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FINEARTS-HF: Improving outcomes in heart failure with preserved or mildly reduced ejection fraction

ABSTRACT

The FINEARTS-HF (Finerenone Trial to Investigate Efficacy and Safety Superior to Placebo in Patients With Heart Failure, N Engl J Med 2024; 391(16):1475–1485) trial evaluated finerenone, a nonsteroidal mineralocorticoid receptor antagonist, in patients with left ventricular ejection fraction 40% or greater. Finerenone reduced the composite risk of hospitalization for heart failure or cardiovascular death by 16% relative to placebo (rate ratio 0.84, $P = .007$), primarily by lowering admissions for heart failure. Finerenone is the first mineralocorticoid receptor antagonist to improve outcomes in this patient population.

KEY POINTS

- Finerenone reduced hospitalizations for heart failure but did not significantly reduce cardiovascular death (8.1% vs 8.7%) or all-cause mortality (16.4% vs 17.4%) compared with placebo.
- About 21% of patients on finerenone had a primary event vs 24% on placebo (3.2% risk reduction, number needed to treat 31).
- Hyperkalemia was more frequent with finerenone, although hospitalization occurred in only 0.5% of patients vs 0.2% with placebo; hypokalemia risk was reduced (4.4% vs 9.7%).
- Future guidelines will likely give finerenone at least a class 2a recommendation for patients with heart failure with preserved ejection fraction.

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Heart failure with preserved ejection fraction (HFpEF) and mildly reduced ejection fraction (HFmrEF) account for roughly half of all heart failure cases and have been difficult to treat.[1] Although morbidity and mortality in HFpEF is similar to heart failure with reduced ejection fraction, until recently no therapy had convincingly improved clinical outcomes in this patient population.

Neurohormonal antagonists like the mineralocorticoid receptor antagonists spironolactone and eplerenone reduce hospitalizations and mortality in patients with heart failure with reduced ejection fraction, but it was uncertain if those benefits extend to patients with HFpEF or HFmrEF.[2,3] The FINEARTS-HF (Finerenone Trial to Investigate Efficacy and Safety Superior to Placebo in Patients With Heart Failure) trial[4] showed that finerenone, a nonsteroidal mineralocorticoid receptor antagonist, helped reduce hospitalizations for heart failure in this patient population. This article discusses the FINEARTS-HF trial, including its rationale, methods, results, and implications for clinical practice.

WHY WAS THE FINEARTS-HF TRIAL NEEDED?

The **TOPCAT** (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist) trial[5] evaluated spironolactone for HFpEF and found no difference between spironolactone and placebo for its

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primary composite end point of death from cardiovascular causes, aborted cardiac arrest, or hospitalization for heart failure. Post hoc analyses hinted at regional discrepancies—patients in the Americas had improved outcomes with spironolactone, whereas those in Russia and Georgia did not—raising concerns about trial conduct and patient selection. TOPCAT's controversy left clinicians unsure whether mineralocorticoid receptor antagonists truly had no role in treating HFpEF or if a more targeted approach could still be beneficial.

Meanwhile, patients with HFpEF often have metabolic comorbidities such as type 2 diabetes and chronic kidney disease that worsen prognosis. Finerenone, a newer, nonsteroidal, and more selective mineralocorticoid receptor antagonist, had already shown promise for these comorbid conditions. In the **FIDELIO-DKD**[6] (Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease) and **FIGARO-DKD**[7] (Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease) trials, finerenone not only slowed kidney disease progression but also modestly reduced cardiovascular events in participants with diabetes and chronic kidney disease, largely by lowering the risk of hospitalization for heart failure by around 29%. These findings suggested that beyond its renal protective effects, finerenone might benefit the heart, especially in patients prone to heart failure.

The therapeutic landscape for HFpEF also began shifting with the emergence of sodium-glucose cotransporter (SGLT) 2 inhibitors. The **EMPEROR-Preserved**[8] (Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction) and **DELIVER**[9] (Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure) trials showed an approximately 20% reduction in hospitalization for heart failure and cardiovascular death in patients with HFpEF, establishing SGLT-2 inhibitors as the first effective therapy for the condition. However, the absolute benefits in both trials were modest (around 3% absolute risk reduction and number needed to treat of approximately 30), and many patients still experienced events.

A large unmet need for additional therapies remained. Before FINEARTS-HF, mineralocorticoid receptor antagonists for HFmrEF and HFpEF only received a class 2b recommendation in the American College of Cardiology and American Heart Association guideline,[1] whereas the European Society of Cardiology guidelines[10] did not offer a corresponding recommendation for HFmrEF and HFpEF due to insufficient evidence.

