Supplementary Appendix

Supplement to: Solomon SD, McMurray JJV, Vaduganathan M, et al. Finerenone in heart failure with mildly reduced or preserved ejection fraction. N Engl J Med 2024;391:1475-85. DOI: 10.1056/NEJMoa2407107

This appendix has been provided by the authors to give readers additional information about the work.

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DEATH

The Clinical Events Committee (CEC) will attribute cause of death according to the responsible underlying disease process rather than the immediate mechanism. Deaths will be classified as cardiovascular, non-cardiovascular, or undetermined, and, where possible, further sub-classified as outlined below. In light of the substantial burden of cardiorespiratory illness contributed by the COVID-19 pandemic and the potential for COVID-19 infection status to influence the adjudication of study endpoints, the CEC will in all cases report whether the death was thought to be related to COVID-19 (positive testing, typical clinical trajectory), possibly related to COVID-19 (inconclusive or absent testing, typical clinical trajectory), unrelated to COVID-19 (testing negative or not done, not suspected).

A. Cardiovascular Death

Cardiovascular death includes death classified in any of the following categories:

1. Fatal Myocardial Infarction (MI):

Fatal MI may be adjudicated in any of the following three scenarios:

a. Death occurring within 14 days after a documented MI, in which there is no conclusive evidence of any other cause of death. Subjects who are being treated for a MI and who die as a result of complications of the MI (eg, sudden death, pump failure, or cardiogenic shock) will be classified as having had a MI-related death.

b. Autopsy evidence of a recent infarct with no conclusive evidence of any other cause of death.

c. An abrupt death that has characteristics suggestive of an acute infarct but does not meet the definition of a MI. Suggestive characteristics are:

-presentation with acute ischemic symptoms

<u>AND</u> one of the following:

- ECG changes indicative of an acute injury
- abnormal cardiac biomarkers
-other evidence (eg, echocardiography, ventriculography, or scintigraphy) of new ventricular wall motion abnormality

2. Heart Failure Death:

Death occurring in the context of clinically worsening symptoms and/or signs of heart failure (HF) without evidence of another cause of death.

Death occurring as a complication of the implantation of a ventricular assist device, cardiac transplant, or other surgery primarily for refractory HF.

Death occurring after referral to hospice specifically for progressive HF.

Note: If worsening HF is secondary to MI, then MI should be listed as the primary cause of death if the subject suffered an MI within 14 days of death (as above).

3. Sudden Death:
Death occurring unexpectedly in an otherwise stable subject. Further classification of sudden death will be as follows:
a. death witnessed or subject last seen alive <1 hour previously ***or***
b. subject last seen alive ≥1 hr and < 24 hrs previously

4. Presumed Sudden Death
Death occurring unexpectedly in an otherwise stable subject last seen alive ≥24 hours previously, with circumstances suggestive of sudden death**.**

5. Presumed Cardiovascular Death:
Death likely due to a cardiovascular cause in which the available clinical data is insufficient to support a more specific cause of death.

6. Fatal Stroke:
Death occurring as a result of a documented stroke. Where possible, the stroke will be further classified as ischemic (non-hemorrhagic), ischemic (non-hemorrhagic) with hemorrhagic conversion, hemorrhagic, or unknown.

7. Fatal Pulmonary Embolism:
Death occurring as a direct result of a documented pulmonary embolism.

8. Cardiovascular Procedure-Related Death:
Death occurring during a cardiovascular procedure or as a result of complications related to a cardiovascular procedure (e.g. percutaneous coronary intervention), usually within 14 days. The CEC will categorize these deaths as related to percutaneous coronary intervention (**PCI-related**), coronary artery bypass-grafting (**CABG-related**), valvular procedures (**valvular)**, or other cardiovascular procedures (**other**).

9. Other Cardiovascular Death:
Death resulting from a specifically documented cardiovascular cause other than those listed above.

B. Non-Cardiovascular Death
If an unequivocal and documented non-cardiovascular cause can be established as the primary cause of death, the event will be classified as non-cardiovascular. Non-cardiovascular deaths will be further classified into the following categories:

A. Infection
B. Malignancy
C. Pulmonary Failure
D. Gastrointestinal – Death due to GI-related abnormalities, including hepatobiliary disease

E. Renal Failure*
F. Accidental/Trauma
G. Suicide
H. Non Intracranial Hemorrhage (not related to CV surgery/procedure)
I. Other Non-CV (Specify)
* Renal Death is defined as death occurring from complications of renal failure (e.g.hyperkalemia, uremia, acidosis) while a patient receives renal replacement therapy (i.e. chronic dialysis or renal transplantation), or after a patient refuses or a physician withholds such therapy or in cases where dialysis is unavailable.

