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► To cite this version:

Orly Vardeny, Muthiah Vaduganathan, Brian L Claggett, Akshay S Desai, Pardeep S Jhund, et al.. Finerenone, Serum Potassium, and Clinical Outcomes in Heart Failure With Mildly Reduced or Preserved Ejection Fraction. JAMA Cardiology, 2025, 10 (1), pp.42-48. 10.1001/jamacardio.2024.4539 . hal-04791611

HAL Id: hal-04791611

<https://hal.univ-lorraine.fr/hal-04791611v1>

Submitted on 19 Nov 2024

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Finerenone, Serum Potassium, and Clinical Outcomes in Heart Failure With Mildly Reduced or Preserved Ejection Fraction

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IMPORTANCE Treatment with finerenone, a nonsteroidal mineralocorticoid receptor antagonist (MRA), improved outcomes in patients with heart failure with mildly reduced or preserved ejection fraction in FINEARTS-HF, but was associated with increased levels of serum potassium in follow-up.

OBJECTIVE To investigate the frequency and predictors of serum potassium level greater than 5.5 mmol/L and less than 3.5 mmol/L and examine the treatment effect associated with finerenone, relative to placebo, on clinical outcomes based on postrandomization potassium levels.

DESIGN, SETTING, AND PARTICIPANTS Secondary analysis of the FINEARTS-HF multicenter, randomized clinical trial, performed between September 14, 2020, and January 10, 2023, with a median follow-up of 32 months (final date of follow-up: June 14, 2024). Patients with heart failure and left ventricular ejection fraction greater than or equal to 40%, New York Heart Association class II to IV symptoms, and elevated natriuretic peptides were included.

INTERVENTION Participants received finerenone or placebo.

MAIN OUTCOMES AND MEASURES The primary outcome was a composite of total worsening heart failure events or cardiovascular death.

RESULTS A total of 6001 participants were included (3003 randomized to receive finerenone and 2998 randomized to receive placebo). The increase in serum potassium was greater in the finerenone group than the placebo group at 1 month (median [IQR] difference, 0.19 [0.17-0.21] mmol/L) and 3 months (median [IQR] difference, 0.23 [0.21-0.25] mmol/L), which persisted for the remainder of trial follow-up. Finerenone increased the risks of potassium level increasing to greater than 5.5 mmol/L (hazard ratio [HR], 2.16 [95% CI, 1.83-2.56]; $P < .001$) and decreased the risks for potassium level decreasing to less than 3.5 mmol/L (HR, 0.46 [95% CI, 0.38-0.56]; $P < .001$). Both low (< 3.5 mmol/L; HR, 2.49 [95% CI, 1.8-3.43]) and high (> 5.5 mmol/L; HR, 1.64 [95% CI, 1.04-2.58]) potassium levels were associated with higher subsequent risks of the primary outcome in both treatment groups. Nevertheless, the risk of the primary outcome was generally lower in patients treated with finerenone compared with placebo, even in those whose potassium level increased to greater than 5.5 mmol/L.

CONCLUSIONS AND RELEVANCE In patients with heart failure with mildly reduced or preserved ejection fraction, finerenone resulted in more frequent hyperkalemia and less frequent hypokalemia. However, with protocol-directed surveillance and dose adjustment, clinical benefit associated with finerenone relative to placebo was maintained even in those whose potassium level increased to greater than 5.5 mmol/L.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: [NCT04435626](https://clinicaltrials.gov/ct2/show/study/NCT04435626)

JAMA Cardiol. doi:10.1001/jamacardio.2024.4539
Published online November 17, 2024.

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Mineralocorticoid receptor antagonists (MRAs) are a key component of guideline-directed medical therapy for heart failure with reduced ejection fraction and may be used in patients with heart failure with mildly reduced or preserved ejection fraction.¹ The favorable mechanistic effects of MRAs on the heart, kidneys, and blood vessels are challenging to disconnect from their effects on electrolyte handling, because blockade of aldosterone universally leads to increases in serum potassium levels. Steroidal MRAs are underused in heart failure with reduced ejection fraction due in large part to the perceived risk of hyperkalemia, despite evidence that clinical efficacy is maintained even in the setting of modest elevations in potassium levels.^{2,3} Conversely, potassium levels less than 3.5 mmol/L are associated with an increased risk for adverse clinical outcomes in patients with heart failure,⁴⁻⁶ and MRAs mitigate the risk for hypokalemia.

