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Efficacy and Tolerability of Finerenone According to the Use and Dosage of Diuretics

A Prespecified Analysis of the FINEARTS-HF Randomized Clinical Trial

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IMPORTANCE Given their kidney actions, it is important to evaluate the efficacy and safety of mineralocorticoid receptor antagonists when combined with other diuretics and whether they have a so-called diuretic-sparing effect in patients with heart failure (HF).

OBJECTIVE To examine the efficacy and tolerability of finerenone related to background diuretic treatment in patients with heart failure with mildly reduced or preserved ejection fraction (HFmrEF/HFpEF).

DESIGN, SETTING, AND PARTICIPANTS This study is a prespecified secondary analysis of the FINEARTS-HF (Finerenone Trial to Investigate Efficacy and Safety Superior to Placebo in Patients With Heart Failure) randomized clinical trial, which was conducted across 653 sites in 37 countries among adults aged 40 years and older with HFmrEF/HFpEF, who were randomized between September 2020 and January 2023. Data analysis was conducted from December 1, 2024, to January 30, 2025.

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. Outcomes were compared between finerenone and placebo according to the following baseline diuretic categories: only a nonloop diuretic (thiazide or thiazide-like); loop diuretic (≤40 mg vs >40 mg furosemide-equivalent dose); and combined nonloop and loop diuretic use.

RESULTS Among 5438 patients, 2496 (45.9%) were female, and mean (SD) age was 72.1 (9.6) years. A total of 684 patients (12.6%) were receiving a nonloop diuretic, 3040 (55.9%) less than or equal to 40 mg furosemide equivalent, 1145 (21.1%) 40 mg or greater furosemide equivalent, and 569 (10.5%) both nonloop and loop diuretics. Compared with placebo, finerenone reduced the risk of the primary end point across all diuretic subgroups: rate ratios were 0.84 (95% CI, 0.47-1.51), 0.86 (95% CI, 0.72-1.02), 0.98 (95% CI, 0.78-1.24), and 0.54 (95% CI, 0.35-0.83) for patients in the nonloop, 40 mg or less loop, more than 40 mg loop, and combined nonloop and loop categories, respectively (*P* for interaction = .18). Compared with placebo, finerenone reduced loop diuretic dose and dose intensification, but not loop diuretic initiation. Safety was consistent across diuretic categories.

CONCLUSIONS AND RELEVANCE In this secondary analysis of the FINEARTS-HF randomized clinical trial, the efficacy and safety of finerenone were consistent across all diuretic subgroups. Compared with placebo, finerenone reduced the use of diuretics in patients with HFmrEF/HFpEF; however, finerenone did not reduce the initiation of new loop diuretic in participants not receiving a loop diuretic at baseline.

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Supplemental content

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Although central to treating congestion in heart failure (HF),[1-3] diuretics have undesirable effects, including neuroendocrine activation and hypokalemia.[4] Overdiuresis can also cause hypovolemia and kidney dysfunction.[5] Moreover, higher diuretic doses have been linked to worse outcomes in HF.[6-11] Although this is probably because a higher diuretic dose is a marker of HF severity,[12] guidelines recommend using the minimum dose needed to maintain dry weight. Judicious dosing is therefore critical with careful monitoring of blood chemistry.[2,3] Dose adjustment may also be needed when conventional diuretics are combined with other drugs enhancing sodium and water excretion, which may have a so-called diuretic-sparing effect, enabling dose reduction or avoiding escalation due to worsening congestion.[13] Specifically, mineralocorticoid receptor antagonists (MRAs) act as potassium-sparing diuretics by antagonizing the effects of aldosterone, thereby inhibiting epithelial sodium channels (ENaC), reducing sodium reabsorption, and decreasing potassium excretion. This mechanism differs from that of loop and thiazide diuretics, and we hypothesized that combination of finerenone with these diuretics may allow for a reduced loop diuretic requirement.

The new nonsteroidal MRA finerenone is the most recent treatment shown to be of benefit in patients with heart failure and mildly reduced or preserved ejection fraction (HFmrEF/HFpEF) in the FINEARTS-HF (Finerenone Trial to Investigate Efficacy and Safety Superior to Placebo in Patients With Heart Failure) randomized clinical trial.[14]

Because finerenone has effects on sodium, potassium, and water excretion, the aim of this prespecified analysis of FINEARTS-HF was to evaluate the efficacy and tolerability of finerenone in relation to background diuretic therapy, including effects on biomarkers reflecting volume status and kidney function. We hypothesized that finereneone would have a diuretic-sparing effect in patients with HFmrEF/HFpEF.

Key Points

Question What are the safety and efficacy of finerenone in patients with heart failure with mildly reduced or preserved ejection fraction (HFmrEF/HFpEF) receiving background diuretics?

Findings In this prespecified secondary analysis of patients with HFmrEF/HFpEF in the FINEARTS-HF randomized clinical trial, the efficacy and safety of finerenone were consistent across subgroups defined by diuretic use, including those receiving only loop diuretics (≤40 mg and >40 mg of furosemide equivalent), only nonloop diuretics, and a combination of both. Finerenone reduced the need for loop diuretic dose intensification and decreased the mean loop diuretic dose compared to placebo.

Meaning These findings demonstrate a diuretic-sparing effect of finerenone in patients with HFmrEF/HFpEF.

Methods

FINEARTS-HF Study Design and Objectives

FINEARTS-HF was a prospective, double-blind, placebo-controlled, event-driven randomized clinical trial that examined the efficacy and safety of finerenone compared with placebo in patients with HFmrEF/HFpEF. The design, baseline characteristics, and primary results are published.[14-16] Ethics committees for the 653 participating institutions in 37 countries approved the protocol (Supplement 1), and all patients gave written consent. The trial followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines (eFigure 1 in Supplement 3).

Study Patients and Treatment

Key inclusion criteria were New York Heart Association (NYHA) class II through IV, diuretic use within 30 days of randomization, a left ventricular ejection fraction (LVEF) of 40% or higher with evidence of structural heart disease (either left atrial enlargement or left ventricular hypertrophy), and an elevated natriuretic peptide level (N-terminal pro-B-type natriuretic peptide [NT-proBNP] >300 pg/mL [or BNP >100 pg/mL] in sinus rhythm or NT-proBNP >900 pg/mL [or BNP >300 pg/mL] in atrial fibrillation). Ambulatory and hospitalized patients were eligible. Patients with prior LVEF less than 40% improving to 40% or higher were also eligible if HF symptoms persisted. Key exclusion criteria were estimated glomerular filtration rate (eGFR) less than 25 mL/min/1.73 m^2, serum potassium greater than 5.0 mEq/L (to convert serum potassium from mEq/L to mmol/L, multiply by 1) at screening or randomization, or symptomatic hypotension with mean systolic blood pressure (SBP) less than 90 mm Hg at screening or randomization. A complete list of exclusion criteria is published.[15]

Eligible participants were randomized in a 1:1 ratio to finerenone or matching placebo. The starting dose was 10 mg once daily for eGFR of 60 mL/min/1.73 m^2 or less, with a maximum of 20 mg once daily, and 20 mg once daily for eGFR greater than 60 mL/min/1.73 m^2, with a maximum of 40 mg once daily.