C. Undetermined Cause of Death

Death in which insufficient data is available to make a reasonable differentiation of cardiovascular or non-cardiovascular cause of death.

NON-FATAL EVENTS

For the purposes of FINEARTS-HF, a **hospitalization** is defined as an unplanned admission to an acute care facility (i.e. hospital, emergency room, observation unit) requiring a change in calendar date from hospital presentation to discharge. As for death, the CEC will report in all cases whether the event was thought to be related to COVID-19 (positive testing, typical clinical trajectory), possibly related to COVID-19 (inconclusive or absent testing, typical clinical trajectory), or unrelated to COVID-19 (testing or not done, not suspected),

A. Hospitalization for Heart Failure

Presentation to an acute care facility requiring an overnight hospitalization (defined as hospital stay of at least 24 hours if precise timing of admission and discharge are available, but otherwise defined as a change in calendar day) with an exacerbation of heart failure requiring treatment meeting the following criteria:

1. Symptoms and signs of heart failure:

One or more of the following symptoms consistent with heart failure:
a. Increasing dyspnea
b. Worsening orthopnea
c. Paroxysmal nocturnal dyspnea
d. Increasing fatigue/ decreasing exercise tolerance
e. Worsening edema/anasarca

AND

Two or more of the following signs consistent with heart failure:

a. Rapid weight gain
b. Pulmonary edema or rales
c. Elevated jugular venous pressure
d. Radiologic signs of heart failure

e. Peripheral edema
f. Increasing abdominal distension or ascites
g. S3 gallop
h. Hepatojugular reflux
i. Elevated brain natriuretic peptide (BNP) or N-terminal pro-BNP (> most recent baseline)
j. Congestive hepatomegaly (i.e. not related to intrinsic liver disease)
k. Invasive/Non-invasive tests showing increased cardiac filling pressures or low cardiac output

AND

2. Treatment

Treatment with intravenous diuretics, intravenous vasodilators, intravenous inotropes, mechanical fluid removal (e.g., ultrafiltration or dialysis), or insertion of an intra-aortic balloon pump for hemodynamic compromise. Initiation of standing oral diuretics or intensification (doubling) of the maintenance diuretic dose will also qualify as treatment.

In applying these criteria, it is understood that the CEC will exercise clinical judgement and assess the totality of evidence supporting the diagnosis of heart failure. In circumstances where there is ample evidence that a heart failure hospitalization has occurred, but not all charter criteria are met due to data limitations, the committee may adjudicate a heart failure event by consensus of the committee members and chair. Accordingly, as part of the study training, reviewers will be encouraged to submit borderline events (where heart failure is probable, but key charter criteria are missing despite query) to the full committee for discussion.

When investigator-reported heart failure hospitalizations are negatively adjudicated by the CEC, events will be further categorized as "Possible heart failure hospitalization not meeting FINEARTS-HF Criteria" (for cases where heart failure may have been present, but criteria were insufficient to meet FINEARTS-HF criteria) or "Not a heart failure hospitalization" (where the available data suggest the primary cause for hospital admission was unrelated to heart failure).

B. Urgent Heart Failure Visits

Urgent, unscheduled office/practice or emergency department visit for heart failure management not requiring overnight hospitalization and associated with all of the following:

1. New or worsening signs and symptoms of heart failure, defined by the same criteria as for the heart failure hospitalization end point above and
2. Intravenous therapy directed at heart failure management

Ambulatory visits for worsening heart failure managed with intensification of oral heart failure therapy will not qualify as study endpoints. For patients with repeated urgent visits in close proximity, including those culminating in an ultimate decision for hospitalization, each discrete clinical episode will be considered separately as a potential event.