In the FINEARTS-HF trial, the nonsteroidal MRA finerenone reduced the risk of cardiovascular death and total worsening heart failure events in patients with symptomatic heart failure and left ventricular ejection fraction greater than or equal to 40%.⁷ This study investigated the frequency and predictors of serum potassium level greater than 5.5 mmol/L and less than 3.5 mmol/L and examined the treatment effect of the nonsteroidal MRA finerenone, relative to placebo, on clinical outcomes based on postrandomization potassium levels.

Methods

Study Design and Patient Selection

FINEARTS-HF was an international, randomized, double-blind, placebo-controlled trial conducted in 634 sites in 37 countries testing the efficacy and safety of finerenone compared with placebo in patients with heart failure and mildly reduced or preserved ejection fraction. The trial design, conduct, and primary results were previously published.⁸ The protocol was approved by local ethics committees at each participating site, and each patient provided written informed consent in accordance with established guidelines. The trial protocol is shown in [Supplement 1](#). The trial was reviewed by an independent monitoring committee. Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines were followed.

The study enrolled patients 40 years or older with symptomatic heart failure (New York Heart Association functional class II-IV) and a left ventricular ejection fraction greater than or equal to 40% within 12 months of enrollment, elevated levels of natriuretic peptides (N-terminal fragment of the prohormone brain natriuretic peptide [NT-proBNP] ≥ 300 pg/mL in those without atrial fibrillation or flutter or ≥ 900 pg/mL in those with atrial fibrillation), evidence of structural heart disease (left atrial enlargement or left ventricular hypertrophy), and use of diuretics for at least 30 days prior to enrollment. Individuals were excluded if they had estimated glomerular filtration rate (eGFR) less than 25 mL/min/1.73 m² or serum potassium greater than 5.0 mmol/L at baseline. Those with a history of hyperkalemia or acute kidney failure during MRA treatment for more than 7 consecutive days, leading to per-

Key Points

Question What is the treatment effect of finerenone, relative to placebo, in patients with heart failure with mildly reduced or preserved ejection fraction based on postrandomization potassium levels?

Findings Among 6001 patients in a clinical trial, finerenone increased potassium levels greater than 5.5 mmol/L and decreased potassium levels less than 3.5 mmol/L. Nevertheless, the risk of the primary outcome was generally lower in patients treated with finerenone compared to placebo, even in those for whom potassium level increased to greater than 5.5 mmol/L.

Meaning With protocol-directed surveillance and dosage adjustment, the clinical benefit associated with finerenone relative to placebo was maintained even in those whose potassium level increased to greater than 5.5 mmol/L.

manent discontinuation of the MRA treatment, were also excluded.

Participants were randomly assigned in a 1:1 ratio to receive finerenone (starting at 10 mg or 20 mg daily, depending on baseline eGFR ≤ 60 or >60 mL/min/1.73 m², respectively) or matching placebo daily in addition to the patient's current therapies or treatment (eFigure 1 in [Supplement 2](#)). Four weeks after randomization, or any time thereafter, treatment doses were titrated to 20 mg or 40 mg daily (depending on eGFR ≤ 60 or >60 mL/min/1.73 m²) or matching placebo daily. Potassium levels were measured at baseline, 30 days after randomization, 90 days after randomization, and every 3 months for the first 12 months, then every 4 months thereafter. Per the protocol, if the postrandomization potassium level was greater than or equal to 5.5 mmol/L, investigators down-titrated or temporarily interrupted the study medication; if the potassium level was greater than or equal to 6.0 mmol/L, drug interruption was advised ([Supplement 1](#)). If the study medication was interrupted, investigators could reinstitute the lowest study medication dose if it was deemed medically acceptable without compromising safety.

Exposure and Outcomes

The primary outcome of the trial was a composite of total (first and recurrent) worsening heart failure events and cardiovascular death. A worsening heart failure event was defined as either an unplanned heart failure hospitalization or a nonhospitalized, unscheduled urgent ambulatory or emergency department visit for heart failure. Secondary outcomes included total worsening heart failure events and all-cause mortality. Clinical outcomes were adjudicated by an independent, blinded end points committee.

Statistical Analyses

Baseline characteristics were compared between participants who had potassium levels greater than 5.5 mmol/L and those who did not, as well as between participants who had potassium levels less than 3.5 mmol/L and those who did not at any scheduled or unscheduled visit after the baseline visit. Data were reported as means and SDs, medians and IQRs, or

percentages and were compared using the χ^2 test for categorical variables and Wilcoxon and *t* tests for nonnormal and normally distributed continuous variables, respectively. Potassium levels at baseline and at each scheduled visit after randomization by treatment assignment were compared.

