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Finerenone and Atrial Fibrillation in Heart Failure
A Secondary Analysis of the FINEARTS-HF Randomized Clinical Trial

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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.

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Atrial 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).[1-3] 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.[1-3] In addition, AF is associated with attenuated efficacy of some therapies, such as β-blockers, in patients with HF and reduced ejection fraction (HFrEF).[4-9] 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.[10,11] 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.[12] 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.[13-19] This has led to the hypothesis that MRA therapy might reduce the incidence of new-onset AF in patients with HF.[17-21]

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 nonsteroidal 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.

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.

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.[22,23] 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 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] ≥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 ≥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^2. A complete list of exclusion criteria is provided in the article describing the study design.[22]

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^2 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^2, 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 ≤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 χ^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%).[24] 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.[24] All models were stratified by geographic region and baseline LVEF (<60% or ≥60%) as prespecified in the statistical analysis plan for the main trial.[23] 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[a]	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. (%)[b]				
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^2	24.5 (6.6)	26.7 (6.6)	29.7 (8.3)	<.001
Volume index, mL/m^2	40.9 (14.8)	48.7 (17.1)	57.1 (22.6)	<.001
eGFR, $mL/min/1.73\ m^2$				
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_2DS_2-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_2DS_2-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.

[a] Includes Australia, Austria, Germany, Denmark, Spain, United Kingdom, Israel, Italy, Netherlands, New Zealand, and Portugal.

[b] 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).[11,25-28]

Previous analyses of trials in HFrEF 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 β-blockers, cardiac resynchronization therapy, and omecamtiv mecarbil.[6-9,29] 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,[30] and no such interaction was identified for this treatment.[28] 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 HFrEF where there was no suggestion of attenuated benefit in patients with AF at baseline.[31,32]

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.[13-19] Because of this puta-

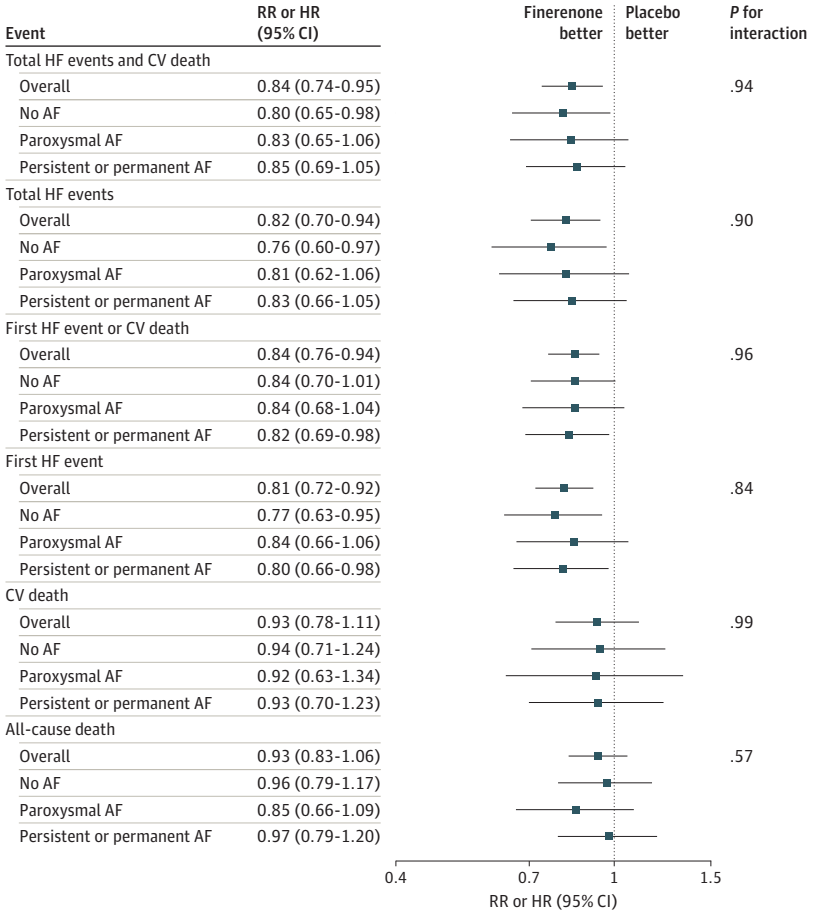
Table 2. Effects of Finerenone Compared With Placebo According to Atrial Fibrillation (AF) Status at Baseline

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)[a]	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)[a]	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)[a]	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)[a]	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)[a]	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)[a]	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)[a]	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.

[a] Stratified by region and left ventricular ejection fraction.

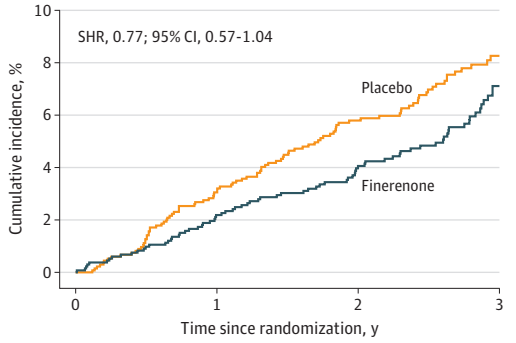
Figure 1. Effects of Finerenone Compared With Placebo According to Atrial Fibrillation (AF) Status at Baseline



Effects of finerenone compared with placebo are shown according to the absence or presence of AF and the type of AF at baseline. Values for the composite of total heart failure (HF) events and cardiovascular (CV) death and for total HF events are expressed as rate ratio (RR) with 95% CI; all other outcomes are expressed as hazard ratio (HR) with 95% CI.

tive role of aldosterone, it has been postulated that MRAs might reduce the incidence of new-onset AF.[21,31] 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.[21,31] 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.[20] 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.[21] Thus, the totality of evidence suggests that MRAs may indeed reduce the risk of new-onset AF in predisposed populations.

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.

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

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.

[a] Patients who had received at least 1 dose of the study drug were included in the safety analysis. All analyses were adjusted for region and left ventricular ejection fraction.

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.[9,11,26,31,33-35] 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.[35] 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.[28,31,33-35] 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.[28] 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.

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