C. End Stage Renal Disease (Initiation of Dialysis or Renal Transplantation)

The occurrence of End-stage renal disease will be defined according any of the following criteria:

1. Initiation of dialysis, defined as follows:
    a. Initiation of dialysis/renal replacement therapy (RRT), sustained for at least 30 days, without subsequent known recovery of renal function (date of event assigned as date of initiation of dialysis)
    b. Initiation of dialysis/RRT with death within 30 days (date of event assigned as date of initiation of dialysis)
    c. Physician recommendation for dialysis/RRT with patient refusal to initiate therapy (date of event assigned as date of physician recommendation for dialysis)
2. Renal transplantation (date of event assigned as date of renal transplantation)

D. New Onset Atrial Fibrillation/ Atrial Flutter

New onset atrial fibrillation or atrial flutter is defined by the identification of any electrographic evidence of atrial fibrillation or atrial flutter in a patient not previously known to have atrial fibrillation or atrial flutter.

Supplementary Methods

Detailed Methods

METHODS

Trial Design and Oversight

FINEARTS-HF was an international, multicenter, parallel-group, event-driven, randomized, double-blind trial in patients with chronic heart failure and left ventricular ejection fraction of 40% or greater, comparing the effect of finerenone, titrated to 20mg (if baseline eGFR ≤60 mL/min/1.73 m²) or 40mg once daily (if baseline eGFR>60 mL/min/1.73 m²) versus placebo, in addition to usual therapy. The Steering Committee designed and oversaw the conduct and analysis of the trial in collaboration with the sponsor (Bayer). The trial protocol was approved by local regulatory authorities and a local or central institutional review board at each trial center. The authors who had access to the data vouch for the accuracy and completeness of the data, and all the authors vouch for the fidelity of the trial to the protocol. Details regarding the design of the trial have been published[1].

Trial Participants

Eligibility requirements included stabilized heart failure in either inpatients or outpatients who were at least 40 years of age, had a left ventricular ejection fraction of 40% or more (including those with prior left ventricular ejection fraction less than 40%), evidence of structural heart disease and elevation of natriuretic peptides. Detailed inclusion and exclusion criteria have been previously published (Table S1 available with the full text of this article online at NEJM.org).

Trial Procedures and Outcomes

All patients provided written informed consent. Patients who met the inclusion and exclusion criteria were randomly assigned to receive finerenone (at a starting dose of 10mg titrated to 20mg once daily in patients with a baseline eGFR £ 60 ml/min/1.73m^2, or a starting dose of 20mg titrated to 40mg once daily in those with a baseline eGFR > 60 ml/min/1.73m^2) or matching placebo. The primary outcome was a composite of cardiovascular death and total worsening heart failure events (defined as either an unplanned hospitalization for heart failure or an urgent heart failure visit). Secondary objectives were to determine whether finerenone was superior to placebo in reducing the total number of worsening heart failure events; in the Kansas City Cardiomyopathy Questionnaire (KCCQ) total symptom score (TSS) at months 6, 9, 12 (scores range from 0 to 100, with higher scores indicating fewer symptoms and physical limitations) and improving NYHA class at month 12; in reducing a composite kidney outcome (defined as a sustained 50% or greater decline in eGFR, a sustained decline in eGFR to < 15 ml/min/1.73m^2 or initiation of chronic dialysis or kidney transplantation); and in reducing all-cause mortality. All primary events were adjudicated by an independent clinical events committee blinded to treatment assignment based on prespecified criteria (Supplementary Appendix). Adverse events and serious adverse events were collected and reported as both treatment-emergent (occurring in patients who received at least one dose of study drug and within 3 days of permanent discontinuation) and throughout the study.

Statistical Analysis

The primary analysis compared the total rate of cardiovascular death and worsening heart failure events (either heart failure hospitalization or urgent heart failure visits) in an intention-to-treat approach using the semiparametric proportional rates method of Lin et al.[2] stratified according to geographic region and baseline

LVEF (<60%, ≥60%). Significance for the primary outcome was set at two-sided $p < 0.0497$ based on an adjustment for the interim analysis.
It was determined that 2375 total (first and recurrent) primary composite events would be required to provide 90% power to detect an overall 19% lower event rate in the finerenone group. We estimated that the target number of events would be obtained by enrolling approximately 5,500 subjects over 24 months with a minimum follow-up of 18 months. Due to blinded event rates being lower than those assumed in the sample size calculation, the planned number of randomized subjects was increased to approximately 6000 in July, 2022. The target number of primary composite events was not changed. Other changes to the secondary endpoints were made prior to the first interim analysis in response to additional emerging knowledge in the field regarding the clinical meaningfulness of various secondary endpoints and their relative likelihood of success.