Trial Outcomes

The primary outcome was the composite of total (first and recurrent) HF events, including unplanned HF hospitalization or urgent HF visit, and cardiovascular death. The secondary outcomes included total HF events (cardiovascular death, cardiovascular death or first HF event, and first HF event were also examined); improvement in NYHA class from baseline to 12 months; change from baseline to 6, 9, and 12 months in the Kansas City Cardiomyopathy Questionnaire total symptom score (KCCQ-TSS); time to first occurrence of composite kidney end point; and time to all-cause death. Due to the small number of kidney events, this end point was not examined in this analysis. The prespecified safety outcomes included incidents of hyperkalemia (serum potassium >5.5 mEq/L or >6.0 mEq/L), hypokalemia (serum potassium <3.5 mEq/L or <4.0 mEq/L), elevation of serum creatine (serum creatinine ≥2.5 mg/dL or ≥3.0 mg/dL), and hypotension (SBP <100 mm Hg).

Statistical Analysis

Loop diuretics were assessed in patients with documented oral administration at standard dosing frequencies, and only those with doses expressed in milligrams were included. Intermittent or as-needed diuretic therapy was not considered. The

nonloop diuretics category comprised patients receiving only thiazide or thiazidelike diuretics (eTable 1 in Supplement 3). Furthermore, as the inclusion criteria required a diuretic within 30 days of randomization, patients without a recorded loop or nonloop diuretic at randomization were excluded.

For patients receiving loop diuretics, the total daily dose was standardized to furosemide-equivalent dosing, with bumetanide, 1 mg; torsemide, 20 mg; and azosemide, 60 mg, considered equivalent to 40 mg of intravenous furosemide or 80 mg of oral furosemide. If the dose was indeterminate at any time point, the patient was excluded for that time but reincluded once the dose became ascertainable. Patients in the nonloop diuretics group at baseline were classified as having a dose of 0 mg until loop diuretic initiation or death (at which point the dose was recorded as missing). Baseline diuretic categories were (1) only nonloop diuretics; (2) only loop diuretics at a furosemide-equivalent dose of 40 mg or less per day; (3) only loop diuretics at a furosemide-equivalent dose of more than 40 mg per day; and (4) both loop and nonloop diuretics. The cutoff value of 40 mg per day for loop diuretics alone was chosen because the median dose of loop diuretics in this study population was 40 mg. Additionally, this cutoff value was used to facilitate comparison with previous similar studies.[17-19] Baseline characteristics were compared across diuretic therapy categories with the use of analysis of variance (ANOVA), Kruskal-Wallis tests, and χ^2 tests. Changes in loop diuretic dose, hematocrit, creatinine, SBP, body weight, potassium, and urine albumin/creatinine ratio (UACR) were analyzed using mixed-effects models for repeated measurements, adjusted for baseline values, follow-up visits, treatment, visit-by-treatment interaction, and stratification factors. In the analysis of loop diuretic dose over time, patients with a recorded dose of 0 mg were excluded. Change in KCCQ-TSS from baseline to 12 months was analyzed using linear regression adjusted for baseline KCCQ-TSS, geographic region, and baseline LVEF strata (<60% or ≥60%).

To assess the effect of finerenone vs placebo by diuretic therapy, time-to-event data were evaluated with Kaplan-Meier curves and Cox proportional hazards models, with treatment as a fixed effect and region and baseline LVEF as stratification factors, reporting hazard ratios (HRs) and 95% confidence intervals. Total events were evaluated using Nelson-Aalen curves and rate ratios (RRs) with 95% confidence intervals from semiparametric proportional rates models,[20] adjusted and stratified for the same variables as the Cox model described previously. Additional models were adjusted for age, sex, heart rate, body mass index, eGFR, NYHA class III or IV, LVEF, myocardial infarction, NT-proBNP [log], diabetes, history of atrial fibrillation, and history of HF hospitalization. The effect of finerenone across baseline furosemide equivalent dose as a continuous variable was modeled using restricted fractional polynominals.[21] The proportion with NYHA class improvement from baseline to 12 months and changes in loop diuretic dose from baseline to 6, 12, and 18 months were analyzed using logistic regression models adjusted for treatment and stratification factors, with odds ratios (ORs) and 95% confidence intervals. All statistical analyses were conducted using STATA version 18 (StataCorp). *P* values were 2-tailed, and $P < .05$ was considered statistically significant.

Results

Among 5438 (90.6%) analyzable patients, 2496 (45.9%) were female, and mean (SD) age was 72.1 (9.6) years. A total of 684 patients (12.6%) were taking nonloop diuretics, 3040 (55.9%) were taking 40 mg or less and 1145 (21.1%) more than 40 mg of furosemide-equivalent loop diuretic, and 569 (10.5%) were taking both nonloop and loop diuretics. Among those prescribed loop diuretics, furosemide was the most used (**Table 1**). The most prescribed daily dose was 40 mg of furosemide or equivalent, taken by 2125 participants (39.1%). A similar proportion of patients in each diuretic group was randomized to finerenone or placebo.

Patient Characteristics According to Diuretic Therapy

Baseline characteristics of patients by diuretic category are shown in Table 1. Patients receiving more than 40 mg of furosemide equivalent were older, more often had a history of HF hospitalization, had worse KCCQ-TSS and NYHA class, higher NT-proBNP levels, and lower LVEF than other groups. They also had lower SBP and eGFR and were more likely to have a history of atrial fibrillation, chronic obstructive pulmonary disease, and anemia. Additionally, these patients were more frequently treated with sodium-glucose cotransporter 2 inhibitors and digoxin. Participants receiving only nonloop diuretics generally had a more favorable clinical profile than patients receiving a loop diuretic, alone or in combination (Table 1). Patients receiving a nonloop diuretic (ie, mainly a thiazide or thiazidelike diuretic), alone or in combination, more often had a history of hypertension than those receiving a loop diuretic only (Table 1).

Clinical Outcomes According to Diuretic Therapy at Baseline

Incidence rates of the primary outcome, total worsening HF events, cardiovascular death or first HF event, first HF event, cardiovascular death, and all-cause death were lowest in patients receiving only nonloop diuretics, intermediate in those taking 40 mg or less furosemide equivalent, and by far the highest in those receiving more than 40 mg of furosemide equivalent. For example, the rate of the primary end point was 4.6 (95% CI, 3.4-6.3) per 100 person-years in the nonloop diuretic group, 13.4 (95% CI, 12.3-14.6) in the 40 mg or less loop group, and 31.9 (95% CI, 28.5-35.7) per 100 person-years in the more than 40 mg loop group.

