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Finerenone in Heart Failure with Mildly Reduced or Preserved Ejection Fraction

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ABSTRACT

BACKGROUND

Steroidal mineralocorticoid receptor antagonists reduce morbidity and mortality among patients with heart failure and reduced ejection fraction, but their efficacy in those with heart failure and mildly reduced or preserved ejection fraction has not been established. Data regarding the efficacy and safety of the nonsteroidal mineralocorticoid receptor antagonist finerenone in patients with heart failure and mildly reduced or preserved ejection fraction are needed.

METHODS

In this international, double-blind trial, we randomly assigned patients with heart failure and a left ventricular ejection fraction of 40% or greater, in a 1:1 ratio, to receive finerenone (at a maximum dose of 20 mg or 40 mg once daily) or matching placebo, in addition to usual therapy. The primary outcome was a composite of total worsening heart failure events (with an event defined as a first or recurrent unplanned hospitalization or urgent visit for heart failure) and death from cardiovascular causes. The components of the primary outcome and safety were also assessed.

RESULTS

Over a median follow-up of 32 months, 1083 primary-outcome events occurred in 624 of 3003 patients in the finerenone group, and 1283 primary-outcome events occurred in 719 of 2998 patients in the placebo group (rate ratio, 0.84; 95% confidence interval [CI], 0.74 to 0.95; P=0.007). The total number of worsening heart failure events was 842 in the finerenone group and 1024 in the placebo group (rate ratio, 0.82; 95% CI, 0.71 to 0.94; P=0.006). The percentage of patients who died from cardiovascular causes was 8.1% and 8.7%, respectively (hazard ratio, 0.93; 95% CI, 0.78 to 1.11). Finerenone was associated with an increased risk of hyperkalemia and a reduced risk of hypokalemia.

CONCLUSIONS

In patients with heart failure and mildly reduced or preserved ejection fraction, finerenone resulted in a significantly lower rate of a composite of total worsening heart failure events and death from cardiovascular causes than placebo. (Funded by Bayer; FINEARTS-HF ClinicalTrials.gov number, NCT04435626.)

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*A list of the committees and investigators in the FINEARTS-HF trial is provided in the Supplementary Appendix, available at NEJM.org.

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CME

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Steroidal mineralocorticoid receptor antagonists reduce morbidity and mortality among patients with heart failure and reduced ejection fraction,[1-3] but their efficacy in those with heart failure and mildly reduced or preserved ejection fraction has not been established, despite the suggestion of a potential benefit in the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial.[4,5] Even with the recent availability of therapeutic options, including sodium–glucose cotransporter 2 (SGLT2) inhibitors, there remains an unmet need in this population.

Finerenone is a nonsteroidal mineralocorticoid receptor antagonist with physiochemical properties that are distinct from those of steroidal mineralocorticoid receptor antagonists, such as spironolactone.[6] In two large outcomes trials involving patients with chronic kidney disease and type 2 diabetes, finerenone reduced the risk of kidney disease progression and cardiovascular events, including hospitalization for heart failure.[7,8] The Finerenone Trial to Investigate Efficacy and Safety Superior to Placebo in Patients with Heart Failure (FINEARTS-HF) was designed to test the hypothesis that finerenone, in addition to usual therapy, would reduce the rate of total worsening heart failure events and death from cardiovascular causes among patients with heart failure and mildly reduced or preserved ejection fraction.

Methods

Trial Design and Oversight

We conducted an international, multicenter, parallel-group, event-driven, double-blind, randomized trial. The steering committee designed and oversaw the conduct of the trial and data analysis, in collaboration with the sponsor (Bayer). The trial protocol (available with the full text of this article at NEJM.org) was approved by institutional review boards or ethics committees at each trial center. The authors who had access to the data (authors from Harvard Medical School, the University of Glasgow, and Bayer) vouch for the accuracy and completeness of the data, and all the authors vouch for the fidelity of the trial to the protocol. Details of the trial design have been published previously.[9] Additional information regarding the trial design is provided in the Supplementary Appendix, available at NEJM.org.

Trial Participants

Eligibility requirements included an age of 40 years or older, symptomatic heart failure, a left ventricular ejection fraction of 40% or greater, evidence of structural heart disease, and elevated levels of natriuretic peptides. Additional information regarding the inclusion and exclusion criteria is provided in Table S1 in the Supplementary Appendix. All the patients provided written informed consent.