Cox proportional hazards regression models were used to examine associations between baseline characteristics and time to postbaseline potassium level greater than 5.5 mmol/L and less than 3.5 mmol/L, adjusting for treatment assignment and the following covariates: age, sex, race, diabetes, hypertension, history of myocardial infarction, New York Heart Association functional class, baseline potassium, eGFR, NT-proBNP level, systolic and diastolic blood pressure, and baseline medications (diuretic, angiotensin receptor neprilysin inhibitor, angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, β -blocker, sodium-glucose cotransporter-2 inhibitor, digoxin, and potassium supplements). Treatment-specific Poisson regression models were used to conduct a landmark analysis 3 months after randomization, estimating via cubic spline models the rate of the primary outcome based on potassium levels observed at that scheduled study visit. Treatment-specific Poisson regression models were also used for a time-updated analysis using the most recent potassium measurement from a scheduled study visit prior to a primary outcome event. Hyperkalemia and hypokalemia adverse events were investigator-reported and did not incorporate potassium levels into the analyses.

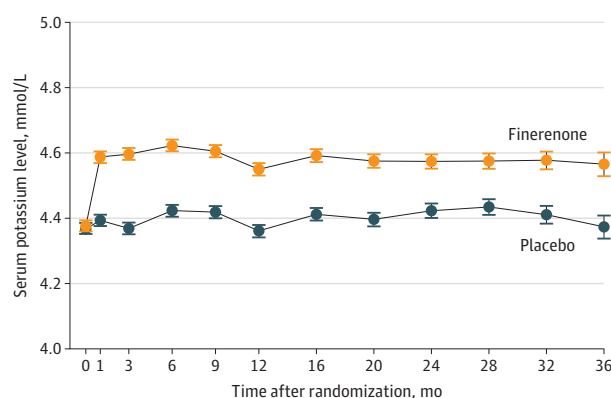
In an additional analysis, we estimated the risks observed in finerenone and placebo groups both before and after an observed potassium level greater than 5.5 mmol/L in time-updated Cox proportional hazards models on time to first cardiovascular death or worsening heart failure event, accounting for serial potassium levels. Patients were initially considered in a window of risk before experiencing a potassium level greater than 5.5 mmol/L. At the point that the potassium level was greater than 5.5 mmol/L, the patient was reclassified. We assessed for an interaction in estimated risks of finerenone and placebo before and after laboratory-measured potassium level greater than 5.5 mmol/L.

Statistical testing was 2-sided, and *P* < .05 indicated statistical significance.

Results

Among 6001 participants analyzed (mean age, 72 years; 2732 female participants), mean (SD) baseline potassium levels were similar between the finerenone (*n* = 3003) and placebo (*n* = 2998) groups (4.38 [0.48] vs 4.37 [0.47] mmol/L; *P* = .51). The mean (SD) doses of study medications were 15.6 (4.3) mg for finerenone and 16.7 (4.0) mg for placebo for the 20-mg daily dose strata and 32.3 (9.1) mg for finerenone and 34.5 (7.8) mg for placebo the 40-mg dose strata. Postrandomization serum potassium measurements in the finerenone and placebo group were 4.59 [0.48] vs 4.39 [0.47] mmol/L, respectively, at month 1 and 4.60 [0.47] vs 4.37 [0.46] mmol/L, respectively, at month 3 (*P* < .001 at both points). The increase in serum potassium was greater in the finerenone group than the placebo group

Figure 1. Potassium Levels During the Study by Treatment



The increase in serum potassium was greater in the finerenone group than the placebo group at 1 month (median [IQR] difference, 0.19 [0.17-0.21] mmol/L) and 3 months (median [IQR] difference, 0.23 [0.21-0.25] mmol/L), which persisted for the remainder of trial follow-up.

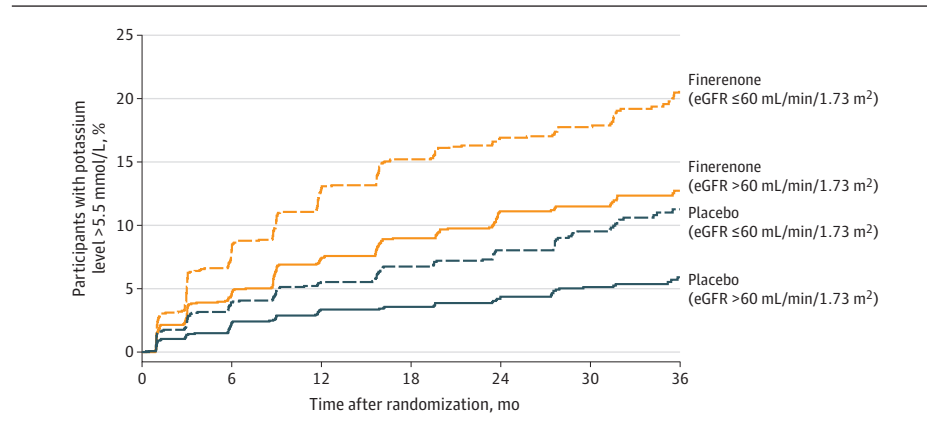
at 1 month (median [IQR] difference, 0.19 [0.17-0.21] mmol/L) and 3 months (median [IQR] difference, 0.23 [0.21-0.25] mmol/L), which persisted for the remainder of trial follow-up (Figure 1).