Among patients receiving both loop and nonloop diuretics, those receiving more than 40 mg of furosemide equivalent had higher event rates than those receiving more than 40 mg of loop diuretic alone. The incidence rate of the primary outcome was 37.8 (95% CI, 26.3-54.3) per 100 person-years. In contrast, among patients receiving both loop and nonloop diuretics, those receiving 40 mg or less exhibited an intermediate event rate, comparable to that observed in patients receiving 40 mg or less of loop diuretic alone. The incidence rate of the primary outcome in this group was 10.2 (95% CI, 7.6-13.9) per 100 person-years (eTable 2 and eFigure 2 in Supplement 3).

Table 1. Baseline Characteristics According to Diuretic Therapy in FINEARTS-HF

Characteristic	Diuretics, No. (%)				*P* value
	Nonloop (n = 684)	Loop (n = 4185)		Nonloop and loop (n = 569)	
		≤40 mg (n = 3040)	>40 mg (n = 1145)		
Dose (furosemide equivalent), mg					
Mean in patients taking a loop diuretic, mean (SD)	NA	31.5 (10.8)	109.2 (88.0)	50.1 (49.9)	NA
Median in patients taking a loop diuretic, median (IQR)	NA	40 (20-40)	80 (80-120)	40 (40-40)	NA
Furosemide-equivalent daily dose ≤40 mg	NA	3040 (100)	0	439 (77.2)	NA
Furosemide-equivalent daily dose >40 mg	NA	0	1145 (100)	130 (22.8)	NA
Loop diuretic					
Azosemide	NA	99 (3.3)	40 (3.5)	5 (0.9)	NA
Bumetanide	NA	0	74 (6.5)	6 (1.1)	NA
Torsemide	NA	738 (24.3)	188 (16.4)	135 (23.7)	NA
Furosemide	NA	2203 (72.5)	843 (73.6)	423 (74.3)	NA
Randomized to finerenone	351 (51.3)	1527 (50.2)	558 (48.7)	295 (51.8)	.59
Age, mean (SD), y	71.5 (8.7)	71.4 (9.8)	74.4 (9.5)	72.2 (9.4)	<.001
Sex					
Female	333 (48.7)	1369 (45.0)	486 (42.4)	308 (54.1)	<.001
Male	351 (51.3)	1671 (55.0)	659 (57.6)	261 (45.9)	
Heart failure characteristics					
NYHA functional class					
II	528 (77.2)	2186 (71.9)	697 (60.9)	357 (62.7)	<.001
III	154 (22.5)	836 (27.5)	438 (38.3)	208 (36.6)	
IV	2 (0.3)	18 (0.6)	9 (0.8)	4 (0.7)	
LVEF, mean (SD), %	55.2 (7.7)	52.0 (7.9)	52.2 (7.6)	53.9 (7.2)	<.001
LVEF ≥60%	195 (28.6)	527 (17.4)	202 (17.7)	124 (21.8)	<.001
History of LVEF <40%	16 (2.3)	146 (4.8)	68 (5.9)	17 (3.0)	<.001
KCCQ total symptom score, mean (SD)	74.1 (20.7)	69.1 (23.4)	60.0 (24.9)	62.5 (23.3)	<.001
Physiological and laboratory measurements					
Systolic blood pressure, mean (SD), mm Hg	133 (14)	129 (15)	128 (17)	132 (15)	<.001
Heart rate, mean (SD), beats/min	70 (11)	72 (12)	72 (12)	72 (12)	.003
Body mass index, mean (SD)[a]	29.5 (5.7)	29.3 (5.9)	31.1 (6.7)	31.8 (6.0)	<.001
Body mass index groups[a]					
<18.5 (Underweight)	4 (0.6)	47 (1.6)	10 (0.9)	1 (0.2)	<.001
18.5 to <25 (Normal weight)	153 (22.4)	697 (23.0)	198 (17.4)	70 (12.4)	
25 to <30 (Overweight)	235 (34.4)	1064 (35.1)	327 (28.7)	172 (30.4)	
30 to <35 (Class I obesity)	191 (27.9)	725 (23.9)	319 (28.0)	163 (28.8)	
≥35 (Class II-III obesity)	101 (14.7)	502 (16.5)	287 (25.2)	160 (28.3)	
NT-proBNP, median (IQR), pg/mL	534 (297-1223)	1019 (451-1901)	1510 (773-2812)	991 (395-1844)	<.001
In patients with AF	1369 (1036-2080)	1676 (1128-2573)	1898 (1309-3187)	1740 (1148-2692)	<.001
In patients without AF	424 (256-723)	618 (319-1305)	924 (444-1984)	525 (273-1099)	<.001
eGFR, median (IQR), mL/min/1.73 m^2	67.8 (53.0-82.0)	62.8 (47.9-79.0)	53.3 (40.4-68.8)	57.9 (45.9-74.5)	<.001
eGFR <60 mL/min/1.73 m^2	262 (38.3)	1369 (45.0)	687 (60.0)	308 (54.1)	<.001
eGFR <45 mL/min/1.73 m^2	81 (11.8)	636 (20.9)	378 (33.0)	132 (23.2)	<.001
eGFR <30 mL/min/1.73 m^2	10 (1.5)	95 (3.1)	68 (5.9)	31 (5.5)	<.001
UACR, mean (SD), mg/g	101 (453)	145 (545)	213 (683)	216 (804)	<.001
Blood urea nitrogen, mean (SD), mg/dL	20.3 (7.3)	21.4 (8.6)	26.8 (11.5)	24.6 (10.5)	<.001
Potassium, mean (SD), mEq/L	4.4 (0.5)	4.4 (0.5)	4.3 (0.5)	4.2 (0.5)	<.001
Sodium, mean (SD), mEq/L	140 (3)	141 (3)	141 (3)	140 (3)	.02
HbA_{1c}, mean (SD), %	6.4 (1.2)	6.4 (1.2)	6.5 (1.2)	6.5 (1.2)	<.001

(continued)

Table 1. Baseline Characteristics According to Diuretic Therapy in FINEARTS-HF (continued)

Characteristic	Diuretics, No. (%)				P value
	Nonloop (n = 684)	Loop (n = 4185)		Nonloop and loop (n = 569)	
		≤40 mg (n = 3040)	>40 mg (n = 1145)		
Medical history					
Hypertension	660 (96.5)	2615 (86.0)	1003 (87.6)	548 (96.3)	<.001
Diabetes	249 (36.5)	1150 (37.9)	538 (47.2)	278 (48.9)	<.001
Myocardial infarction	201 (29.4)	794 (26.1)	276 (24.1)	109 (19.2)	<.001
AF (history)	264 (38.6)	1594 (52.4)	800 (69.9)	309 (54.3)	<.001
Chronic obstructive pulmonary disease	63 (9.2)	373 (12.3)	189 (16.5)	75 (13.2)	<.001
Any prior hospitalization for HF	226 (33.0)	1878 (61.8)	835 (72.9)	317 (55.7)	<.001
Stroke	76 (11.1)	441 (14.5)	167 (14.6)	63 (11.1)	.02
Anemia	125 (19.3)	762 (26.5)	418 (38.6)	137 (25.4)	<.001
Treatments					
β-Blocker	565 (82.6)	2602 (85.6)	982 (85.8)	475 (83.5)	.14
ACE inhibitor	276 (40.4)	1049 (34.5)	421 (36.8)	206 (36.2)	.03
ARB	327 (47.8)	981 (32.3)	340 (29.7)	297 (52.2)	<.001
ARNI	15 (2.2)	327 (10.8)	80 (7.0)	10 (1.8)	<.001
SGLT2i	51 (7.5)	402 (13.2)	203 (17.7)	78 (13.7)	<.001
Digoxin	19 (2.8)	254 (8.4)	108 (9.4)	48 (8.4)	<.001

Abbreviations: ACE, angiotensin-converting enzyme; AF, atrial fibrillation; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; eGFR, estimated glomerular filtration rate; GLP, glucagon-like peptide; HbA_{1c}, glycated hemoglobin; 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; SGLT2i, sodium-glucose cotransporter 2 inhibitor; UACR, urine albumin to creatinine ratio.