The secondary hypotheses were tested hierarchically as follows based on the rejection of the primary null hypothesis: total HF events; KCCQ total symptom score improvement and NYHA class improvement (tested simultaneously using the Bonferroni–Holm procedure); and the composite kidney endpoint. KCCQ change was estimated using a model that assumed a common treatment effect across months 6, 9, and 12. If the primary null hypothesis was rejected, all-cause mortality would be tested outside this hierarchy at a nominal two-sided significance level of 5% for regulatory purposes only.

One non-binding interim analysis for futility was performed when approximately 30% of the required total number of primary endpoint events were observed, and one formal interim analysis for efficacy was performed when approximately two-thirds of the required total number of primary endpoint events were observed. Following both pre-specified interim analyses, the Data Monitoring Committee recommended continuing the trial unchanged.

Supplementary Statistical Methods

Heirarchical analysis for secondary endpoints:

The secondary endpoints were analyzed in hierarchical fashion. If the null hypothesis is rejected for the primary endpoint, the first secondary endpoint will be tested at the $p = 0.04967$ level. If the null hypothesis is rejected for the first secondary endpoint, type I error is preserved for testing the next two secondary endpoints (KCCQ and NYHA Class) via the Bonferroni-Holm procedure, which ensures family-wise error rate control (Holm, S., 1979. A simple sequentially rejective multiple test procedure. Scandinavian journal of statistics, pp.65-70.), and allows simultaneous testing of the endpoints without requiring them to be ordered. These were not ordered because they are considered complementary (one being patient-reported and the other being physician-reported), and we did not a priori have knowledge about which would be more likely to be modified by finerenone. If at least one of the hypotheses of the two endpoints NYHA class and KCCQ can be rejected at the two-sided (0.04967/2) significance level, the remaining of the two endpoints will be tested at the 0.04967 significance level. Proceeding to the next secondary endpoint would only occur if both NYHA class and KCCQ were successful. NYHA Class and KCCQ were assessed on the same hierarchical level because these were considered complimentary assessments, one being physician reported and one being patient reported.

Supplementary Figures and Tables

Figure S1. Patient Flow.

