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Finerenone in Heart Failure With Improved Ejection Fraction
The FINEARTS-HF Randomized Clinical Trial

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IMPORTANCE Patients with chronic heart failure (HF) and left ventricular ejection fraction (LVEF) less than 40% who experience LVEF improvement to 40% or higher (HFimpEF) may still face residual risks.

OBJECTIVE To assess the clinical profiles, risk, and treatment response to finerenone in participants with HFimpEF.

DESIGN, SETTING, AND PARTICIPANTS A total of 6001 patients with HE, LVEF of 40% or higher, New York Heart Association class II to IV symptoms, and elevated natriuretic peptide levels, were enrolled between September 14, 2020, and January 10, 2023. Patients with a prior history of LVEF less than 40% were included. Data analysis was conducted between September 1 to December 10, 2024.

INTERVENTION Participants received finerenone (titrated to 20 mg or 40 mg) or placebo.

MAIN OUTCOMES AND MEASURES The primary end point was the composite of cardiovascular (CV) death and total (first and recurrent) worsening HF events.

RESULTS Of the 6001 participants (mean [SD] age, 72 [9.7], years; 3269 male [55%]), 273 (5%) had a prior LVEF less than 40%. Among those with a prior LVEF of less than 40%, the median recorded prior LVEF was 35% [IQR, 30%-37%], with a median improvement of 12% [IQR, 8%-17%]. Over a median follow-up of 2.6 years, those with a history of LVEF of less than 40% experienced higher rates of the primary outcome of a composite of CV death and worsening of HF events (21.4 per 100 patient-years vs 16.0 per 100 patient-years) than did those whose LVEF was consistently 40% or higher. After adjustment for clinically relevant covariates; however, this rate ratio (RR) was not statistically different (absolute RR, 1.13; 95% CI, 0.85-1.49, P = .39). The treatment effect of finerenone on the primary outcome was consistent among those with a history of LVEF less than 40% and those with LVEF that was consistently 40% or higher (P for interaction = .36). Owing to higher baseline risk, the absolute risk reduction was greater among those with HFimpEF (9.2 vs 2.5 per 100 patient-years). Patients with HFimpEF tended to develop more hypotension with finerenone treatment, but otherwise, the safety profile of finerenone was similar in patients with and without previous LVEF less than 40%.

CONCLUSIONS AND RELEVANCE In this prespecified analysis of a randomized clinical trial, patients with HFimpEF remained at high risk of CV events, underscoring the need for continued management despite LVEF improvement. The treatment benefits of finerenone observed among the overall population of patients with HF with preserved EF were consistent among patients with HFimpEF.

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Supplemental content

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Advancements managing heart failure with reduced ejection fraction have led to a growing population of patients with heart failure with improved EF (HFimpEF).[1] However, knowledge gaps persist due to the historical lack of a standardized definition and exclusion of HFimpEF from major HF trials. This analysis examines clinical profiles, risk, and finerenone response in patients with HFimpEF compared with those with LVEF consistently 40% or higher who were enrolled in Finerenone Trial to Investigate Efficacy and Safety Superior to Placebo in Patients With Heart Failure (FINEARTS-HF) study.

Key Points

Question Do the treatment benefits of finerenone extend to patients with heart failure with improved ejection fraction (HFimpEF)?

Findings In this prespecified analysis of a randomized clinical trial involving 6001 patients with symptomatic HF, participants with HFimpEF demonstrated similar elevated residual risk of cardiovascular events to those with left ventricular EF (LVEF) consistently 40% or higher. Finerenone, consistently reduced the relative risk in the HFimpEF population. Although hypotension was more common with finerenone in these patients, there was no difference in serious adverse events compared with those with LVEF consistently 40% or higher.

Meaning Patients with HFimpEF remain at heightened risk of adverse outcomes, but finerenone safely and effectively mitigated this risk in this high-risk population.