SI conversion factor: to convert serum potassium and sodium from mEq/L to mmol/L, multiply by 1.

[a] Calculated as weight in kilograms divided by height in meters squared.

Effect of Finerenone According to Diuretic Therapy at Baseline

The benefit of finerenone compared to placebo did not differ among patients receiving nonloop diuretics alone, loop diuretics alone (≤40 mg or >40 mg), or the combination of these (**Table 2**; **Figure 1**). For example, the finerenone vs placebo rate ratio for the primary end point was 0.84 (95% CI, 0.47-1.51), 0.86 (95% CI, 0.72-1.02), 0.98 (95% CI, 0.78-1.24), and 0.54 (95% CI, 0.35-0.83), respectively, for these groups (*P* for interaction = .18). Moreover, when baseline loop diuretic dose was analyzed as a continuous variable, the effect of finerenone remained consistent across a broad range of loop diuretic doses for all evaluated outcomes (eFigure 3 in Supplement 3).

The mean increase (ie, improvement) in KCCQ-TSS from baseline to 12 months was greater with finerenone than with placebo across all subgroups, regardless of whether they were receiving loop diuretics alone, nonloop diuretics alone, or a combination of both; the placebo-corrected changes in KCCQ-TSS from baseline to 12 months were 2.1 (95% CI, −0.2 to 4.4), 2.2 (95% CI, 0.9 to 3.5), 0.3 (95% CI, −2.3 to 2.9), and 1.4 (95% CI, −1.9 to 4.7), respectively (*P* for interaction = .54; Table 2).

Tolerability and Safety According to Diuretic Therapy

Examination of patients assigned to placebo showed that hypotension, elevated creatinine, and hypokalemia were more common in patients receiving more than 40 mg of furosemide equivalent than in those taking 40 mg or less of furosemide equivalent or a nonloop diuretic alone (**Table 3**). The highest rate of hypokalemia was observed in the combination diuretic group.

Finerenone increased the incidence of hypotension and hyperkalemia (potassium >5.5 mEq/L) and reduced the risk of hypokalemia. These differences were consistent across all diuretic categories (Table 3). Additionally, the tolerability and safety of finerenone remained consistent regardless of whether patients experienced a loop diuretic dose increase or decrease after randomization. Notably, even among patients whose loop diuretic dose increased after randomization, finerenone significantly reduced the incidence of hypokalemia compared with placebo (eTable 3 in Supplement 3).

Change in Diuretic Dose After Randomization

Among 684 patients not receiving loop diuretics at baseline, 152 initiated loop diuretic therapy during the follow-up period. There was no significant difference in initiation between the randomized treatment groups (HR, 0.98; 95% CI, 0.71-1.36; *P* = .91; eFigure 4A in Supplement 3).

Among 4754 participants receiving loop diuretics at baseline, the mean (SD) baseline furosemide equivalent dose was similar between randomized treatment groups: 51 (54) mg in the finerenone group and 54 (61) mg in the placebo group; median (IQR) doses were 40 (20-60) mg vs 40 (20-60) mg, respectively. Finerenone prolonged the time to intensification of loop diuretic after randomization compared with placebo (HR, 0.84; 95% CI, 0.74-0.95; *P* = .005; eFigure 4B in Supplement 3).

Table 2. Effect of Randomized Treatment on Outcomes According to Diuretic Therapy in the FINEARTS-HF Trial