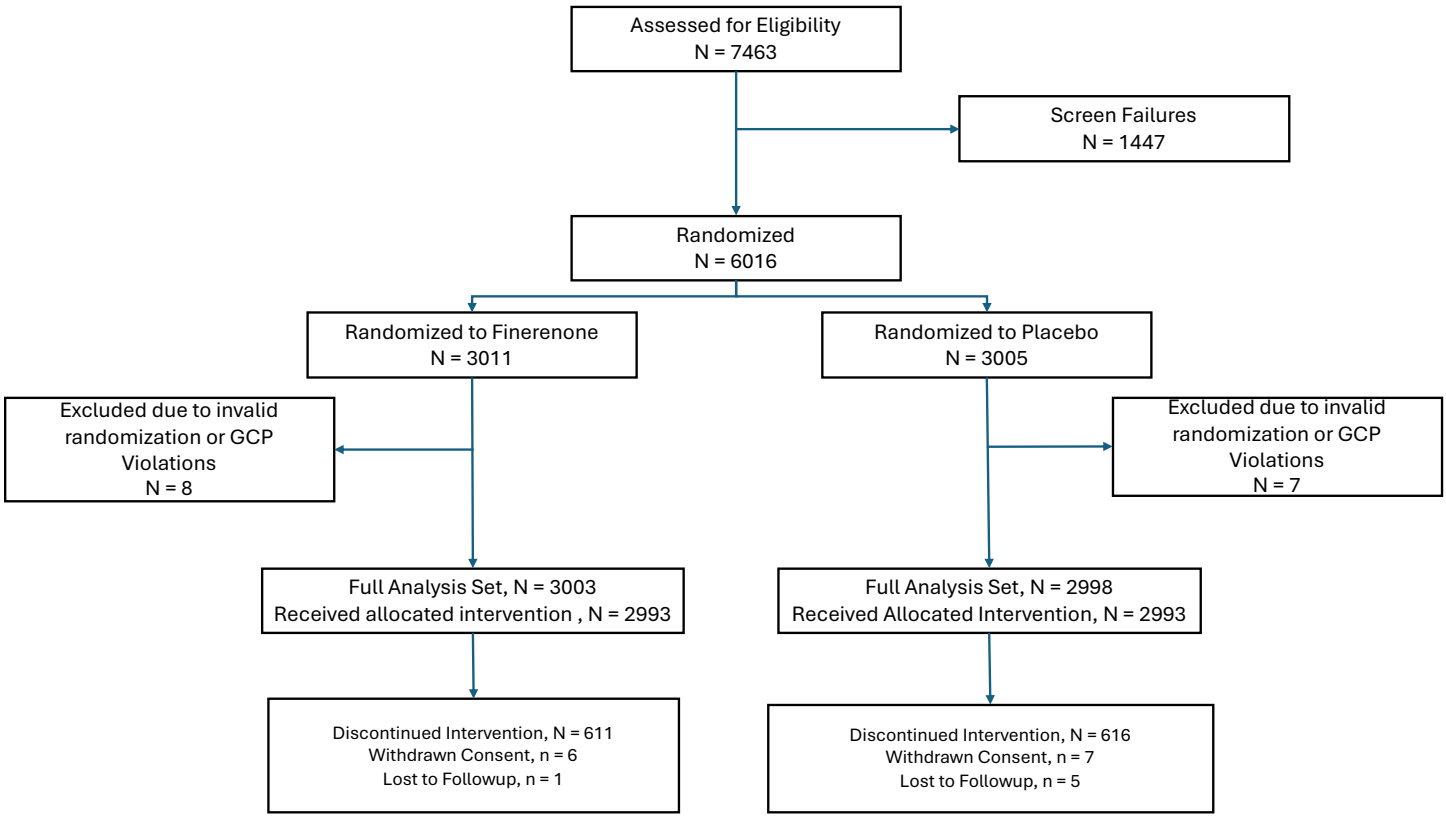

Figure S2. Forest Plot for Prespecified Subgroups for Time to First Cardiovascular Death or Heart Failure Event