Participants who received finerenone had an increased risk for potassium level greater than 5.5 mmol/L and greater than 6.0 mmol/L at any point relative to placebo (>5.5 mmol/L: hazard ratio [HR], 2.16 [95% CI, 1.83-2.56]; *P* < .001; >6.0 mmol/L: HR, 2.07 [95% CI, 1.4-3.0]; *P* < .001) and had a decreased risk for potassium level less than 3.5 mmol/L (HR, 0.46 [95% CI, 0.38-0.56]; *P* < .001). The risk for potassium elevation to greater than 5.5 mmol/L after randomization was similar across target dosing strata (20-mg strata: HR, 2.02 [95% CI, 1.63-2.50]; 40-mg strata: HR, 2.35 [95% CI, 1.80-3.05]; interaction *P* = .39) (Figure 2).

Regardless of treatment assignment, patients who had a potassium level greater than 5.5 mmol/L during follow-up were more likely to be men and have a history of diabetes, myocardial infarction, and recent worsening heart failure events; worse baseline kidney function; and higher baseline potassium levels (eTable 1 in Supplement 2). Those who had a potassium level less than 3.5 mmol/L were more likely to be women and have a history of hospitalization for heart failure, history of atrial fibrillation, a higher baseline urine albumin:creatinine ratio, and lower baseline potassium levels (eTable 2 in Supplement 2). Baseline characteristics that were associated with potassium level greater than 5.5 mmol/L in multivariable models included type 2 diabetes; higher baseline potassium, serum creatinine, urine albumin:creatinine ratio, and NT-proBNP levels; Asian race; and lower body mass index. Clinical characteristics that were associated with any potassium level less than 3.5 mmol/L were Asian race, lower baseline Kansas City Cardiomyopathy Questionnaire total symptom scores, lower baseline potassium levels, and higher NT-proBNP levels (Table).

Hyperkalemia and hypokalemia adverse events leading to hospitalizations were infrequent (hyperkalemia events: 0.5% in the finerenone group vs 0.2% in the placebo group; hypokalemia events: 0.1% in the finerenone group vs 0.2% in the

Figure 2. Incidence of Potassium Greater Than 5.5 mmol/L



Dosing was based on estimated glomerular filtration rate (eGFR) >60 mL/min/1.73 m² (target dose: 40 mg daily) or ≤60 mL/min/1.73 m² (target dose: 20 mg daily) at study baseline.

Table. Characteristics Associated With Potassium Greater Than 5.5 mmol/L and Less Than 3.5 mmol/L

Variable	Hazard ratio (95% CI)	P value	χ ²
Potassium >5.5 mmol/L			
Potassium (per 0.5 mmol/L)	1.80 (1.68-1.93)	<.001	284.7
Randomized to receive finerenone	2.17 (1.83-2.57)	<.001	80.8
Creatinine (per 0.1 mg/dL)	1.03 (1.02-1.05)	<.001	33.4
Race^a			
Asian	0.52 (0.40-0.69)	<.001	23.7
Black	0.96 (0.45-2.03)		
White	Reference		
Other	1.26 (0.83-1.92)		
UACR (per doubling)	1.07 (1.03-1.10)	<.001	15.3
Type 2 diabetes	1.38 (1.16-1.63)	<.001	13.6
BMI	0.89 (0.83-0.96)	.003	8.9
NT-proBNP (per doubling)	1.08 (1.03-1.14)	.004	8.2
Potassium <3.5 mmol/L			
Potassium (per 0.5 mmol/L)	0.36 (0.32-0.40)	<.001	345.4
Randomized to receive finerenone	0.46 (0.38-0.56)	<.001	57.4
Race^a			
Asian	1.85 (1.48-2.32)	<.001	29.5
Black	1.50 (0.74-3.03)		
White	Reference		
Other	0.95 (0.49-1.85)		
KCCQ-TSS (per 10 points)	0.93 (0.89-0.96)	<.001	13.4
NT-proBNP (per doubling)	1.09 (1.03-1.16)	.005	7.8

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire total symptom score; NT-proBNP, N-terminal fragment of the prohormone brain natriuretic peptide; UACR, urine albumin:creatinine ratio.