FINEARTS-HF was therefore designed to definitively test whether finerenone, with its favorable pharmacologic profile and previous success in related patient populations, could improve outcomes in patients with HFpEF or HFmrEF. It aimed to resolve the uncertainty left by TOPCAT[5] and expand the therapeutic options for a heterogenous group of patients who had long been stuck with symptomatic treatment alone.

HOW WAS THE TRIAL DONE?

FINEARTS-HF was a multinational, randomized, double-blind, placebo-controlled trial.[4]

Study population and treatment

The trial enrolled 6,001 patients with symptomatic chronic heart failure (New York Heart Association class II–IV) and left ventricular ejection fraction 40% or greater. The median follow-up was 32 months.

Key inclusion criteria ensured patients truly had HFpEF or HFmrEF with evidence of structural heart disease: an elevated natriuretic peptide level consistent with heart failure and either left atrial enlargement or left ventricular hypertrophy. Approximately 36% had a left ventricular ejection fraction of 40% to 50% (mildly reduced), and the rest had left ventricular ejection fraction greater than 50% (preserved); the mean left ventricular ejection fraction was 53%.

Major exclusion criteria were as follows:

- Significant renal dysfunction (estimated glomerular filtration rate [eGFR] < 25 mL/min/1.73 m^2 or serum potassium level > 5.0 mmol/L) at baseline
- Recent acute coronary events
- Uncontrolled hypertension
- Other serious comorbid conditions that could confound dyspnea.

The mean age of the cohort was 72 years; 46% were female; and common comorbidities included hypertension (around 90%), type 2 diabetes (41%), and chronic kidney disease (eGFR < 60 mL/min/1.73 m^2 in 48%). Notably, 60% had a previous hospitalization for heart failure and 84% were enrolled within 3 months of a heart failure exacerbation, indicating a high-risk population.

Baseline medical therapy reflected contemporary practice: approximately 80% were receiving renin-angiotensin system blockers, approximately 87% were receiving diuretics, and only 14% were receiving an SGLT-2 inhibitor (the trial started before SGLT-2 inhibitors were standard for HFpEF).

Patients were randomized 1:1 to finerenone or placebo in addition to their usual care. Finerenone was started at 20 mg once daily (or 10 mg with a baseline

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eGFR < 60 mL/min/1.73 m^2) and titrated up to 40 mg (20 mg in patients with a lower eGFR) after 4 weeks if permitted based on renal function and potassium levels.

End points and event-driven analysis

FINEARTS-HF was event driven and used a composite primary end point of total heart failure events (defined as first or recurrent unplanned hospitalizations for heart failure or urgent heart failure visits requiring intravenous therapy) plus cardiovascular death. A recurrent-event statistical approach was used to analyze the composite end point. Unlike earlier HFpEF trials that only focused on time to first event, the recurrent-event statistical analysis used by FINEARTS-HF analyzed total heart failure events (first and recurrent hospitalizations or urgent heart failure visits) in addition to cardiovascular death. This approach captured the cumulative burden of morbidity with heart failure, which is particularly relevant in HFpEF because repeated hospitalizations contribute substantially to impaired quality of life, increased healthcare utilization, and worse prognosis.

A traditional time-to-first-event analysis of cardiovascular death or first hospitalization for heart failure was also assessed as a secondary end point. Other secondary end points included components of the primary outcome, all-cause mortality, change in quality of life (Kansas City Cardiomyopathy Questionnaire score, which ranges from 0 to 100, with higher scores indicating better health status) at 12 months, kidney disease progression, and safety outcomes. Prespecified subgroup analyses examined consistency of the primary outcome across left ventricular ejection fraction categories (40%–50% and > 50%), sex, baseline SGLT-2 inhibitor use, presence of improved left ventricular ejection fraction, and other factors.

WHAT DID THE TRIAL SHOW?

Finerenone significantly improved the primary composite outcome of cardiovascular death or total heart failure events in patients with HFpEF or HFmrEF, making finerenone the first mineralocorticoid receptor antagonist to meet its primary end point in this patient population.[4]

Reduced hospitalizations but no mortality benefit

Event rates were 14.9 per 100 patient-years in the finerenone group vs 17.7 per 100 patient-years with placebo (rate ratio 0.84, 95% confidence interval [CI] 0.74–0.95, P = .007). Over a median follow-up of 32 months, 20.8% of patients treated with finerenone experienced cardiovascular death or a first hospitalization for heart failure compared with 24.0% of those taking placebo, yielding an absolute risk reduction of 3.2%. This translates to roughly 1 fewer hospitalization for heart failure or cardiovascular death per 30 to 35 patients treated for 3 years (number needed to treat 31). The magnitude of benefit is comparable to results from SGLT-2 inhibitor trials for HFpEF (eg, a 3.3% absolute risk reduction and a number needed to treat of approximately 31 with empagliflozin[8]), and was primarily due to a nearly 18% reduction in recurrent hospitalizations for heart failure (842 vs 1,024 events).