Outcome	Diuretics								*P* value for interaction
	Nonloop (n = 684)		Loop (n = 4185)				Nonloop and loop		
			≤40 mg (n = 3040)		>40 mg (n = 1145)				
	Placebo (n = 333)	Finerenone (n = 351)	Placebo (n = 1513)	Finerenone (n = 1527)	Placebo (n = 587)	Finerenone (n = 558)	Placebo (n = 274)	Finerenone (n = 295)	
Primary composite outcome									
No. of events	44	38	528	470	432	397	139	83	NA
Event rate (95% CI)[a]	5.0 (3.1 to 8.1)	4.3 (2.9 to 6.2)	14.3 (12.8 to 16.1)	12.5 (10.9 to 14.3)	32.6 (28.1 to 37.8)	31.2 (26.2 to 37.1)	20.6 (14.9 to 28.5)	11.6 (8.2 to 16.3)	NA
Rate difference (95% CI)	−0.8 (−3.7 to 2.2)		−1.8 (−4.2 to 0.5)		−1.4 (−8.7 to 5.9)		−9.0 (−16.9 to −1.1)		.68
RR (95% CI)[b]	0.84 (0.47 to 1.51)		0.86 (0.72 to 1.02)		0.98 (0.78 to 1.24)		0.54 (0.35 to 0.83)		.18
RR (95% CI)[c]	0.87 (0.48 to 1.57)		0.80 (0.67 to 0.95)		0.97 (0.78 to 1.21)		0.58 (0.37 to 0.90)		.11
Total HF events									
No. of events	31	17	407	364	349	326	119	61	NA
Event rate (95% CI)[a]	3.5 (2.0 to 6.4)	1.9 (1.0 to 3.5)	11.0 (9.7 to 12.6)	9.7 (8.3 to 11.3)	26.3 (22.3 to 31.1)	25.6 (21.2 to 30.9)	17.6 (12.3 to 25.2)	8.5 (5.5 to 13.1)	NA
Rate difference (95% CI)	−1.6 (−4.2 to 0.9)		−1.4 (−3.4 to 0.7)		−0.7 (−7.3 to 5.8)		−9.1 (−16.6 to −1.7)		.33
RR (95% CI)[b]	0.54 (0.24 to 1.23)		0.86 (0.70 to 1.05)		1.01 (0.79 to 1.30)		0.47 (0.28 to 0.79)		.07
RR (95% CI)[c]	0.57 (0.25 to 1.28)		0.80 (0.66 to 0.98)		0.99 (0.78 to 1.26)		0.50 (0.30 to 0.85)		.051
Cardiovascular death or first HF event									
No. of events	27	33	341	290	227	195	59	54	NA
Event rate (95% CI)[a]	3.2 (2.2 to 4.6)	3.8 (2.7 to 5.4)	10.2 (9.2 to 11.4)	8.3 (7.4 to 9.4)	20.8 (18.3 to 23.7)	18.1 (15.8 to 20.9)	9.6 (7.4 to 12.4)	8.0 (6.2 to 10.5)	NA
Rate difference (95% CI)	0.7 (−1.2 to 2.5)		−1.9 (−3.4 to −0.4)		−2.7 (−6.6 to 1.2)		−1.6 (−4.9 to 1.8)		.47
HR (95% CI)[b]	1.15 (0.69 to 1.91)		0.80 (0.69 to 0.94)		0.90 (0.74 to 1.09)		0.77 (0.53 to 1.12)		.45
HR (95% CI)[c]	1.15 (0.66 to 1.98)		0.74 (0.63 to 0.87)		0.89 (0.73 to 1.09)		0.83 (0.56 to 1.23)		.17
First HF event									
No. of events	19	14	259	223	190	164	51	37	NA
Event rate (95% CI)[a]	2.2 (1.4 to 3.5)	1.6 (1.0 to 2.7)	7.8 (6.9 to 8.8)	6.4 (5.6 to 7.3)	17.5 (15.1 to 20.1)	15.3 (13.1 to 17.8)	8.3 (6.3 to 10.9)	5.5 (4.0 to 7.6)	NA
Rate difference (95% CI)	−0.6 (−2.0 to 0.8)		−1.4 (−2.7 to −0.08)		−2.2 (−5.8 to 1.4)		−2.8 (−5.8 to 0.2)		.37
HR (95% CI)[b]	0.68 (0.34 to 1.36)		0.81 (0.67 to 0.97)		0.90 (0.73 to 1.12)		0.62 (0.41 to 0.96)		.54
HR (95% CI)[c]	0.67 (0.32 to 1.42)		0.75 (0.62 to 0.90)		0.91 (0.73 to 1.13)		0.61 (0.39 to 0.97)		.35
Cardiovascular death									
No. of events	13	21	121	106	84	71	20	23	NA
Event rate (95% CI)[a]	1.5 (0.9 to 2.6)	2.4 (1.6 to 3.7)	3.3 (2.8 to 3.9)	2.8 (2.3 to 3.4)	6.4 (5.1 to 7.9)	5.6 (4.4 to 7.1)	3.0 (1.9 to 4.6)	3.2 (2.1 to 4.9)	NA
Rate difference (95% CI)	0.9 (−0.5 to 2.2)		−0.5 (−1.3 to 0.3)		−0.8 (−2.7 to 1.1)		0.3 (−1.7 to 2.2)		.18
HR (95% CI)[b]	1.56 (0.78-3.14)		0.86 (0.67 to 1.12)		0.86 (0.63 to 1.19)		0.95 (0.52 to 1.75)		.41
HR (95% CI)[c]	1.48 (0.69 to 3.19)		0.80 (0.61 to 1.04)		0.86 (0.62 to 1.20)		1.00 (0.52 to 1.92)		.26
All-cause death									
No. of events	31	39	246	212	158	144	41	52	NA
Event rate (95% CI)[a]	3.5 (2.5 to 5.0)	4.4 (3.2 to 6.0)	6.7 (5.9 to 7.6)	5.6 (4.9 to 6.4)	11.9 (10.2 to 13.9)	11.3 (9.6 to 13.3)	6.1 (4.5 to 8.3)	7.2 (5.5 to 9.5)	NA
Rate difference (95% CI)	0.8 (−1.0 to 2.7)		−1.0 (−2.2 to 0.08)		−0.6 (−3.2 to 2.0)		1.2 (−1.6 to 3.9)		.38
HR (95% CI)[b]	1.21 (0.75 to 1.94)		0.85 (0.70-1.02)		0.94 (0.75 to 1.18)		1.15 (0.76 to 1.74)		.32
HR (95% CI)[c]	1.13 (0.68 to 1.88)		0.83 (0.68 to 1.00)		0.94 (0.74 to 1.19)		1.27 (0.82 to 1.97)		.30

(continued)

Table 2. Effect of Randomized Treatment on Outcomes According to Diuretic Therapy in the FINEARTS-HF Trial (continued)

Outcome	Diuretics								*P* value for interaction
	Nonloop (n = 684)		Loop (n = 4185)				Nonloop and loop		
			≤40 mg (n = 3040)		>40 mg (n = 1145)				
	Placebo (n = 333)	Finerenone (n = 351)	Placebo (n = 1513)	Finerenone (n = 1527)	Placebo (n = 587)	Finerenone (n = 558)	Placebo (n = 274)	Finerenone (n = 295)	
Improvement in NYHA functional class from baseline to 12 mo									
No. (%)	57 (17)	57 (16)	267 (18)	285 (19)	106 (18)	112 (20)	52 (19)	57 (19)	NA
OR (95% CI)[b]	0.93 (0.62 to 1.39)		1.07 (0.89 to 1.29)		1.12 (0.83 to 1.52)		1.03 (0.68 to 1.58)		.89
Change in KCCQ total symptom score from baseline to 12 mo									
Mean change (95% CI)	4.9 (2.9 to 6.8)	6.9 (5.1 to 8.8)	5.7 (4.6 to 6.8)	7.8 (6.8 to 8.9)	9.1 (6.9 to 11.4)	9.4 (7.2 to 11.6)	7.5 (4.6 to 10.4)	8.9 (6.1 to 11.7)	NA
Difference (95% CI)	2.1 (−0.2 to 4.4)		2.2 (0.9 to 3.5)		0.3 (−2.3 to 2.9)		1.4 (−1.9 to 4.7)		.54

Abbreviations: HF, hospitalization; HR, hazard ratio; KCCQ, Kansas City Cardiomyopathy Questionnaire; NA, not applicable; NYHA, New York Heart Association; RR, rate ratio.

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

[b] Models were stratified by region and baseline left ventricular ejection fraction (<60% or ≥60%).

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

For most patients, there was no change in loop diuretic dose at 6, 12, and 18 months (79.4%, 73.2%, and 68.9%, respectively; eTable 4 in Supplement 3). However, patients randomized to finerenone were less likely to experience a dose increase compared to placebo (6 months: 7.4% vs 9.5%; $P = .007$; 12 months: 10.0% vs 13.9%; $P < .001$; 18 months: 12.0% vs 16.6%; $P < .001$) and more likely to experience a dose decrease or discontinuation (6 months: 15.0% vs 9.3%; $P < .001$; 12 months: 18.0% vs 11.6%; $P < .001$; 18 months: 19.9% vs 13.6%; $P < .001$). Discontinuation rates in the finerenone vs placebo group were: 5.8% vs 3.9% at 6 months ($P = .003$), 7.6% vs 4.9% at 12 months ($P < .001$), and 8.9% vs 5.8% at 18 months ($P < .001$) (eTable 4 in Supplement 3). At 12 months, loop diuretic dose increased by 4.2 mg (95% CI, 1.9-6.4) in the placebo group but remained relatively stable in the finerenone group, with a change of −0.3 mg (95% CI, −2.6 to 2.0) (difference, −4.5 mg; 95% CI, −7.7 to −1.2; $P = .007$; **Figure 2**). Stratified analysis by baseline diuretic category showed similar trends, with assignment to finerenone associated with lower loop diuretic dose (eFigure 5 in Supplement 3).