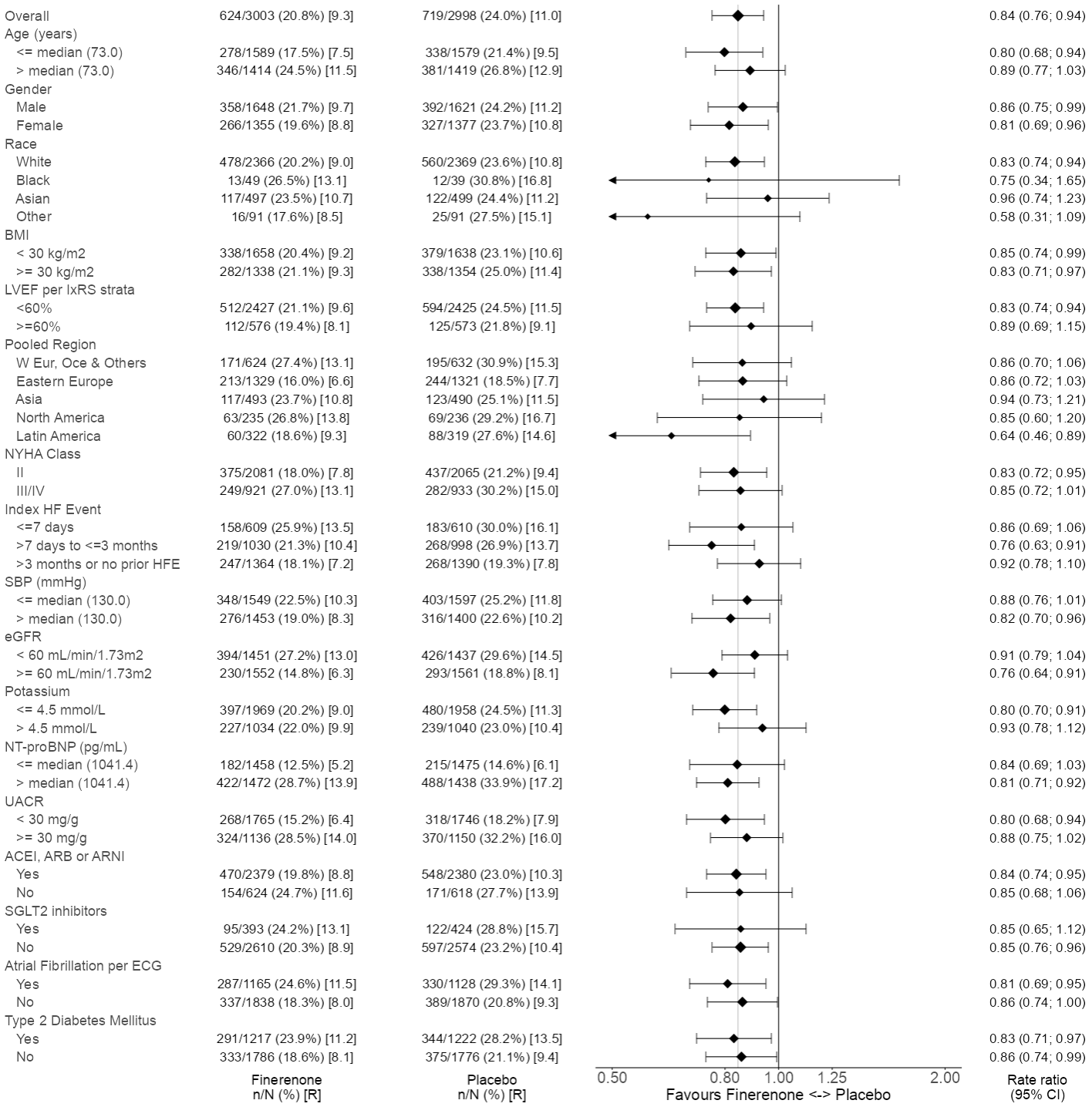

Table S1. Detailed Inclusion and Exclusion Criteria

Study Population: Patients with a diagnosis of HF, NYHA class II–IV, and documented LVEF of ≥40%.

Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

- Participant must be aged 40 years and older, at the time of signing the informed consent.

Type of Participant and Disease Characteristics:

- Diagnosis of heart failure with NYHA class II–IV, ambulatory or hospitalized primarily for heart failure (if a hospitalized patient cannot be randomized as an in-patient, randomization as soon as possible after discharge is encouraged)
- On diuretic treatment for at least 30 days prior to randomization
- Documented LVEF of ≥40% measured by any modality within the last 12 months, at the latest at screening; if several values are available, the most recent one shall be reported. If LVEF was not measured in the past 12 months, a new measurement may be done at screening
- Structural heart abnormalities based on any local imaging measurement within the last 12 months, latest at screening, defined by at least 1 of the following findings:
  - LAD ≥3.8cm, LAA ≥20cm^2, LAVI >30 mL/m^2, LVMI ≥115 g/m^2 (♂) / 95 g/m^2 (♀), septal thickness or posterior wall thickness ≥1.1 cm
- NT-proBNP ≥300 pg/mL (BNP ≥100 pg/mL) in sinus rhythm and patient does not have an ongoing diagnosis of paroxysmal atrial fibrillation or NT-proBNP ≥900 pg/mL (BNP ≥300 pg/mL) in atrial fibrillation (or if atrial fibrillation status is unknown or if patient has an ongoing diagnosis of paroxysmal atrial fibrillation) for participants obtained at the following time:
  - Within 90 days prior to randomization if patient had been hospitalized for HF requiring initiation or change in HF therapy or if patient had an urgent visit for HF requiring intravenous (IV) diuretic therapy, both within 90 days prior to randomization

  OR
  - Within 30 days prior to randomization if patient has not been hospitalized for HF nor had an urgent HF visit within the past 90 days.

Sex

- Male or female. Women of childbearing potential can only be included in the study if a pregnancy test is negative at screening and baseline and if they agree to use adequate contraception which is consistent with local regulations regarding the methods for contraception for those participating in clinical trials.