^a Race was included in the analysis for reporting transparency and for readers to assess generalizability of results. Race was determined by the participant based on fixed categories. "Other" included American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, multiple races, or not reported (n = 17).

placebo group) and there were no hyperkalemia- or hypokalemia-related deaths in either group (Figure 3). During a median follow-up of 2.6 years, 3-month potassium levels at both ends of the measurement spectrum (<3.5 and >5.5 mmol/L) were associated with increased subsequent risks of the primary outcome in both treatment groups. Nevertheless, finerenone was associated with lower risks compared with placebo (Figure 4). In a time-updated model using the most recent potassium level, risk of the primary outcome was increased in those who had a potassium measurement greater than 5.5 mmol/L (HR, 1.64 [95% CI, 1.04-2.58]) or less than 3.5 mmol/L

(HR, 2.49 [95% CI, 1.80-3.43]) compared with those whose potassium levels remained between 3.5 and 5.5 mmol/L (eFigure 2 in Supplement 2).

In an analysis that examined the incidence of cardiovascular death or first worsening heart failure event before and after a potassium measurement of greater than 5.5 mmol/L, finerenone was consistently associated with a lower risk compared with placebo in participants who did vs did not have a potassium level greater than 5.5 mmol/L during follow-up (HR, 0.84 [95% CI, 0.55-1.30] vs 0.83 [95% CI, 0.74-0.92]; interaction $P = .72$).

Figure 3. Incidence of Investigator-Reported Potassium-Related Events

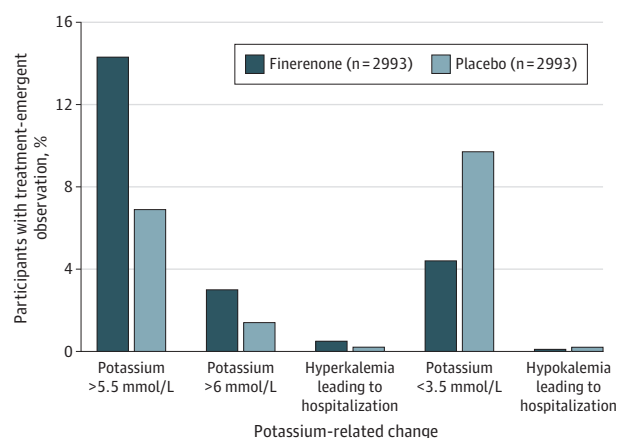
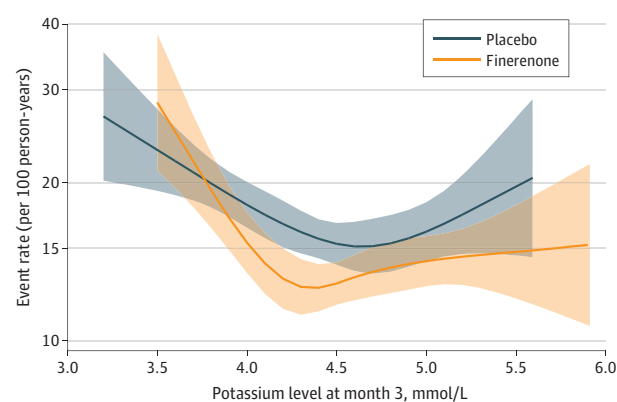


Figure 4. Rates of Cardiovascular Death or Worsening Heart Failure



Discussion

In this analysis of patients with heart failure and mildly reduced or preserved ejection fraction, patients randomized to receive finerenone had more frequent potassium elevation to greater than 5.5 mmol/L and less frequent potassium decrease to less than 3.5 mmol/L compared with individuals receiving placebo. The incidence of potassium level greater than 6.0 mmol/L was relatively infrequent, but was more commonly observed in the finerenone group. Hospitalizations due to hyperkalemia were uncommon, and there were no deaths related to hyperkalemia during the trial. Patients with potassium levels greater than 5.5 mmol/L or less than 3.5 mmol/L were both associated with a higher risk of adverse clinical outcomes regardless of treatment assignment, but the benefits associated with finerenone relative to placebo on worsening heart failure or cardiovascular death were maintained even in those with early increase (1 month after randomization) in potassium levels to greater than 5.5 mmol/L.