Trial Procedures and Outcomes

Patients who met the eligibility requirements were randomly assigned in a 1:1 ratio to receive finerenone or matching placebo, in addition to their usual therapy. Finerenone was administered at a maximum dose of 20 mg or 40 mg once daily, depending on the baseline estimated glomerular filtration rate (eGFR). The primary outcome was a composite of total worsening heart failure events and death from cardiovascular causes. A worsening heart failure event was defined as a first or recurrent unplanned hospitalization or urgent visit for heart failure. All primary-outcome events were adjudicated by an independent committee whose members were unaware of the trial-group assignments.

The following secondary outcomes were included in a multiple-testing procedure: total worsening heart failure events; the change from baseline in the total symptom score on the Kansas City Cardiomyopathy Questionnaire (KCCQ; scores range from 0 to 100, with higher scores indicating fewer symptoms and physical limitations) at months 6, 9, and 12; improvement in the New York Heart Association (NYHA) functional class at month 12; and a kidney composite outcome (a composite of a sustained decrease in the eGFR of ≥50%, a sustained decline in the eGFR to <15 ml per minute per 1.73 m^2 of body-surface area, or the initiation of long-term dialysis or kidney transplantation), assessed in a time-to-event analysis. Death from cardiovascular causes and death from any cause were also assessed. In a prespecified sensitivity analysis, a composite of the first worsening heart failure event or death from cardiovascular causes was assessed in a time-to-event analysis. Data regarding adverse events were collected throughout the trial. Adverse events that occurred in patients who had received at least one dose of finerenone or placebo and occurred during treatment or up

to 3 days after permanent discontinuation of finerenone or placebo are reported. Additional information regarding trial procedures and outcomes is provided in the Supplementary Appendix.

STATISTICAL ANALYSIS

We estimated that a total of 2375 primary-outcome events would provide the trial with 90% power to detect a 19% lower event rate in the finerenone group than in the placebo group. The primary analysis was performed according to an intention-to-treat approach with the semiparametric proportional rates method,[10] stratified according to geographic region and baseline left ventricular ejection fraction (<60% or ≥60%), with a two-sided alpha level of 0.0497, which was based on an adjustment made after the interim efficacy analysis. The primary outcome was assessed in 17 prespecified subgroups.

The secondary outcomes were tested in hierarchical order as follows: total worsening heart failure events, the change from baseline in the KCCQ total symptom score and improvement in the NYHA functional class (tested simultaneously with the use of the Holm–Bonferroni procedure), and the kidney composite outcome. Two interim analyses were performed, one for futility and the other for efficacy. After both interim analyses, the data and safety monitoring committee recommended that the trial proceed unchanged. Additional information regarding the statistical analysis is provided in the Supplementary Appendix.

RESULTS

ENROLLMENT, RANDOMIZATION, AND FOLLOW-UP

From September 14, 2020, through January 10, 2023, a total of 7463 patients from 654 sites across 37 countries were screened (Fig. S1), and 6016 were randomly assigned to receive finerenone or placebo. One patient underwent randomization twice in error, and both entries were excluded from the analysis; 13 patients from a single site were excluded owing to serious violations of Good Clinical Practice guidelines. Therefore, 6001 patients were included in the efficacy analysis. By the end of the trial (June 14, 2024), 13 patients had withdrawn consent, and 6 were lost to follow-up. The median duration of follow-up was 32 months.

The characteristics of the patients at baseline appeared to be balanced between the two trial groups (Table 1). The mean (±SD) left ventricular ejection fraction was 53±8%. The majority of patients (69.1%) were in NYHA functional class II, and 1219 patients (20.3%) were enrolled during or within 7 days after a heart failure event. At baseline, 84.9% of the patients were being treated with beta-blockers, 35.9% with angiotensin-converting–enzyme inhibitors, 35.0% with angiotensin-receptor blockers, 8.5% with angiotensin receptor–neprilysin inhibitors, and 13.6% with SGLT2 inhibitors.[11]