Informed Consent

- Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

- eGFR <25 mL/min/1.73 m² at either screening or randomization visit.
  NOTE: one reassessment of eGFR is allowed at the screening and randomization visit, respectively
- Serum/plasma potassium >5.0 mmol/L at either screening or randomization visit. NOTE: one reassessment of potassium is allowed at the screening and randomization visit, respectively

- Acute inflammatory heart disease, e.g. acute myocarditis, within 90 days prior to randomization
- Myocardial infarction or any event which could have reduced the ejection fraction within 90 days prior to randomization
- Coronary artery bypass graft surgery in the 90 days prior to randomization
- Percutaneous coronary intervention in the 30 days prior to randomization
- Stroke or transient ischemic cerebral attack within 90 days prior to randomization
- Probable alternative cause of participants' HF symptoms that in the opinion of the investigator primarily accounts for patient's dyspnea such as significant pulmonary disease, anemia or obesity. Specifically, patients with the below are excluded:
  - Severe pulmonary disease requiring home oxygen, or chronic oral steroid therapy
  - History of primary pulmonary arterial hypertension
  - Hemoglobin <10 g/dl
  - Valvular heart disease considered by the investigator to be clinically significant
  - Body mass index (BMI) >50 kg/m^2 at screening
- Systolic blood pressure (SBP) ≥160 mmHg if not on treatment with ≥3 blood pressure lowering medications or ≥180 mmHg irrespective of treatments on 2 consecutive measurements at least 2-minute apart, at screening or at randomization
- Life-threatening or uncontrolled arrhythmias at screening and/or randomization including but not limited to sustained ventricular tachycardia and atrial fibrillation, or atrial flutter with resting ventricular rate >110 bpm
- Symptomatic hypotension with mean systolic blood pressure <90 mmHg at screening or at randomization
- Any primary cause of HF scheduled for surgery, e.g. valve disease such as severe aortic stenosis or severe mitral regurgitation by the time of screening or randomization
- History of peripartum cardiomyopathy, chemotherapy induced cardiomyopathy, viral myocarditis, right heart failure in absence of left-sided structural disease, pericardial constriction, genetic hypertrophic cardiomyopathy, or infiltrative cardiomyopathy including amyloidosis
- Presence of left ventricular assist device by the time of screening or randomization
- History of hyperkalemia or acute renal failure during MRA treatment for >7 consecutive days, leading to permanent discontinuation of the MRA treatment
- Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotrophin urine or serum test
- Known hypersensitivity to the study intervention (active substance or excipients)
- Hepatic insufficiency classified as Child-Pugh C at screening or randomization
- Addison's disease.

Prior/Concomitant Therapy

- Requirement of any IV vasodilating drug (e.g. nitrates, nitroprusside), any IV natriuretic peptide (e.g. nesiritide, carperitide), any IV positive inotropic agents, or mechanical support (intra-aortic balloon pump, endotracheal intubation, mechanical ventilation, or any ventricular assist device) within 24 hours prior to randomization
- Participants who require treatment with more than one ACEI, ARB or angiotensin-receptor neprilysin inhibitor (ARNI), or two simultaneously at randomization
- Continuous (at least 90 days) treatment with an MRA (e.g. spironolactone, eplerenone, canrenone, esaxerenone) within 12 months prior to screening. Last intake at least 30 days before randomization. Treatment with MRA should not be interrupted with the purpose of enrollment into the study
- Concomitant treatment with any renin inhibitor or potassium-sparing diuretic that cannot be stopped prior to randomization and for the duration of the treatment period
- Concomitant systemic therapy with potent cytochrome P450 isoenzyme 3A4 (CYP3A4) inhibitors (e.g. itraconazole, ritonavir, indinavir, cobicistat, clarithromycin) or moderate or potent CYP3A4 inducers, that cannot be discontinued 7 days prior to randomization and for the duration of the treatment period.

Other Exclusions

- Any other condition or therapy, which would make the participant unsuitable for this study and will not allow participation for the full planned study period (e.g. active malignancy or other condition limiting life expectancy to less than 12 months)
- Previous assignment to treatment during this study

- Participation in another interventional clinical study (e.g. Phase 1 to 3 clinical studies) or treatment with another investigational medicinal product within 30 days prior to randomization
- Close affiliation with the investigational site; e.g. a close relative of the investigator, dependent person (e.g. employee or student of the investigational site)
- Known current alcohol and/or illicit drug abuse that may interfere with the participant's safety and/or compliance at the discretion of the investigator
- Participant is in custody by order of an authority or a court of law.

Table S2. Patients with adverse events during randomized treatment through the end of the study*

Table S2. Patients with Adverse Events during Randomized Treatment through the end of study*.