Baseline characteristics associated with potassium level greater than 5.5 mmol/L included potassium levels at randomization, higher serum creatinine and urine albumin:creatinine

ratio, and type 2 diabetes, while individuals of Asian descent were less likely to have hyperkalemia. These factors were consistent with those noted in previous trials of steroidal MRAs in patients with heart failure and in the FIDELIO-DKD study in patients with type 2 diabetes and chronic kidney disease.^{2,3,9} Importantly, finerenone dosing in the FINEARTS-HF trial was based on baseline kidney function, and those with eGFR less than or equal to 60 mL/min/1.73 m² had their dose titrated to half the dose that patients with eGFR greater than 60 mL/min/1.73 m² were receiving. Although the absolute incidences of potassium level greater than 5.5 mmol/L were higher among those with lower eGFR, the relative risk between finerenone and placebo were similar within each dose strata. As such, the magnified risk of elevated potassium with kidney dysfunction may be mitigated by appropriate target dosing of finerenone, mirroring the trial protocol approach. Notably, higher NT-proBNP levels were associated with both potassium levels greater than 5.5 mmol/L and less than 3.5 mmol/L, suggesting that potassium levels at both extremes of the spectrum may be, at least in part, reflective of worse disease severity.

Although head-to-head comparisons of finerenone to steroidal MRAs at the doses used in the FINEARTS-HF study are not available, the mean placebo-corrected increase in potassium in FINEARTS-HF after dose titration was 0.23 mmol/L, and, in the TOPCAT-Americas study, the posttitration difference with spironolactone was 0.29 mmol/L.^{2,10} Differences in study populations and use of concomitant medications that could affect potassium were dissimilar between the studies, thus comparisons of potassium changes between steroidal and nonsteroidal MRAs are challenging. The findings of a preserved benefit associated with finerenone despite elevations in potassium levels are consistent with analyses from RALES and EMPHASIS-HF studies, in which the benefits associated with MRAs were maintained despite elevation in serum potassium.^{2,3} Similar findings were seen in a post hoc analysis of the TOPCAT-Americas study.¹⁰

Derangements in serum potassium levels are regularly encountered in patients with heart failure, and may result from disease progression, concomitant chronic kidney disease, and use of medications that alter potassium homeostasis (loop or thiazide diuretics, renin-angiotensin-system inhibitors, angiotensin receptor neprilysin inhibitors, β -blockers, and MRAs).¹¹ Patients with HF are particularly susceptible to arrhythmias induced by hypokalemia or hyperkalemia, and potassium levels at both ends of the measurement spectrum have been shown to be associated with heightened risks of mortality.^{12,13} Although clinicians are particularly concerned about the risk of hyperkalemia, which often results in permanent discontinuation of life-saving guideline-directed medical therapy, there may be underappreciation of adverse sequelae resulting from hypokalemia. In FINEARTS-HF, the risk for a primary outcome event following a potassium level less than 3.5 mmol/L was higher than when the potassium level was greater than 5.5 mmol/L. This result is consistent with those from the PARAGON-HF study⁵ and in observational datasets.^{14,15} Thus, some of the benefits attributable to MRAs may relate to their reducing the risk for hypokalemia.¹⁶

Limitations

Findings from this analysis should be viewed in the context of their limitations. First, this study excluded individuals with baseline potassium levels greater than 5.0 mmol/L and eGFR less than 25 mL/min/1.73 m²; thus, the generalizability of these data to a wider group of patients with heart failure with mildly reduced or preserved ejection fraction is uncertain. Second, the study offered protocolized recommendations for correcting potassium (by either dose reduction or temporary discontinuation) when the laboratory measurement was greater than or equal to 5.5 mmol/L, but prompt correction of potassium was not mandated when potassium levels were less than 3.5 mmol/L during the trial. Third, the granular reasons for permanent study medication discontinuation were not captured, and it was not possible to definitively determine the percentage of patients who discontinued the study medication due to increased potassium levels.

Conclusion

In patients with heart failure with mildly reduced or preserved ejection fraction, finerenone resulted in early modest increases in potassium levels. However, the clinical benefit associated with finerenone was maintained even in the setting of elevated potassium, and the risk of hypokalemia was reduced with finerenone. Appropriate dose selection according to baseline kidney function and dose adjustments in response to potassium levels while receiving treatment, in keeping with the trial protocol, may mitigate risks of serious hyperkalemia and optimize treatment continuation in clinical practice. These data suggest a favorable risk to benefit ratio for the use of finerenone in select patients with heart failure with mildly reduced or preserved ejection fraction in the setting of protocolized surveillance and follow-up.

ARTICLE INFORMATION

Accepted for Publication: October 23, 2024.

Published Online: November 17, 2024.

doi:10.1001/jamacardio.2024.4539

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Author Contributions: Drs Solomon and Claggett had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Vardeny, Vaduganathan, Lam, Shah, Voors, Zannad, Pitt, Merkely, Lay-Flurrie, Scalise, Solomon.