Methods

The FINEARTS-HF study was a randomized, double-blind, placebo-controlled clinical trial involving symptomatic patients with HF whose LVEF was 40% or higher, allocated to receive either finerenone or placebo along with usual therapy (eFigure 1 in Supplement 2). The design and primary results have been published.[2] The trial protocol is shown in Supplement 1. The protocol was approved by the local ethics committees at each site, and an independent monitoring committee reviewed the trial. All patients provided written informed consent. The Consolidated Standards of Reporting Trials (CONSORT) guidelines were followed.

Exposure and Outcomes

HFimpEF status was collected at screening. The primary outcome was a composite of cardiovascular (CV) death and total (first and recurrent) HF events defined as either unplanned HF hospitalizations or urgent HF visits. Secondary outcomes included total HF events and all-cause mortality. Clinical outcomes were adjudicated by an independent, blinded end points committee.

Statistical Analysis

The primary outcome and total HF events by HFimpEF status were compared using recurrent events analyses based on the Lin, Wei, Yang, and Ying model,[3] stratified by geographic region and baseline LVEF (<60%, ≥60%). CV death and all-cause mortality were analyzed using the stratified Cox proportional hazards model. A sensitivity analysis excluded patients with a history of LVEF of 40% or less who had an LVEF improvement of less than 10%, aligning with the universal definition of HF for HFimpEF.[1] Models were adjusted for LVEF, sex, age, N-terminal pro-B-type natriuretic peptide (NT-proBNP), estimated glomerular filtration rate (eGFR), body mass index (BMI), history of hypertension and myocardial infarction (MI), and baseline use of angiotensin II receptor blockers (ARBs), angiotensin receptor neprilysin (ARN) inhibitors, β-blockers, and sodium-glucose cotransporter 2 (SGLT2) inhibitors. Treatment effect of finerenone vs placebo was evaluated including an interaction term between HFimpEF status in the stratified models. Safety data were evaluated using logistic regression. Statistical analyses were performed using Stata version 18 (StataCorp).

Results

Baseline Characteristics

Of the 6001 patients (mean [SD] age, 72 [9.7], years; 3269 male [55%]) randomized, 273 (5%) had HFimpEF. Among those with prior LVEF less than 40%, the median recorded prior LVEF was 35% (IQR, 30%-37%), with a median improvement of 12% (IQR, 8%-17%; eFigure 2 in Supplement 2). Among the 273 patients with HFimpEF, 147 were randomized to finerenone and 126 to placebo. Compared with participants with LVEF consistently 40% or higher, those with history of LVEF less than 40% were younger, less likely to be women, more likely to have a prior HF hospitalization and previous MI, and less likely to have a history of hypertension or atrial fibrillation. Participants with HFimpEF also had lower BMI and enrollment LVEF but similar eGFR and NT-proBNP. Finally, compared with participants with LVEF consistently 40% or higher, those with a history of LVEF less than 40% were more often treated with β-blockers, ARN inhibitors, and SGLT2 inhibitors at baseline (**Table 1**).

Clinical Event Rates

During 2.6 years of median follow-up, participants with a prior LVEF less than 40% experienced a higher risk of the primary outcome than did those with consistently preserved LVEF (21.4 per 100 patient-years vs 16.0 per 100 patient-years; unadjusted rate ratio [RR], 1.33; 95% CI, 1.01-1.75; $P = .04$). However, this difference was attenuated after covariate adjustment (absolute RR, 1.13; 95% CI, 0.85-1.49; $P = .40$). Sensitivity analysis excluding participants with a history of LVEF less than 40% and who had experienced less than 10% improvement in LVEF showed consistent results (19.5% vs 16.0% per 100 patient-years; adjusted hazard ratio [HR], 1.06; 95% CI, 0.75-1.52; $P = .73$). Participants with prior LVEF less than 40% had similar risks of secondary outcomes to those with LVEF consistently 40% or higher (eTable 1 in Supplement 2).