Cardiovascular and all-cause mortality were not significantly different between the finerenone and placebo groups (cardiovascular death 8.1% vs 8.7%, hazard ratio 0.93, 95% CI 0.78–1.11; all-cause mortality 16.4% vs 17.4%, hazard ratio 0.93, 95% CI 0.83–1.06), mirroring other HFpEF trials like EMPEROR-Preserved,[8] where treatment improved heart failure outcomes without a clear reduction in mortality.

The benefit seen with finerenone underscores the ability of the recurrent-event design to reveal clinically meaningful treatment effects that may not be apparent in time-to-first-event analyses.

Improved patient symptoms

Finerenone also produced modest improvements in patient-reported health status, as measured by a mean symptom score increase of 8.0 points on the Kansas City Cardiomyopathy Questionnaire vs −6.4 points for placebo at 12 months (between-group difference +1.6, P < .001). Renal outcomes for finerenone were neutral, with no significant difference in the renal dysfunction composite end point (2.5% finerenone vs 1.8% placebo; hazard ratio 1.33, 95% CI 0.94–1.89).[4] Subgroup analyses showed consistent benefits across sex, left ventricular ejection fraction spectrum (40%–50% vs > 50%), and SGLT-2 inhibitor use, with higher absolute risk reductions in patients with recently improved left ventricular ejection fraction.

Safety profile requires monitoring

Safety analysis revealed that hyperkalemia greater than 5.5 mmol/L occurred more frequently with finerenone (14.3%) than placebo (6.9%), though serious hyperkalemia that required hospitalization was rare (0.5% vs 0.2%). Systolic hypotension (< 100 mm Hg) was more frequent with finerenone (18.5% vs 12.4% with placebo). Notably, finerenone reduced the incidence of hypokalemia (4.4%) compared with placebo (9.7%). Overall tolerability was favorable with appropriate monitoring of laboratory values.

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HOW WILL THESE FINDINGS CHANGE PRACTICE?

The results from FINEARTS-HF[4] are likely to shape the therapeutic approach to patients with left ventricular ejection fraction 40% or greater. Finerenone offers a new evidence-based therapy for patients with HFpEF or HFmrEF, along with standard care. It is especially relevant for patients with comorbid diabetes or chronic kidney disease, who constituted a large subset of the FINEARTS-HF study population and would derive parallel benefits observed in previous finerenone trials (FIDELIO-DKD[6] and FIGARO-DKD[7]). Finerenone appears poised to join SGLT-2 inhibitors as a disease-modifying therapy in these patient populations.

Based on the trial's findings and previous neutral results with older mineralocorticoid receptor antagonists, guideline committees may consider upgrading the current class 2b (weak) recommendation for mineralocorticoid receptor antagonists in HFmrEF and HFpEF to at least class 2a (moderate) for appropriately selected patients. Finerenone's significant absolute risk reduction and a number needed to treat of 31, which is similar to that observed with SGLT-2 inhibitors for HFpEF, supports its role as an additive rather than an alternative disease-modifying therapy.

Targeted patient selection

Clinicians should focus on identifying patients who mirror the trial cohort—those with recently decompensated heart failure, elevated natriuretic peptide levels, left ventricular ejection fraction 40% or greater, eGFR 25 mL/min/1.73 m² or greater, and serum potassium level 5.0 mmol/L or less—as they derive the greatest absolute benefit. The starting finerenone dose is 20 mg daily, or 10 mg daily if eGFR is less than 60 mL/min/1.73 m². Laboratory values should be monitored 1 to 2 weeks after initiation or dose adjustment, and the dose titrated to 40 mg if renal function and potassium levels permit.

Finerenone can also be coprescribed with SGLT-2 inhibitors. FINEARTS-HF showed that treatment effects were consistent irrespective of SGLT-2 inhibitor use.