Temporal Changes in Biomarkers According to Diuretic Therapy

From baseline to 12 months, the placebo-corrected increases in creatinine and potassium, as well as the decreases in SBP, hematocrit, body weight, and UACR with finerenone, were consistent across all subgroups (eFigure 6 in Supplement 3).

Discussion

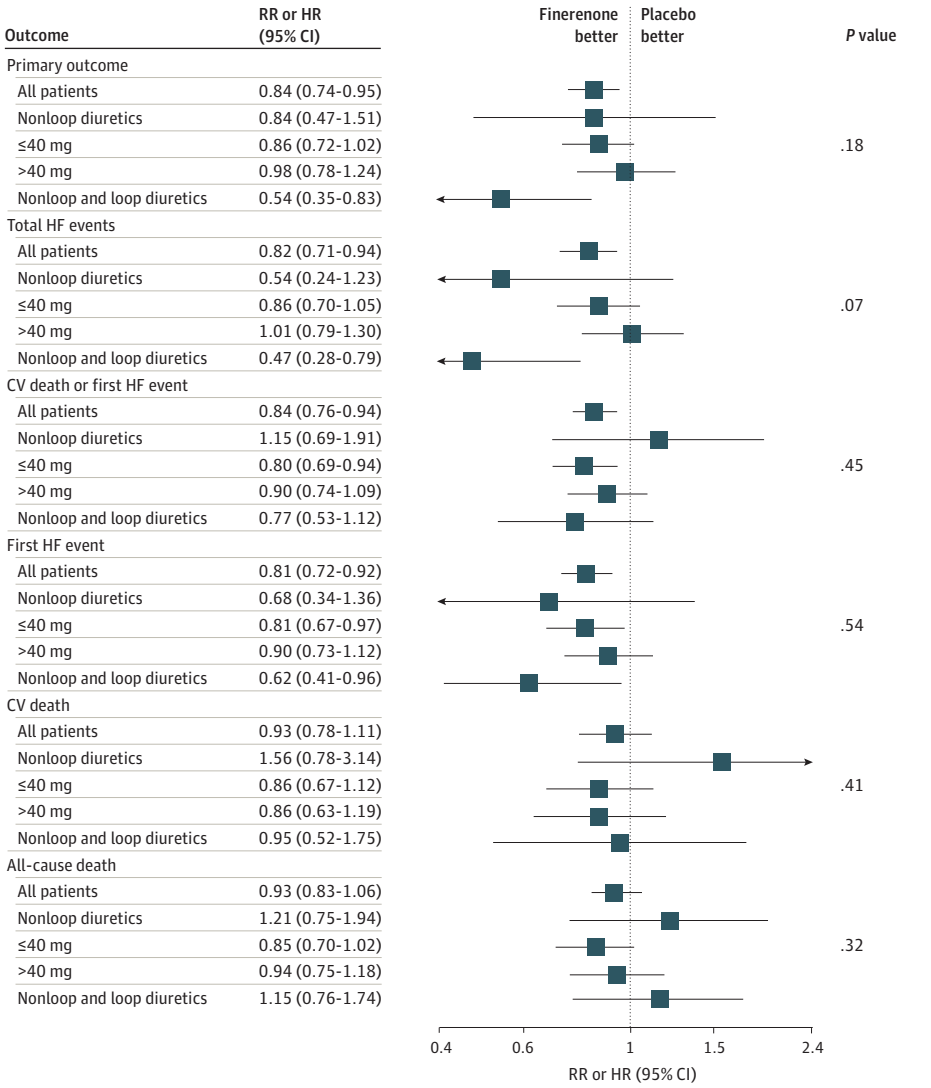
In this prespecified analysis of the FINEARTS-HF randomized clinical trial, the efficacy and safety of finerenone were consistent across all subgroups defined by diuretic use, including patients prescribed loop diuretics alone (both ≤40 mg or >40 mg of furosemide equivalent), nonloop diuretics alone, and those receiving both types of diuretic. Notably, the proportion of patients having an increase in loop diuretic dose after randomization was smaller and the proportion having a decrease in diuretic dose larger in the finerenone group compared to the placebo group. However, finerenone did not significantly reduce the initiation of a new loop diuretic among patients not receiving loop diuretics at baseline.

In this study, the mean and median furosemide-equivalent doses were 52 mg and 40 mg, respectively, with the largest proportion (2125 participants [39.1%]) receiving a daily dose equivalent to 40 mg of furosemide. The median baseline furosemide dose was also 40 mg in each of the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist),[9] PARAGON-HF (Prospective Comparison of ARNI with ARB Global Outcomes in HF With Preserved Ejection Fraction),[17] and EMPEROR-Preserved trials (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction).[18]

As expected, patients receiving more than 40 mg of furosemide equivalent exhibited a poorer clinical profile and had a higher risk for the primary composite outcome (and its components), as well as all-cause death, compared with those receiving the equivalent of 40 mg or less of furosemide (or a nonloop diuretic). These findings align with previous studies demonstrating a dose-dependent association between loop diuretic dose and worse outcomes in both HFrEF and, more recently, HFmrEF/HFpEF.[7,8,10,17-19,22,23]

Despite the significant differences in patient characteristics according to loop diuretic dose or diuretic category, the benefits of finerenone were generally consistent across all subgroups. While the effect of finerenone might appear larger in patients receiving only nonloop diuretics and both loop and nonloop diuretics, these subgroups were relatively small, with few events, and the wide confidence intervals around the point estimates highlight the limited statistical power within these groups. Notably, changes in SBP, body weight, serum creatinine, hematocrit, potassium, and UACR with finerenone did not differ by loop diuretic dose or category.

Figure 1. Effect of Finerenone on Key Outcomes in FINEARTS-HF According to Diuretic Therapy at Baseline



This Figure shows the effects of finerenone compared with placebo on clinical outcomes (primary composite outcome: total heart failure [HF] events, cardiovascular death or first HF event, first HF event, cardiovascular death, and all-cause death) and overall in the trial and according to diuretic therapy at baseline. CV indicates cardiovascular; HR, hazard ratio; RR, rate ratio.