EFFICACY

A total of 1083 primary-outcome events occurred in 624 of 3003 patients in the finerenone group, and 1283 primary-outcome events occurred in 719 of 2998 patients in the placebo group (rate ratio, 0.84; 95% confidence interval [CI], 0.74 to 0.95; P=0.007) (Table 2 and Fig. 1). One patient in each group had a worsening heart failure event and died from cardiovascular causes on the same day; for the primary outcome, only the fatal event was counted. The total number of worsening heart failure events was 842 in the finerenone group and 1024 in the placebo group (rate ratio, 0.82; 95% CI, 0.71 to 0.94; P=0.006). A total of 242 patients (8.1%) in the finerenone group and 260 patients (8.7%) in the placebo group died from cardiovascular causes (hazard ratio, 0.93; 95% CI, 0.78 to 1.11). In a sensitivity analysis of a composite of the first worsening heart failure event or death from cardiovascular causes, the risk was lower in the finerenone group than in the placebo group (hazard ratio, 0.84; 95% CI, 0.76 to 0.94). The results for the primary outcome were consistent across all prespecified subgroups (Fig. 2 and Fig. S2), including those defined according to baseline left ventricular ejection fraction (<60% or ≥60%) and baseline use of SGLT2 inhibitors (yes or no).

The least-squares mean (±SE) change from baseline in the KCCQ total symptom score, which was estimated as a common treatment effect across months 6, 9, and 12, was 8.0±0.3 points in the finerenone group and 6.4±0.3 points in the placebo group (difference, 1.6 points; 95% CI, 0.8 to 2.3; P<0.001). Improvement in the NYHA functional class at month 12 was observed in 557 patients (18.6%) in the finerenone group and 553 patients (18.4%) in the placebo group (odds ratio, 1.01; 95% CI, 0.88 to 1.15). A kidney com-

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Finerenone (N=3003)	Placebo (N=2998)
Age — yr	71.9±9.6	72.0±9.7
Female sex — no. (%)	1355 (45.1)	1377 (45.9)
Race — no. (%)†		
Asian	497 (16.6)	499 (16.6)
Black	49 (1.6)	39 (1.3)
Other	91 (3.0)	91 (3.0)
White	2366 (78.8)	2369 (79.0)
Geographic region — no. (%)		
Asia	493 (16.4)	490 (16.3)
Eastern Europe	1329 (44.3)	1321 (44.1)
Latin America	322 (10.7)	319 (10.6)
North America	235 (7.8)	236 (7.9)
Western Europe, Oceania, or other	624 (20.8)	632 (21.1)
Any previous hospitalization for heart failure — no. (%)	1797 (59.8)	1822 (60.8)
Time since heart failure event at randomization — no. (%)		
≤7 days	609 (20.3)	610 (20.3)
>7 days to 3 mo	1030 (34.3)	998 (33.3)
>3 mo or no index event	1364 (45.4)	1390 (46.4)
Systolic blood pressure — mm Hg	129.5±15.3	129.3±15.3
Body-mass index‡	29.9±6.1	30.0±6.1
Serum creatinine level — mg/dl	1.1±0.3	1.1±0.4
Estimated glomerular filtration rate		
Value — ml/min/1.73 m^2	61.9±19.4	62.3±20.0
<60 ml/min/1.73 m^2 — no. (%)	1451 (48.3)	1437 (47.9)
Median urinary albumin:creatinine ratio (IQR) — mg/g	18 (7–67)	19 (7–66)
Serum potassium level — mmol/liter	4.4±0.5	4.4±0.5
Left ventricular ejection fraction		
Value — %	52.6±7.8	52.5±7.8
<50% — no. (%)	1093 (36.5)	1079 (36.0)
≥50% to <60% — no. (%)	1329 (44.3)	1345 (44.9)
≥60% — no. (%)	575 (19.2)	572 (19.1)
Median NT-proBNP level (IQR) — pg/ml	1053 (467–1937)	1028 (433–1963)
NYHA functional class — no. (%)		
Missing	1 (<0.1)	0
II	2081 (69.3)	2065 (68.9)
III	903 (30.1)	910 (30.4)
IV	18 (0.6)	23 (0.8)
Medical history — no. (%)		
Hypertension	2640 (87.9)	2685 (89.6)
Type 2 diabetes mellitus§	1217 (40.5)	1222 (40.8)
Atrial fibrillation on ECG at baseline	1165 (38.8)	1128 (37.6)

Table 1. (Continued.)