Acquisition, analysis, or interpretation of data: Vardeny, Vaduganathan, Claggett, Desai, Jhund, Senni, Voors, Zannad, Matsumoto, Zieroth, Yilmaz, Lay-Flurrie, Viswanathan, Horvat-Broecker, McMurray.

Drafting of the manuscript: Vardeny, Claggett, Scalise.

Critical review of the manuscript for important intellectual content: Vaduganathan, Claggett, Desai, Jhund, Lam, Senni, Shah, Voors, Zannad, Pitt, Matsumoto, Merkely, Zieroth, Yilmaz, Lay-Flurrie, Viswanathan, Horvat-Broecker, McMurray, Solomon.

Statistical analysis: Claggett, Jhund, Lay-Flurrie, Solomon.

Obtained funding: Solomon.

Supervision: Zannad, Merkely, Zieroth, Yilmaz, Scalise, Solomon.

Other - steering committee member of FINEARTS-HF: Lam.

Conflict of Interest Disclosures: Dr Vardeny reported receiving grants from AstraZeneca and Cardior and institutional research support from Bayer and Cardurion outside the submitted work. Dr Vaduganathan reported receiving research grant support from, serving on advisory boards for, or having speaker engagements with American Regent, Amgen, AstraZeneca, Bayer AG, Baxter Healthcare, BMS, Boehringer Ingelheim, Chiesi, Cytokinetics, Fresenius Medical Care, Idorsia Pharmaceuticals, Lexicon Pharmaceuticals, Merck, Milestone Pharmaceuticals, Novartis, Novo Nordisk, Pharmacosmos, Relypsa, Roche Diagnostics, Sanofi, and Tricog Health and serving on clinical trial committees for AstraZeneca, Galmed, Novartis, Bayer AG, Occlutech, and Impulse Dynamics outside the submitted work. Dr Claggett reported receiving personal fees for statistical consulting from Alnylam, Cardior, Cardurion, Cytokinetics, CVRx, Intellia, Rocket, and Eli Lilly consulting outside the submitted work. Dr Desai reported receiving institutional research grants and personal fees from Bayer during the conduct of the study and institutional research grants from Abbott, Alnylam, AstraZeneca, DevPro Biopharma, Novartis, Pfizer and personal fees for consulting from Abbott, Alnylam, AstraZeneca, Avidity Biopharma, Axon Therapeutics, Biofourmis, Boston Scientific, Endotronix, GlaxoSmithKline, Icon Clinical Research, Novartis, Parexel, Porter Health,

Regeneron, Roche, River2Renal, scPharmaceuticals, Veristat, Verily, and Zydus outside the submitted work. Dr Jhund reported receiving grants from Boehringer Ingelheim, Roche Diagnostics, Analog Devices, and AstraZeneca and personal fees from ProAdwise outside the submitted work and serving as director of Global Clinical Trial Partners. Dr Lam reported serving on a steering committee for FINEARTS-HF for Bayer during the conduct of the study and receiving research support from Novo Nordisk and Roche Diagnostics; serving as a consultant or on an advisory board or steering or executive committee for Alnylam Pharma, AnaCardio AB, Applied Therapeutics, AstraZeneca, Bayer, Biopeutics, Boehringer Ingelheim, Boston Scientific, Bristol Myers Squibb, Coteria, CPC Clinical Research, Eli Lilly, Impulse Dynamics, Intellia Therapeutics, Ionis Pharmaceutical, Janssen Research & Development LLC, Medscape/WebMD Global LLC, Merck, Novartis, Novo Nordisk, Quidel Corporation, Radcliffe Group Ltd., Roche, and Us2.AI, serving as co-founder and nonexecutive director of Us2.AI outside the submitted work and having a patent for PCT/SG2016/050217 pending for a method for diagnosis and prognosis of chronic heart failure and a patent for 10,702, 247 issued for automated clinical workflow that recognizes and analyses 2-dimensional and Doppler echo images for cardiac measurements and the diagnosis, prediction, and prognosis of heart disease. Dr Senni reported receiving personal fees from Novartis, Merck, MSD, Abbott, Vifor, Novo Nordisk, Boehringer, AstraZeneca, Cardurion, and Bayer outside the submitted work. Dr Shah reported receiving personal fees from Bayer for consulting during the conduct of the study. Dr Voors reported receiving consultancy reimbursement to institution from Bayer outside the submitted work. Dr Zannad reported receiving personal fees from Bayer during the conduct of the study and personal fees from 89bio, Applied Therapeutics, Bayer, Betagenon, Biopeutics, Boehringer, CVRx, Cardior, Cambrian, Cerenopharmaceutical, Cellprothera, CVCT, Lupin, Merck, Northsea, Otsuka, Owkin, Salubris, and Viatrix outside the submitted work. Dr Pitt reported receiving personal fees from Bayer outside the submitted work; having a patent for US 9931412 issued for site-specific delivery of eplerenone to the myocardium; and consulting for and/or having stock options in AstraZeneca, Boehringer