Table 1. Baseline Patient Characteristics by Heart Failure With Improved Ejection Fraction

	Left ventricular ejection fraction, No. (%) of patients		
	Consistently ≥40% (n = 5728)	History of <40% (n = 273)	*P* value
Age, mean (SD), y	72.1 (9.6)	70.1 (10.4)	.001
Sex			
Women	2664 (46.5)	68 (24.9)	.001
Men	3064 (53.5)	205 (75.1)	
Race[a]			
Asian	909 (15.9)	87 (31.9)	.001
Black	86 (1.5)	2 (0.7)	
White	4555 (79.5)	180 (65.9)	
Other	178 (3.1)	4 (1.5)	
Region			
Asia	895 (15.6)	88 (32.2)	.98
Eastern Europe	2595 (45.3)	55 (20.1)	
Latin America	633 (11.1)	8 (2.9)	
North America	426 (7.4)	45 (16.5)	
Western Europe, Oceania, and others	1179 (20.6)	77 (28.2)	
Any prior HF hospitalization	3433 (59.9)	186 (68.1)	.007
Recency of HF event			
≤7 d from randomization	1183 (20.7)	36 (13.2)	.01
>7 d-≤3 mo	1931 (33.7)	97 (35.5)	
>3 mo or no index HF event	2614 (45.6)	140 (51.3)	
Systolic blood pressure, mean (SD) mm Hg	129.6 (15.3)	125.0 (15.6)	.001
BMI, mean (SD)	30.0 (6.1)	28.2 (5.7)	.001
Creatinine, mean (SD), mg/dL	1.1 (0.3)	1.2 (0.7)	.001
eGFR, mean (SD), mL/min/1.73 m^2	62.1 (19.6)	61.4 (21.5)	.54
eGFR <60 mL/min/1.73 m^2	2748 (48.0)	140 (51.3)	.29
UACR, mg/g	18 (7-67)	19 (8-66)	.47
Potassium, mean (SD), mmol/L	4.4 (0.5)	4.4 (0.5)	.02
LVEF, mean (SD), %	52.9 (7.8)	46.3 (5.6)	.001
NT-proBNP, pg/mL	1038 (444-1937)	1075 (496-2211)	.10
NYHA class			
II	3942 (68.8)	204 (74.7)	.04
III	1746 (30.5)	67 (24.5)	
IV	39 (0.7)	2 (0.7)	
History of hypertension	5110 (89.2)	215 (78.8)	.001
Diabetes	2331 (40.7)	108 (39.6)	.71
Atrial fibrillation on baseline electrocardiogram	2218 (38.7)	75 (27.5)	.001
History of stroke	676 (11.8)	32 (11.7)	.97
History of myocardial infarction	1445 (25.2)	96 (35.2)	.001
Medication use			
β-Blocker	4849 (84.7)	246 (90.1)	.01
ACE inhibitor	2071 (36.2)	84 (30.8)	.07
ARB	2043 (35.7)	59 (21.6)	.001
ARN inhibitor	418 (7.3)	95 (34.8)	.001
Calcium channel blocker	1927 (33.6)	41 (15.0)	.001
SGLT-2 inhibitor	744 (13.0)	73 (26.7)	.001
Loop diuretic	4987 (87.1)	252 (92.3)	.01

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blockers; ARN, angiotensin receptor/neprilysin; BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; eGFR, estimated glomerular filtration rate; HF, heart failure; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro–B-type natriuretic peptide; NYHA, New York Heart Association; SGLT2, sodium-glucose cotransporter 2; UACR, urine albumin-creatinine ratio.