Characteristic	Finerenone (N = 3003)	Placebo (N = 2998)
Stroke	355 (11.8)	353 (11.8)
Myocardial infarction	784 (26.1)	757 (25.3)
Previous left ventricular ejection fraction <40%	147 (4.9)	126 (4.2)
Medication use — no. (%)		
Beta-blocker	2541 (84.6)	2554 (85.2)
Angiotensin-converting–enzyme inhibitor	1083 (36.1)	1072 (35.8)
Angiotensin-receptor blocker	1047 (34.9)	1055 (35.2)
Angiotensin receptor–neprilysin inhibitor	256 (8.5)	257 (8.6)
Calcium-channel blocker	958 (31.9)	1010 (33.7)
Sodium–glucose cotransporter 2 inhibitor	393 (13.1)	424 (14.1)
Loop diuretic	2618 (87.2)	2621 (87.4)
Thiazide diuretic	429 (14.3)	402 (13.4)
Potassium supplement	349 (11.6)	365 (12.2)
Glucagon-like peptide-1 receptor agonist	79 (2.6)	88 (2.9)

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. ECG denotes electrocardiography, IQR interquartile range, NT-proBNP N-terminal pro–B-type natriuretic peptide, and NYHA New York Heart Association.
† Race was determined by the patient.
‡ Body-mass index is the weight in kilograms divided by the square of the height in meters.
§ An additional 8 patients in the finerenone group and 7 patients in the placebo group were reported to have type 1 diabetes mellitus.

posite outcome event occurred in 75 patients (2.5%) and 55 patients (1.8%), respectively (hazard ratio, 1.33; 95% CI, 0.94 to 1.89). A total of 491 patients (16.4%) in the finerenone group and 522 patients (17.4%) in the placebo group died from any cause (hazard ratio, 0.93; 95% CI, 0.83 to 1.06).

SAFETY

Among the patients who had received at least one dose, 611 (20.4%) in the finerenone group and 616 (20.6%) in the placebo group discontinued finerenone or placebo for reasons other than death. At the end-of-trial visit, among the patients who were continuing therapy, 68.4% in the finerenone group and 78.4% in the placebo group were taking the individualized target dose.

Serious adverse events occurred in 1157 patients (38.7%) in the finerenone group and 1213 patients (40.5%) in the placebo group (Table 3 and Table S2). Increases in creatinine and potassium levels were more common with finerenone than with placebo; potassium levels greater than 6.0 mmol per liter occurred in 86 patients (3.0%) in the finerenone group and 41 patients (1.4%) in the placebo group. No episodes of hyperkalemia led to death, and hyperkalemia led to hospitalization in 16 patients (0.5%) in the finerenone group and 6 patients (0.2%) in the placebo group. Hypokalemia, defined as a potassium level of less than 3.5 mmol per liter, was less common with finerenone than with placebo. The mean systolic blood pressure at 6 months was lower in the finerenone group than in the placebo group (difference, −3.4 mm Hg; 95% CI, −2.6 to −4.2), but adjustment for the change in blood pressure at 1 month did not attenuate the observed treatment effect on the primary outcome. The most common adverse events are summarized in Table S3.

DISCUSSION

In patients with heart failure and mildly reduced or preserved ejection fraction, finerenone resulted in a significantly lower rate of a composite of total worsening heart failure events and death from cardiovascular causes (the primary outcome) than placebo. For each component of the primary

