;9(18):e016239. doi:10.1161/JAHA.119.016239
- Gómez AM, Rueda A, Sainte-Marie Y, et al. Mineralocorticoid modulation of cardiac ryanodine receptor activity is associated with downregulation of FK506-binding proteins. *Circulation*. 2009;119(16):2179-2187. doi:10.1161/CIRCULATIONAHA.108.805804
- Tsai CT, Chiang FT, Tseng CD, et al. Increased expression of mineralocorticoid receptor in human atrial fibrillation and a cellular model of atrial fibrillation. *J Am Coll Cardiol*. 2010;55(8):758-770. doi:10.1016/j.jacc.2009.09.045
- Lammers C, Dartsch T, Brandt MC, et al. Spironolactone prevents aldosterone induced increased duration of atrial fibrillation in rat. *Cell Physiol Biochem*. 2012;29(5-6):833-840. doi:10.1159/000178483
- Denham NC, Pearman CM, Caldwell JL, et al. Calcium in the pathophysiology of atrial fibrillation and heart failure. *Front Physiol*. 2018;9:1380. doi:10.3389/fphys.2018.01380
- Buffolo F, Tetti M, Mulatero P, Monticone S. Aldosterone as a mediator of cardiovascular damage. *Hypertension*. 2022;79(9):1899-1911. doi:10.1161/HYPERTENSIONAHA.122.17964
- Rossi GP, Sacchetti A, Visentin P, et al. Changes in left ventricular anatomy and function in hypertension and primary aldosteronism. *Hypertension*. 1996;27(5):1039-1045. doi:10.1161/01.HYP.27.5.1039
- Reil JC, Hohl M, Selejan S, et al. Aldosterone promotes atrial fibrillation. *Eur Heart J*. 2012;33(16):2098-2108. doi:10.1093/eurheartj/ehr266
- Filippatos G, Bakris GL, Pitt B, et al; FIDELIO-DKD Investigators. Finerenone reduces new-onset atrial fibrillation in patients with chronic kidney disease and type 2 diabetes. *J Am Coll Cardiol*. 2021;78(2):142-152. doi:10.1016/j.jacc.2021.04.079
- Orlani A, Healey JS, Kowalik K, et al. Mineralocorticoid receptor antagonists and atrial fibrillation: a meta-analysis of clinical trials. *Eur Heart J*. 2024;45(10):756-774. doi:10.1093/eurheartj/ehad811
- 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/ehfj.3266
- 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
- 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(4):711-730. doi:10.1111/1467-9868.00259
- Ahmed MI, White M, Ekundayo OJ, et al. A history of atrial fibrillation and outcomes in chronic advanced systolic heart failure: a propensity-matched study. *Eur Heart J*. 2009;30(16):2029-2037. doi:10.1093/eurheartj/ehp222
- Butt JH, Docherty KF, Jhund PS, et al. Dapagliflozin and atrial fibrillation in heart failure with reduced ejection fraction: insights from DAPA-HF. *Eur J Heart Fail*. 2022;24(3):513-525. doi:10.1002/ehfj.2381

27. Ponikowski P, Alemanyeh W, Oto A, et al; VICTORIA Study Group. Vericiguat in patients with atrial fibrillation and heart failure with reduced ejection fraction: insights from the VICTORIA trial. *Eur J Heart Fail*. 2021;23(8):1300-1312. doi:10.1002/ejhf.2285
28. Butt JH, Kondo T, Jhund PS, et al. Atrial fibrillation and dapagliflozin efficacy in patients with preserved or mildly reduced ejection fraction. *J Am Coll Cardiol*. 2022;80(18):1705-1717. doi:10.1016/j.jacc.2022.08.718
29. Healey JS, Hohnloser SH, Exner DV, et al; RAFT Investigators. Cardiac resynchronization therapy in patients with permanent atrial fibrillation: results from the Resynchronization for Ambulatory Heart Failure Trial (RAFT). *Circ Heart Fail*. 2012;5(5):566-570. doi:10.1161/CIRCHEARTFAILURE.112.968867
30. Van Gelder IC, Rienstra M, Bunting KV, et al; ESC Scientific Document Group. 2024 ESC guidelines for the management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J*. 2024;45(36):3314-3414. doi:10.1093/eurheartj/ehae176
31. Swedberg K, Zannad F, McMurray JJ, et al; EMPHASIS-HF Study Investigators. Eplerenone and atrial fibrillation in mild systolic heart failure: results from the EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure) study. *J Am Coll Cardiol*. 2012;59(18):1598-1603. doi:10.1016/j.jacc.2011.11.063
32. 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
33. Cikes M, Planinc I, Claggett B, et al. Atrial fibrillation in heart failure with preserved ejection fraction: the PARAGON-HF trial. *JACC Heart Fail*. 2022;10(5):336-346. doi:10.1016/j.jchf.2022.01.018
34. Filippatos G, Farmakis D, Butler J, et al; EMPEROR-Preserved Trial Committees and Investigators. Empagliflozin in heart failure with preserved ejection fraction with and without atrial fibrillation. *Eur J Heart Fail*. 2023;25(7):970-977. doi:10.1002/ejhf.2861
35. Mogensen UM, Jhund PS, Abraham WT, et al; PARADIGM-HF and ATMOSPHERE Investigators and Committees. Type of atrial fibrillation and outcomes in patients with heart failure and reduced ejection fraction. *J Am Coll Cardiol*. 2017;70(20):2490-2500. doi:10.1016/j.jacc.2017.09.027