As previously discussed, MRAs reduce sodium reabsorption along the distal nephron through effects on ENaC. This mechanism is distinct from that of loop and thiazide diuretics. Consequently, the addition of an MRA may amplify the natriuresis induced by loop and thiazide diuretics and reduce the dose needed of these diuretics (or any increase in their dose required). Although the mean loop diuretic dose after randomization was significantly lower in the finerenone group than in the placebo group, diuretic dose increased during follow-up in both treatment groups, suggesting progressive worsening of HF over time (or development of diuretic resistance or both these characteristics). The beneficial effects of finerenone on NYHA class, KCCQ scores, and hospitalization for HF are also consistent with slowing or prevention of progression of HF. However, it is difficult to know whether a lower dose of diuretic is just a marker of this more benign course or whether a lower dose of diuretic itself contributes to slower progression (eg, by mitigating against electrolyte disturbances, neurohormonal activation, and kidney dysfunction [and the adverse consequences of these]). This was primarily because fewer patients taking finerenone required intensification of diuretic therapy, although more patients taking finerenone also had a decrease in diuretic dose. Similar findings have been reported in the TOPCAT Americas,[9] EMPEROR-Preserved,[18] and DELIVER trials.[19] There was no significant difference between the finerenone and placebo groups in loop diuretic initiation. This is probably because relatively few patients were not receiving loop diuretics at baseline and generally had a more favorable profile, limiting the need for initiation (77 receiving finerenone vs 75 receiving placebo). The finding of less need for diuretic intensification is an important clinical finding. Diuretic intensification is a recognized marker of worsening HF and is associated with poor clinical outcomes. This effect of finerenone was observed early and persisted, suggesting the benefits extend beyond any initial decongestive effect. This is supported by sustained effects on biomarkers,

Table 3. Laboratory Safety Assessments and Hypotension According to Diuretic Therapy in FINEARTS-HF

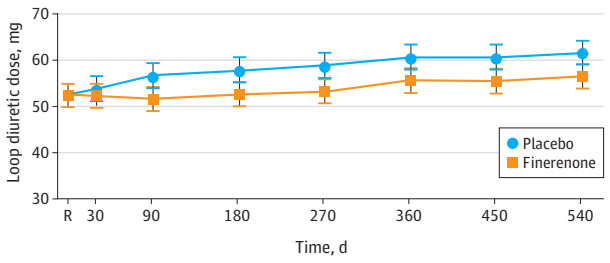
	Diuretics								
			Loop (n = 4185)						
	Nonloop (n = 684)		≤40 mg (n = 3040)		>40 mg (n = 1145)		Nonloop and loop (n = 569)		*P* value for interaction
	Placebo	Finerenone	Placebo	Finerenone	Placebo	Finerenone	Placebo	Finerenone	
Hypotension									
Systolic blood pressure <100 mm Hg, No. (%)	20 (6.1)	40 (11.8)	200 (13.6)	306 (20.6)	94 (16.6)	122 (22.7)	23 (8.8)	26 (9.1)	NA
OR (95% CI)[a]	2.24 (1.25-4.02)		1.69 (1.38-2.08)		1.50 (1.09-2.05)		1.18 (0.63-2.22)		.42
Elevated serum creatinine, No. (%)									
≥2.5 mg/dL, No. (%)	5 (1.5)	5 (1.5)	32 (2.2)	76 (5.1)	33 (5.9)	43 (8.1)	10 (3.8)	9 (3.2)	NA
OR (95% CI)[a]	-		2.41 (1.58-3.67)		1.47 (0.91-2.36)		-		.11
≥3.0 mg/dL, No. (%)	1 (0.6)	4 (1.2)	13 (0.9)	28 (1.9)	12 (2.1)	19 (3.6)	4 (1.5)	4 (1.4)	NA
OR (95% CI)[a]	-		2.16 (1.11-4.19)		1.76 (0.84-3.69)		-		.64
Elevated serum potassium									
>5.5 mEq/L, No. (%)	18 (5.5)	44 (13.0)	113 (7.8)	212 (14.3)	36 (6.4)	72 (13.5)	12 (4.6)	44 (15.6)	NA
OR (95% CI)[a]	2.66 (1.48-4.75)		2.04 (1.60-2.60)		2.26 (1.48-3.46)		3.80 (1.94-7.44)		.37
>6.0 mEq/L, No. (%)	2 (0.6)	10 (2.9)	22 (1.5)	47 (3.2)	7 (1.2)	13 (2.4)	7 (2.7)	8 (2.8)	NA
OR (95% CI)[a]	-		2.17 (1.30-3.63)		1.96 (0.77-4.99)		-		.36
Decreased serum potassium									
<3.5 mEq/L, No. (%)	30 (9.2)	7 (2.1)	118 (8.1)	55 (3.7)	67 (11.9)	34 (6.4)	41 (15.7)	23 (8.2)	NA
OR (95% CI)[a]	0.20 (0.09-0.47)		0.43 (0.31-0.60)		0.49 (0.32-0.76)		0.47 (0.27-0.81)		.26
<4.0 mEq/L, No. (%)	157 (48.2)	84 (24.8)	609 (41.8)	374 (25.2)	282 (50.1)	196 (36.6)	159 (50.9)	102 (36.2)	NA
OR (95% CI)[a]	0.35 (0.25-0.49)		0.45 (0.39-0.53)		0.57 (0.44-0.72)		0.36 (0.25-0.52)		.07

Abbreviations: NA, not applicable; OR, odds ratio.

SI conversion factor: to convert serum potassium from mEq/L to mmol/L, multiply by 1.

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

Figure 2. Change in Loop Diuretic Dose Over Time in FINEARTS-HF



This Figure shows the changes in loop diuretic dose over time according to treatment assignment. Dots represent geometric means, and error bars represent 95% confidence intervals. The mean placebo-corrected difference from randomization to 12 months was −4.5 mg (95% CI, −7.7 to −1.2 mg; *P* = .007). Placebo: 4.2 mg (95% CI, 1.9-6.4 mg). Finerenone: −0.3 mg (95% CI, −2.6 to 2.0 mg). The mean placebo-corrected difference from randomization to 18 months was −5.0 mg (95% CI, −8.6 to −1.5 mg; *P* = .005). Placebo: 9.4 mg (95% CI, 7.0-11.9 mg). Finerenone: 4.4 mg (95% CI, 1.9-6.9 mg). R indicates randomization.

such as UACR, which changed little between baseline and 12 months in the placebo group but was significantly reduced by finerenone across all diuretic subgroups. Albuminuria is a well-established predictor of adverse outcomes across a broad range of patients, including those with HFmrEF and HFpEF.[24,25] These observations are consistent with prior findings that disease-modifying drugs without diuretic activity can reduce diuretic requirement in HFrEF.[23]

The tolerability and safety of finerenone were consistent across all diuretic subgroups. Importantly, among patients receiving high doses of loop diuretics, finerenone did not significantly increase the incidence of elevated creatinine levels but did decrease hypokalemia compared with placebo. Even when hypokalemia was defined as a serum potassium below 4.0 mEq/L—a threshold associated with adverse outcomes[26]—finerenone significantly decreased its incidence compared with placebo. Additionally, the tolerability and safety of finerenone remained consistent regardless of loop diuretic dose increase or decrease after randomization. Notably, even among patients whose dose increased after randomization, finerenone significantly reduced hypokalemia incidence compared with placebo.