Table 2. Primary and Secondary Outcomes.*

Outcome	Finerenone (N=3003)	Placebo (N=2998)	Finerenone vs. Placebo
Primary outcome and components			
Total worsening heart failure events and death from cardiovascular causes			
Total no. of events†	1083	1283	—
Events per 100 patient-yr	14.9	17.7	—
Rate ratio (95% CI)	—	—	0.84 (0.74–0.95)
P value	—	—	0.007
Total worsening heart failure events			
Total no. of events	842	1024	—
Rate ratio (95% CI)	—	—	0.82 (0.71–0.94)
P value	—	—	0.006
Death from cardiovascular causes			
No. of patients (%)	242 (8.1)	260 (8.7)	—
Hazard ratio (95% CI)	—	—	0.93 (0.78–1.11)
Secondary outcomes			
Change from baseline in KCCQ total symptom score at 6, 9, and 12 mo‡			
Estimate across 6, 9, and 12 mo	8.0±0.3	6.4±0.3	—
Difference (95% CI)	—	—	1.6 (0.8–2.3)
P value	—	—	<0.001
Improvement in NYHA functional class at 12 mo			
No. of patients/total no. (%)	557/3002 (18.6)	553/2998 (18.4)	—
Odds ratio (95% CI)	—	—	1.01 (0.88–1.15)
Kidney composite outcome§			
No. of patients (%)	75 (2.5)	55 (1.8)	—
Hazard ratio (95% CI)	—	—	1.33 (0.94–1.89)
Death from any cause			
No. of patients (%)	491 (16.4)	522 (17.4)	—
Hazard ratio (95% CI)	—	—	0.93 (0.83–1.06)
First worsening heart failure event or death from cardiovascular causes			
No. of patients (%)	624 (20.8)	719 (24.0)	—
Hazard ratio (95% CI)	—	—	0.84 (0.76–0.94)

* Plus–minus values are least-squares means ±SE.
† One patient in each group had a worsening heart failure event and died from cardiovascular causes on the same day; for the primary outcome, only the fatal event was counted.
‡ For the total symptom score on the Kansas City Cardiomyopathy Questionnaire (KCCQ), scores range from 0 to 100, with higher scores indicating fewer symptoms and physical limitations.
§ The kidney composite outcome was defined as a composite of a sustained decrease in the estimated glomerular filtration rate (eGFR) of 50% or greater, a sustained decline in the eGFR to less than 15 ml per minute per 1.73 m^2 of body-surface area, or the initiation of long-term dialysis or kidney transplantation, assessed in a time-to-event analysis.

outcome, the rate was lower in the finerenone group than in the placebo group, and the results for the primary outcome were consistent across all prespecified subgroups. Finerenone was associated with a moderate benefit with respect to improvement in patient-reported health status, as measured by the KCCQ total symptom score, but not with respect to improvement in the