Ingelheim, Lexicon, scPharmaceuticals, SQInnovations, G3 Pharmaceuticals, KBP BioSciences, Sarfex Pharmaceuticals, Cereno Scientific, Sea Star Medical, Anacardio, Prointel, Brainstorm Medical, and Vifor; and a US patent pending 63/045,783 for histone-modulating agents for the prevention and protection of organ damage. Dr Merkely reported receiving personal fees from AstraZeneca, Abbott, Boehringer Ingelheim, Novartis, Biotronik, CSL Behring, Daiichi Sankyo, and Medtronic and grants from Boston Scientific outside the submitted work. Dr Zieroth reported receiving personal fees from Bayer during the conduct of the study and personal fees from Abbott, AstraZeneca, BMS, Boehringer Ingelheim, Cytokinetics, Edwards, Eli Lilly, GSK, Medtronic, Merck, Novartis, Novo Nordisk, Pfizer, Salubris Bio, and Vifor outside the submitted work. Dr Yilmaz reported receiving institutional fees from Bayer, Amgen, Novartis, AstraZeneca, Boehringer Ingelheim, Novo Nordisk, and Albert Health outside the submitted work. Dr McMurray reported receiving personal lecture fees from Abbott, Alkerm, AstraZeneca, Blue Ocean Scientific Solutions Ltd, Boehringer Ingelheim, Canadian Medical and Surgical Knowledge, Emcure Pharmaceuticals Ltd, Eris Lifesciences, European Academy of CME, Hikma Pharmaceuticals, Imagica Health, Intas Pharmaceuticals, J.B. Chemicals & Pharmaceuticals Ltd., Lupin Pharmaceuticals, Medscape/Heart.Org, ProAdWise Communications, Radcliffe Cardiology, Sun Pharmaceuticals, The Corpus, Translation Research Group, and Translational Medicine Academy; receiving personal consultancy fees from Alnylam Pharmaceuticals, Amgen, AnaCardio, AstraZeneca, Bayer, Berlin Cures, BMS, Cardurion, Cytokinetics, Ionis Pharmaceuticals, Novartis, Regeneron Pharmaceuticals, and River2Renal; receiving payment to Glasgow University from Novartis, Cytokinetics, Amgen, GSK, Cardurion, AstraZeneca, British Heart Foundation, National Institute for Health- National Heart Lung, and Blood Institute (NIH-NHLBI), Boehringer Ingelheim, SQ Innovations, and Catalyze Group; receiving personal fees as director from Global Clinical Trial Partners Ltd.; and receiving personal fees from WIRB-Copernicus Group Clinical Inc for serving on a data and safety monitoring board outside the submitted work. Dr Solomon reported receiving grants from Alexion, Alnylam, Applied Therapeutics, AstraZeneca, Bellerophon, Bayer, BMS, Boston Scientific, Cytokinetics, Edgewise, Eidos/BridgeBio, Gossamer, GSK, Ionis, Lilly, NIH/NHLBI, Novartis, Novo Nordisk, Respicardia, Sanofi Pasteur, Tenaya, TheracosBio, and Us2.AI and grants and personal fees from Abbott, Action, Akros, Alexion, Alnylam, Amgen, Arena, AstraZeneca, Bayer, BMS, Cardior, Cardurion, Corvia, Cytokinetics, GSK, Lilly, Novartis, Roche, TheracosBio, Quantum Genomics, Tenaya,

Sanofi-Pasteur, Dinaqor, Trembeau, CellProThera, Moderna, American Regent, Sarepta, Lexicon, Anacardio, Akros, Valo outside the submitted work. No other disclosures were reported.

Funding/Support: The FINEARTS-HF study was funded by Bayer.

Role of the Funder/Sponsor: Bayer was involved in the design and conduct of the study, including collection, management, analysis, and interpretation of the data. The manuscript was prepared by the academic authors and reviewed by the funder. The decision to submit the manuscript for publication was made by all authors.

Meeting Presentation: This paper was presented at AHA Scientific Sessions 2024; November 17, 2024; Chicago, Illinois.

Data Sharing Statement: See Supplement 3.

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