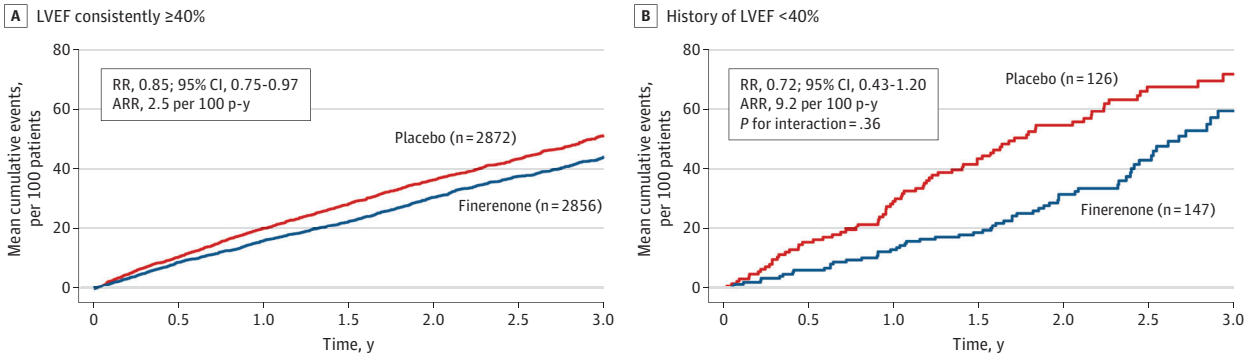
SI conversion factor: To convert creatinine from mg/dL to μmol/L, multiply by 88.4.

[a] Other race includes American Indian, Alaska Native, Native Hawaiian, Other Pacific Islander, or unreported, and was determined by self-identification.

Treatment Effect of Finerenone by HFimpEF Status

HFimpEF status did not significantly modify the treatment effect of finerenone on the primary outcome. Among participants with a history of LVEF less than 40%, the RR of the primary outcome with finerenone compared with placebo was 0.72 (95% CI, 0.43-1.20) with an absolute risk reduction of 9.2 per 100 patient-years compared with an RR of 0.85 (95% CI, 0.75-0.97) and an adjusted RR of 2.5 per 100 patient-years in

Figure. Kaplan-Meier Curve for Total Heart Failure Events and Cardiovascular Death



LVEF indicates left ventricular ejection fraction; RR, risk reduction; ARR, absolute risk reduction.

Table 2. Treatment Effect Estimates by Heart Failure With Improved Ejection Fraction Status

	Left ventricular ejection fraction				
	Consistently ≥40%		History of <40%		
	Placebo (n = 2872)	Finerenone (n = 2856)	Placebo (n = 126)	Finerenone (n = 147)	*P* for interaction
Total worsening heart failure events and death from cardiovascular causes					
Events	1205	1023	78	60	
Per 100 patient-years	17.3	14.8	26.4	17.2	.36
Rate ratio	1 [Reference]	0.85 (0.75-0.97)	1 [Reference]	0.72 (0.43-1.20)	
Total worsening heart failure events					
Events	959	793	65	49	
Per 100 patient-years	13.8	11.4	22.0	14.0	.42
Rate ratio	1 [Reference]	0.83 (0.71-0.96)	1 [Reference]	0.72 (0.41-1.24)	
Death from cardiovascular causes					
Events, No. (%)	247 (8.6)	231 (8.1)	13 (10.3)	11 (7.5)	
Per 100 patient-years	3.6	3.3	4.4	3.1	.52
Hazard ratio	1 [Reference]	0.94 (0.79-1.13)	1 [Reference]	0.73 (0.32-1.67)	
Worsening heart failure event or death from cardiovascular causes					
Events, No. (%)	681 (23.7)	590 (20.7)	38 (30.2)	34 (23.1)	
Per 100 patient-years	10.9	9.2	14.6	10.7	.55
Hazard ratio	1 [Reference]	0.85 (0.76-0.95)	1 [Reference]	0.74 (0.46-1.19)	
Heart failure hospitalization or death from cardiovascular causes					
Events, No. (%)	630 (21.9)	566 (19.8)	34 (27.0)	33 (22.4)	
Per 100 patient-years	9.9	8.8	12.9	10.2	.66
Hazard ratio	1 [Reference]	0.89 (0.79-1.00)	1 [Reference]	0.81 (0.49-1.31)	
Death from any cause					
Events, No. (%)	499 (17.4)	473 (16.6)	23 (18.3)	18 (12.2)	
Per 100 patient-years	7.2	6.8	7.7	52	.27
Hazard ratio	1 [Reference]	0.95 (0.84-1.08)	1 [Reference]	0.70 (0.37-1.32)	