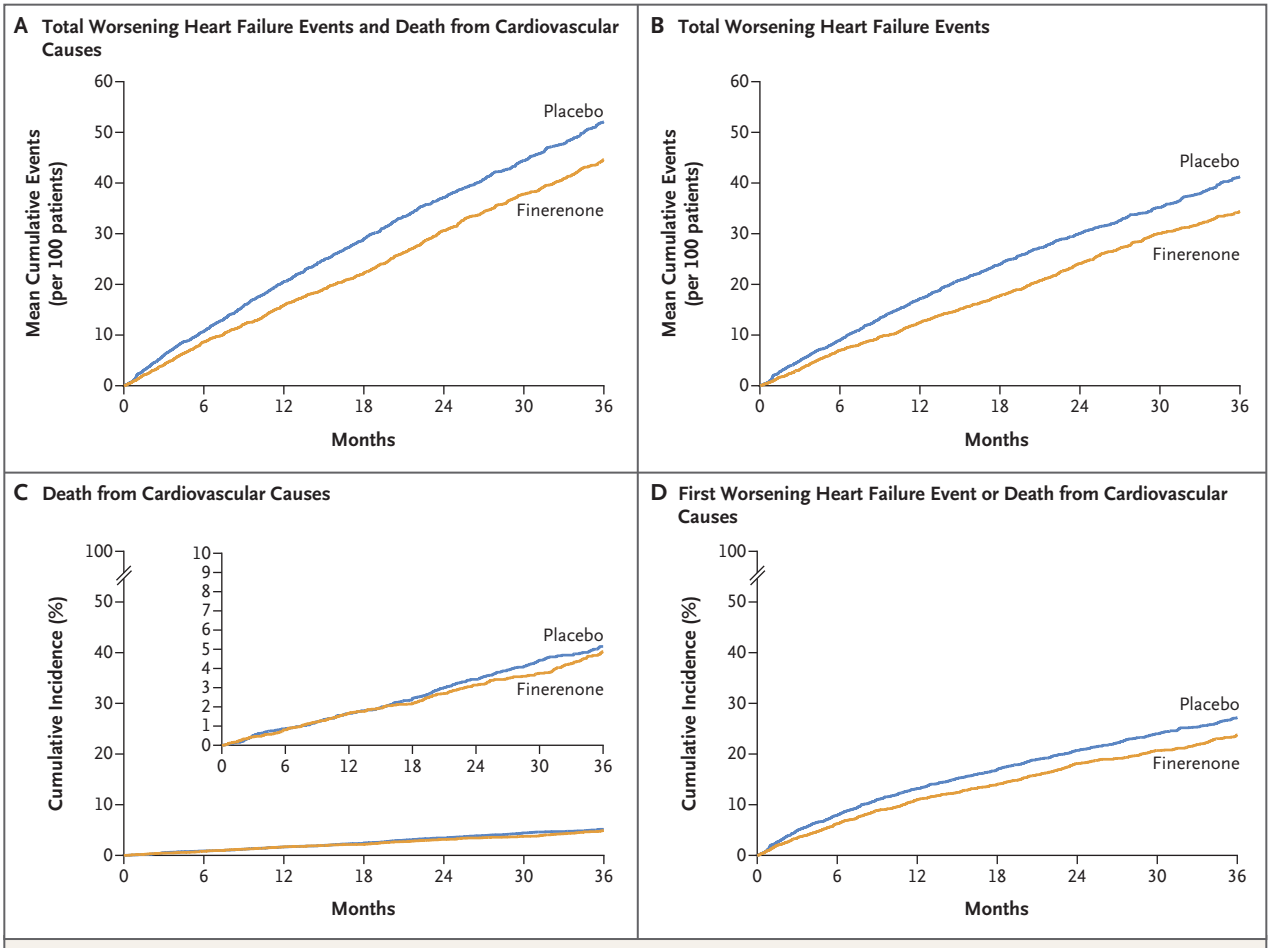

Figure 1. Primary Outcome and Its Components.

Panel A shows the cumulative-incidence plot for the composite of total worsening heart failure events and death from cardiovascular causes (the primary outcome). Panel B shows the cumulative-incidence plot for total worsening heart failure events. Panel C shows the Kaplan–Meier plot for death from cardiovascular causes. The inset shows the same data on an enlarged y axis. Panel D shows the Kaplan–Meier plot for the composite of the first worsening heart failure event or death from cardiovascular causes.

NYHA functional class or the risk of the kidney composite outcome. The overall incidence of serious adverse events was similar in the two trial groups, although elevated creatinine levels and hyperkalemia occurred more frequently and hypokalemia occurred less frequently in the finerenone group than in the placebo group.

In the TOPCAT trial, which tested the steroidal mineralocorticoid receptor antagonist spironolactone as compared with placebo in patients with heart failure and mildly reduced or preserved ejection fraction, the results for the primary outcome (a composite of death from cardiovascular causes, aborted cardiac arrest, or hospitalization for the management of heart failure) did not meet the criterion for significance.[4] However, post hoc analyses revealed differential event rates, trial-drug use, and treatment effects according to geographic region, with a suggestion of benefit in the Americas.[5] In the FINEARTS-HF trial, which tested the nonsteroidal mineralocorticoid receptor antagonist finerenone as compared with placebo in a similar patient population, finerenone resulted in a significantly lower rate of the primary outcome (a composite of total worsening heart failure events and death from cardiovascular causes).

We used a total-events analysis because this approach takes into account clinically meaningful repeat events and has been used in several contemporary trials.[12,13] Results of the more traditional time-to-first-event analysis appeared