Limitations

This study has several limitations. Furosemide-equivalent loop diuretic doses were unavailable in a small number of patients in FINEARTS-HF, and changes in loop diuretic doses were assessed only at specific time points, without accounting for potential fluctuations between these intervals. Furthermore, data on other measures of diuretic efficacy, such as urinary out-

put, were unavailable. Although we carried out comprehensive adjustment for variables that differed between diuretic groups, incomplete adjustment or unmeasured variables may have resulted in residual confounding. Our findings are primarily applicable to patients with HFmrEF/HFpEF with NYHA class II through IV who met the trial's inclusion and exclusion criteria and were receiving standard diuretic therapy. Additionally, in some subgroups, particularly in patients receiving only nonloop diuretics and in those receiving both loop and nonloop diuretics, the small size of these subgroups limits the robustness of these findings.

Conclusions

In this prespecified analysis of the FINEARTS-HF randomized clinical trial, the benefits of finerenone were consistent across all diuretic subgroups. Compared to placebo, finerenone did not significantly reduce the initiation of a loop diuretic in patients not taking loop diuretics at baseline; however, finerenone reduced the need for loop diuretic dose intensification and led to a decrease in the mean loop diuretic dose. Initiating finerenone therapy may facilitate a reduction in loop diuretic requirements.

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Acquisition, analysis, or interpretation of data: Chimura, Jhund, Henderson, Yang, Claggett, Desai, Rohwedder, Lage, Mueller, Schou, Lam, Senni, Voors, Zannad, Pitt, Vaduganathan, McMurray.
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Data Sharing Statement: See Supplement 4.

REFERENCES

1. Cody RJ, Kubo SH, Pickworth KK. Diuretic treatment for the sodium retention of congestive heart failure. *Arch Intern Med*. 1994;154(17):1905-1914. doi:10.1001/archinte.1994.00420170045004

2. 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

3. McDonagh TA, Metra M, Adamo M, et al; Authors/Task Force Members; ESC Scientific Document Group. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: developed by the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure of the European Society of Cardiology (ESC). with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail*. 2022;24(1):4-131. doi:10.1002/ejhf.2333

4. Bayliss J, Norell M, Canepa-Anson R, Sutton G, Poole-Wilson P. Untreated heart failure: clinical and neuroendocrine effects of introducing diuretics. *Br Heart J*. 1987;57(1):17-22. doi:10.1136/hrt.57.1.17

5. Butler J, Forman DE, Abraham WT, et al. Relationship between heart failure treatment and development of worsening renal function among hospitalized patients. *Am Heart J*. 2004;147(2):331-338. doi:10.1016/j.ahj.2003.08.012

6. Eshaghian S, Horwich TB, Fonarow GC. Relation of loop diuretic dose to mortality in advanced heart failure. *Am J Cardiol*. 2006;97(12):1759-1764. doi:10.1016/j.amjcard.2005.12.072

7. Hasselblad V, Gattis Stough W, Shah MR, et al. Relation between dose of loop diuretics and outcomes in a heart failure population: results of the ESCAPE trial. *Eur J Heart Fail*. 2007;9(10):1064-1069. doi:10.1016/j.ejheart.2007.07.011

8. Peacock WF, Costanzo MR, De Marco T, et al; ADHERE Scientific Advisory Committee and Investigators. Impact of intravenous loop diuretics on outcomes of patients hospitalized with acute decompensated heart failure: insights from the ADHERE registry. *Cardiology*. 2009;113(1):12-19. doi:10.1159/000164149

9. Kalogeropoulos AP, Thankachen J, Butler J, Fang JC. Diuretic and renal effects of spironolactone and heart failure hospitalizations: a TOPCAT Americas analysis. *Eur J Heart Fail*. 2020;22(9):1600-1610. doi:10.1002/ejhf.1917

10. Abdel-Qadir HM, Tu JV, Yun L, Austin PC, Newton GE, Lee DS. Diuretic dose and long-term outcomes in elderly patients with heart failure after hospitalization. *Am Heart J*. 2010;160(2):264-271.e1. doi:10.1016/j.ahj.2010.05.032

11. Domanski M, Tian X, Haigney M, Pitt B. Diuretic use, progressive heart failure, and death in patients in the DIG study. *J Card Fail*. 2006;12(5):327-332. doi:10.1016/j.cardfail.2006.03.006

12. Ellison DH. Diuretic therapy and resistance in congestive heart failure. *Cardiology*. 2001;96(3-4):132-143. doi:10.1159/000047397

13. Cox ZL, Collins SP, Hernandez GA, et al. Efficacy and safety of dapagliflozin in patients with acute heart failure. *J Am Coll Cardiol*. 2024;83(14):1295-1306. doi:10.1016/j.jacc.2024.02.009

14. 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

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

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

17. Chatur S, Claggett BL, Vardeny O, et al. Sacubitril/valsartan and loop diuretic requirement in heart failure with preserved ejection fraction in the PARAGON-HF trial. *Eur J Heart Fail*. 2023;25(1):87-94. doi:10.1002/ejhf.2703

18. Butler J, Usman MS, Filippatos G, et al. Safety and efficacy of empagliflozin and diuretic use in patients with heart failure and preserved ejection fraction: a post hoc analysis of the EMPEROR-Preserved trial. *JAMA Cardiol*. 2023;8(7):640-649. doi:10.1001/jamacardio.2023.1090

19. Chatur S, Vaduganathan M, Claggett B, et al. Dapagliflozin and diuretic utilization in heart failure with mildly reduced or preserved ejection fraction: the DELIVER trial. *Eur Heart J*. 2023;44(31):2930-2943. doi:10.1093/eurheartj/ehad283

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

21. Royston P, Sauerbrei W. A new approach to modelling interactions between treatment and continuous covariates in clinical trials by using fractional polynomials. *Stat Med*. 2004;23(16):2509-2525. doi:10.1002/sim.1815

22. Ezekowitz J, Alemayehu W, Edelmann F, et al; VICTORIA Study Group. Diuretic use and outcomes in patients with heart failure with reduced ejection fraction: insights from the VICTORIA trial. *Eur J Heart Fail*. 2024;26(3):628-637. doi:10.1002/ejhf.3179

23. Jackson AM, Dewan P, Anand IS, et al. Dapagliflozin and diuretic use in patients with heart failure and reduced ejection fraction in DAPA-HF. *Circulation*. 2020;142(11):1040-1054. doi:10.1161/CIRCULATIONAHA.120.047077

24. Jackson CE, Solomon SD, Gerstein HC, et al; CHARM Investigators and Committees. Albuminuria in chronic heart failure: prevalence and prognostic importance. *Lancet*. 2009;374(9689):543-550. doi:10.1016/S0140-6736(09)61378-7

25. Selvaraj S, Claggett B, Shah SJ, et al. Prognostic value of albuminuria and influence of spironolactone in heart failure with preserved ejection fraction. *Circ Heart Fail*. 2018;11(11):e005288. doi:10.1161/CIRCHEARTFAILURE.118.005288

26. Pitt B, Agarwal R, Anker SD, et al. Hypokalaemia in patients with type 2 diabetes and chronic kidney disease: the effect of finerenone-a FIDELITY analysis. *Eur Heart J Cardiovasc Pharmacother*. 2025;11(1):10-19. doi:10.1093/ehjcvp/pvae074