Cost and accessibility

When integrating finerenone into routine practice, clinicians should keep in mind that because a generic version is not available, finerenone is generally more expensive than older mineralocorticoid receptor antagonists such as spironolactone, but its cost is comparable to other contemporary disease-modifying drugs for HFpEF, including SGLT-2 inhibitors. Many insurance companies already cover finerenone for patients with diabetes and chronic kidney disease, which may facilitate access for those with an overlapping cardiorenal comorbidity. As guideline recommendations expand, broader coverage and improved accessibility are anticipated.

CONTROVERSIES AND UNANSWERED QUESTIONS

Despite the benefit shown by finerenone in patients with HFpEF or HFmrEF, several questions remain unanswered that could be the basis for future research.

Is the benefit due to a mineralocorticoid receptor antagonist class effect or unique to finerenone?

TOPCAT[5] raised doubts about using spironolactone for HFpEF due to regional inconsistencies and a largely neutral outcome, leaving it unclear whether finerenone's efficacy was due to a class effect or its unique pharmacology. Finerenone is more selective, nonsteroidal, and associated with fewer off-target effects compared with older steroidal mineralocorticoid receptor antagonists. It is possible that issues with how TOPCAT was conducted masked spironolactone's true benefit, but mechanistic data suggest finerenone's antifibrotic and anti-inflammatory effects may be distinct. Direct comparative or head-to-head studies are needed to confirm whether the benefit extends across all mineralocorticoid receptor antagonists.

Which patient subgroups derive the greatest absolute benefit?

HFpEF and HFmrEF are heterogeneous, and subgroups include obesity-predominant, atrial fibrillation–related, hypertensive left ventricular hypertrophy, and ischemic phenotypes. In FINEARTS-HF,[4] patients with elevated brain natriuretic peptide and recent hospitalization for heart failure derived the greatest absolute benefit, as these are higher-risk groups with higher event rates. Lower-risk patients, though they may achieve similar relative risk reductions, may not experience the same absolute gains. Future studies should stratify responses by clinical and biomarker-defined phenotypes to personalize therapy.

What is the best way to manage hyperkalemia risk in multidrug regimens?

Hyperkalemia remains a key concern when mineralocorticoid receptor antagonists are combined with other neurohormonal agents (eg, angiotensin receptor-neprilysin inhibitors plus angiotensin-converting enzyme inhibitor and angiotensin II receptor blocker plus SGLT-2 inhibitor plus finerenone), especially in patients with chronic kidney disease or diabetes. Hyperkalemia was common in FINEARTS-HF,[4] but

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serious events were rare with careful monitoring. Practical solutions include baseline potassium level and eGFR screening and then repeating the checks soon after initiation or dose titration, and using potassium binders when necessary. Integrating SGLT-2 inhibitors, which lower hyperkalemia risk, may also mitigate this issue, but real-world strategies must be validated.

Will longer follow-up or combination therapy show a mortality benefit?

FINEARTS-HF showed reduction in hospitalizations for heart failure without a mortality benefit over roughly 3 years, similar to previous drug trials for HFpEF. It remains uncertain whether longer observation could reveal delayed survival gains, especially as hospitalizations themselves predict mortality. Combination regimens (finerenone plus an SGLT-2 inhibitor with or without angiotensin receptor-neprilysin inhibitors) may work together to reduce risk and provide a mortality benefit. Dedicated longer-term and combination trials will be required to resolve this critical question.

FUTURE DIRECTIONS

Future finerenone trials should focus on the following:

- Combination therapy trials with finerenone plus an SGLT-2 inhibitor with or without angiotensin receptor-neprilysin inhibitors to test efficacy and safety of add-on treatment
- Earlier initiation (eg, in the hospital after decompensation) or use in broader HFpEF and HFmrEF patient populations
- Mechanistic substudies on cardiac fibrosis, diastolic function, or cardiac remodeling to identify patients most likely to respond
- Phenotype-based strategies (eg, obesity-predominant HFpEF) and integration with metabolic therapies such as glucagon-like peptide 1 receptor agonists
- Guideline implementation and monitoring workflows to safely scale use.

THE BOTTOM LINE

FINEARTS-HF[4] established finerenone as an effective medical therapy to reduce hospitalizations for heart failure in patients with HFpEF or HFmrEF. The absolute benefit was modest, with a neutral mortality benefit and the need to monitor potassium levels and eGFR, but clinically meaningful in a common, high-burden condition. Finerenone provides a significant benefit comparable to what has been seen with SGLT-2 inhibitors for HFpEF, and should be considered as an add-on treatment for eligible patients with HFpEF or HFmrEF to reduce rehospitalizations.

DISCLOSURES

Dr. Salahuddin reports no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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