participants with LVEF consistently 40% or higher, *P* for interaction, .36; **Figure**). No significant treatment interaction by HFimpEF status was observed for the secondary outcomes (**Table 2**).

Safety Outcomes by HFimpEF Status

Rates of hyperkalemia were similar between the HFimpEF population and those with LVEF consistently 40% or higher (*P* for interaction = .60), but the rates of systolic blood pressure less than 100 mm Hg tended to be higher in the HFimpEF group *P* for interaction = .04; eTable 2 in Supplement 2). Otherwise, the safety and tolerability of finerenone were comparable between groups.

Discussion

In this prespecified analysis, patients with prior LVEF less than 40% had similar adverse CV events to the rest of the trial population, highlighting that LVEF improvement does not equate

to cardiac recovery or eliminate residual HF risk. Importantly, these patients derived comparable benefits from the addition of finerenone as those with consistently preserved LVEF (≥40%). These data support the consideration of finerenone alongside other medical therapies (such as SGLT2 inhibitors) in the management of HFimpEF.

Patients with HFimpEF remain at significant risk of adverse outcomes.[4,5] Despite LVEF improvement, persistent cardiac structural and functional abnormalities likely predispose patients with HFimpEF to recurrent LV dysfunction,[6] underscoring the importance of continuing guideline-directed medical therapy.[7] Recent trials like Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure (DELIVER)[4,8,9] and FINEARTS-HF demonstrate the incremental efficacy of addition of novel therapies in this population. Herein, we show that finerenone reduces morbidity and mortality in symptomatic participants, including those with prior LVEF less than 40%.

Although finerenone use was associated with higher rates of hyperkalemia and hypotension, severe hyperkalemia remained rare and the risk of hypokalemia was reduced, mitigating diuretic-associated electrolyte disturbances. Hypotension related to finerenone was more frequent in participants with HFimpEF than in those with LVEF consistently at 40% or higher. These findings, observed in a closely monitored clinical trial, highlight the need for future studies to evaluate the frequency and implications of hypotension when finerenone is integrated in usual clinical practice. The safety and tolerability profile of finerenone was otherwise comparable between groups.

Limitations

This study has limitations. Patients with prior LVEF less than 40% comprised only 5% of the FINEARTS-HF population. Additionally, the HFimpEF definition used herein differs slightly from current guidelines, such as the universal definition of HF[1] and the 2022 American College of Cardiology/American Heart Association/Heart Failure Society of America guidelines,[10] which require a baseline LVEF of 40% or less, a 10-point or more improvement, and a subsequent LVEF higher than 40%. However, our sensitivity analysis excluding patients with less than 10% LVEF improvement supports the robustness of these findings. Baseline data on HF timing, etiology, and prior therapies were not collected, and LVEF trajectories during follow-up are unknown. Future studies in HFimpEF should aim to capture these data more comprehensively.

Conclusions

In summary, in this high-risk cohort of patients with HF, finerenone demonstrated consistent safety and efficacy in reducing adverse CV outcomes regardless of prior history of LVEF less than 40%. Although hypotension related to finerenone was more common in patients with HFimpEF, the safety and tolerability profile of finerenone was otherwise similar to the rest of the trial population. These findings support the safety and efficacy of finerenone in patients with HFimpEF and emphasize the ongoing need for optimized medical management to address residual risks in HFimpEF.

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