Subgroup	Finerenone	Placebo	Rate Ratio (95% CI)
	no. of events		
Age			
≤73 yr	468	623	0.76 (0.63–0.92)
>73 yr	615	660	0.92 (0.77–1.09)
Sex			
Male	632	691	0.88 (0.74–1.04)
Female	451	592	0.78 (0.65–0.95)
Race			
Asian	211	218	0.96 (0.72–1.29)
Black	29	22	0.98 (0.37–2.62)
Other	34	57	0.60 (0.26–1.42)
White	809	986	0.82 (0.71–0.95)
Geographic region			
Asia	211	218	0.95 (0.71–1.27)
Eastern Europe	322	389	0.83 (0.67–1.03)
Latin America	106	163	0.65 (0.43–0.98)
North America	122	118	0.98 (0.67–1.45)
Western Europe, Oceania, or other	322	395	0.82 (0.64–1.06)
NYHA functional class			
II	646	741	0.86 (0.73–1.02)
III or IV	437	542	0.79 (0.65–0.96)
Left ventricular ejection fraction			
<60%	877	1061	0.82 (0.71–0.94)
≥60%	206	222	0.94 (0.70–1.26)
NT-proBNP level at baseline			
≤1041 pg/ml	266	342	0.78 (0.62–0.99)
>1041 pg/ml	782	918	0.83 (0.71–0.96)
Time since heart failure event at randomization			
≤7 days	270	372	0.74 (0.57–0.95)
>7 days to 3 mo	404	492	0.79 (0.64–0.97)
>3 mo or no index event	409	419	0.99 (0.81–1.21)
ACEI, ARB, or ARNI use at baseline			
No	288	332	0.85 (0.66–1.11)
Yes	795	951	0.83 (0.72–0.96)
SGLT2 inhibitor use at baseline			
No	907	1049	0.85 (0.74–0.98)
Yes	176	234	0.83 (0.60–1.16)
Atrial fibrillation at baseline			
Yes	521	621	0.80 (0.66–0.97)
No	562	662	0.85 (0.72–1.01)
Diabetes mellitus at baseline			
Yes	524	638	0.83 (0.69–1.00)
No	559	645	0.85 (0.71–1.01)
Body-mass index			
<30	586	648	0.88 (0.74–1.05)
≥30	486	632	0.79 (0.66–0.95)
eGFR at baseline			
<60 ml/min/1.73 m^2	727	796	0.91 (0.78–1.07)
≥60 ml/min/1.73 m^2	356	487	0.72 (0.59–0.88)
Serum potassium level at baseline			
≤4.5 mmol/liter	714	875	0.81 (0.69–0.95)
>4.5 mmol/liter	369	408	0.91 (0.74–1.11)
Systolic blood pressure at baseline			
≤130 mm Hg	608	740	0.85 (0.72–1.01)
>130 mm Hg	475	543	0.84 (0.69–1.02)
Urinary albumin:creatinine ratio at baseline			
<30 mg/g	429	518	0.81 (0.67–0.97)
≥30 mg/g	601	705	0.88 (0.74–1.05)

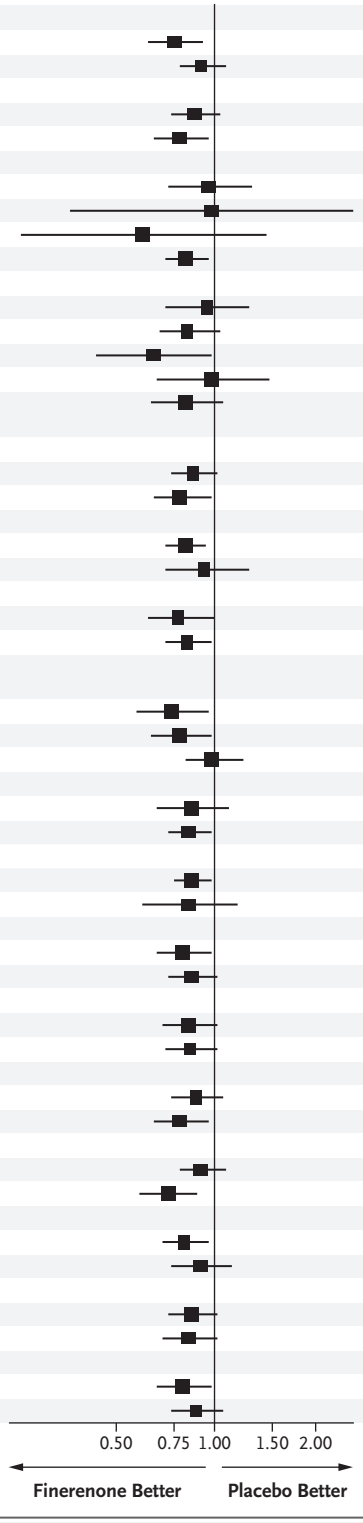

Figure 2 (facing page). Subgroup Analysis of the Primary Outcome.

The confidence intervals in the subgroup analysis have not been adjusted for multiplicity and therefore should not be interpreted as representing hypothesis tests of effects within the subgroups. Race was determined by the patient. Body-mass index is the weight in kilograms divided by the square of the height in meters. ACEI denotes angiotensin-converting–enzyme inhibitor, ARB angiotensin-receptor blocker, ARNI angiotensin receptor–neprilysin inhibitor, eGFR estimated glomerular filtration rate, NT-proBNP N-terminal pro–B-type natriuretic peptide, NYHA New York Heart Association, and SGLT2 sodium–glucose cotransporter 2.

to be similar to the results of the primary analysis. We did not observe any heterogeneity in the treatment effect with respect to the primary outcome in any of the prespecified subgroups. It is important to note that the results for the primary outcome among patients who were taking SGLT2 inhibitors at baseline — the only treatment with a strong guideline recommendation in this population — were similar to the results among those who were not taking SGLT2 inhibitors. The benefit with respect to improvement in the KCCQ total symptom score that was observed in the finerenone group appeared to be similar to that noted with other treatments for heart failure.[12,14,15] However, finerenone did not show a benefit with respect to improvement in the NYHA functional class, a physician-reported measure of functional status, a finding that possibly reflects the relative insensitivity of this classification.[16,17]

We found no evidence that finerenone resulted in a lower risk of the secondary kidney composite outcome than placebo in these patients, who were at low risk for kidney disease progression, with a low prevalence of albuminuria and small numbers of kidney events. Although finerenone reduced the risk of a similar kidney outcome in patients with kidney disease and diabetes,[7,8] other inhibitors of the renin–angiotensin–aldosterone system that had a nephroprotective effect in patients with chronic kidney disease and type 2 diabetes have failed to show similar benefits in patients with heart failure.[18-21] Hyperkalemia was more common in the finerenone group but led to hospitalization in few patients (0.5% in the finerenone group and 0.2% in the placebo group) and caused no deaths.

Our trial had limitations. The trial enrolled few Black patients owing to the global distribution of enrollment, although the percentage of

Table 3. Safety Outcomes.*

Event	Finerenone (N=2993)	Placebo (N=2993)
	no. of patients/total no. (%)	
Any serious adverse event	1157/2993 (38.7)	1213/2993 (40.5)
Serum creatinine level ≥3.0 mg/dl	57/2897 (2.0)	34/2888 (1.2)
Serum potassium level		
>5.5 mmol/liter	413/2898 (14.3)	199/2889 (6.9)
>6.0 mmol/liter	86/2898 (3.0)	41/2889 (1.4)
<3.5 mmol/liter	127/2898 (4.4)	281/2889 (9.7)
Investigator-reported hyperkalemia	289/2993 (9.7)	125/2993 (4.2)
Hyperkalemia that led to hospitalization	16/2993 (0.5)	6/2993 (0.2)
Hyperkalemia that led to death	0/2993	0/2993
Systolic blood pressure <100 mm Hg	538/2911 (18.5)	361/2904 (12.4)

* Events that occurred in patients who had received at least one dose of finerenone or placebo and occurred during treatment or up to 3 days after permanent discontinuation of finerenone or placebo are reported. All safety events that occurred at any time during the trial period are shown in Table S2. All safety analyses were restricted to the 5986 patients who had received at least one dose of finerenone or placebo. The data reported on creatinine, potassium, and systolic blood pressure levels were further restricted to patients with at least one assessment (5785, 5787, and 5815 patients, respectively).

Black patients was proportional to the population percentage on a regional basis (Table S4). Although the trial was conducted during the coronavirus disease 2019 (Covid-19) pandemic, similar results were observed after censoring data after a first episode of Covid-19. All the prespecified subgroups were underpowered, so the results of the subgroup analysis should be interpreted with caution. Finally, we cannot determine on the basis of these data whether similar benefits would have been observed with other mineralocorticoid receptor antagonists.

In patients with heart failure and mildly reduced or preserved ejection fraction, finerenone resulted in a significantly lower rate of a composite of total worsening heart failure events and death from cardiovascular causes than placebo and was associated with better patient-reported health status as well as an increased risk of hyperkalemia but a decreased risk of hypokalemia.

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A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

APPENDIX

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