Event	Finerenone (N = 2993)	Placebo (N = 2993)
Any Serious adverse event — no. (%)	1359 (45.4)	1378 (46.0)
Serum creatinine ≥3.0 mg/dl — no. (%)	77 (2.6)	45 (1.5)
Serum potassium — no. (%)		
>5.5 mmol/liter	426 (14.6)	207 (7.1)
>6.0 mmol/liter	90 (3.1)	44 (1.5)
< 3.5 mmol/liter	145 (5.0)	299 (10.3)
Investigator-Reported Hyperkalemia — no. (%)	311 (10.4)	136 (4.5)
Hyperkalemia leading to Hospitalization — no. (%)	24 (0.8)	7 (0.2)
Hyperkalemia leading to Death — no. (%)	0 (0)	0 (0)
Systolic blood pressure <100 mm Hg — no. (%)	556 (19.0)	374 (12.7)

* Defined as all safety events that occurred in patients who received at least one dose of study drug and up until end of study data collection. All safety analyses were restricted to the 5986 patients who received at least one dose of study drug. Counts of patients with abnormal creatinine, potassium, and systolic blood pressure values were further restricted to patients with at least one post-baseline assessment (n=5849, 5836, and 5869 respectively).

Table S3. Serious Adverse Events, Adverse Events Leading to Discontinuation, and Other Adverse Events of Interest

Table S3.1: Number of subjects with a treatment-emergent SAE (>=0.5% in Finerenone group), by preferred term*

	Finerenone n=2993	Placebo n=2993
Pneumonia	87 (2.9 %)	110 (3.7 %)
Atrial fibrillation	77 (2.6 %)	74 (2.5 %)
COVID-19	69 (2.3 %)	71 (2.4 %)
Acute kidney injury	54 (1.8 %)	28 (0.9 %)
Death	29 (1.0 %)	52 (1.7 %)
Angina unstable	38 (1.3 %)	36 (1.2 %)
Anaemia	34 (1.1 %)	31 (1.0 %)
COVID-19 pneumonia	28 (0.9 %)	30 (1.0 %)
Urinary tract infection	29 (1.0 %)	26 (0.9 %)
Syncope	25 (0.8 %)	22 (0.7 %)
Chest pain	23 (0.8 %)	22 (0.7 %)
Chronic obstructive pulmonary disease	18 (0.6 %)	27 (0.9 %)
Angina pectoris	17 (0.6 %)	26 (0.9 %)
Cellulitis	17 (0.6 %)	24 (0.8 %)
Sepsis	25 (0.8 %)	16 (0.5 %)
Coronary artery disease	20 (0.7 %)	17 (0.6 %)
Cardiac failure	18 (0.6 %)	18 (0.6 %)
Sudden death	16 (0.5 %)	17 (0.6 %)
Femur fracture	15 (0.5 %)	17 (0.6 %)
Fall	15 (0.5 %)	14 (0.5 %)
Gastrointestinal haemorrhage	17 (0.6 %)	8 (0.3 %)
Hyperkalaemia	19 (0.6 %)	6 (0.2 %)

* Treatment emergent SAE is defined as any event occurring after a patient has received one dose of study drug and within 3 days of permanent discontinuation

Table S3.2: Number of subjects with AE of death or leading to death (>=0.2% in Finerenone group), by preferred term

	Finerenone n=2993	Placebo n=2993
Death	70 (2.3 %)	97 (3.2 %)
Pneumonia	27 (0.9 %)	23 (0.8 %)
Sudden death	20 (0.7 %)	26 (0.9 %)
Sudden cardiac death	18 (0.6 %)	19 (0.6 %)
Sepsis	19 (0.6 %)	7 (0.2 %)
Septic shock	12 (0.4 %)	12 (0.4 %)
COVID-19	7 (0.2 %)	17 (0.6 %)
Cardiac arrest	12 (0.4 %)	12 (0.4 %)
COVID-19 pneumonia	9 (0.3 %)	10 (0.3 %)
Cardiac failure	6 (0.2 %)	12 (0.4 %)
Respiratory failure	7 (0.2 %)	4 (0.1 %)
Lung neoplasm malignant	7 (0.2 %)	3 (0.1 %)

Table S4. Supplementary table on the representativeness of study participants

Disease, problem or condition under investigation	Heart failure with mildly reduced or preserved ejection fraction (HFmrEF or HFpEF)
Sex and gender	In patients with heart failure, the proportion of women increases with increasing left ventricular ejection fraction. Among patients with heart failure and reduced ejection fraction, women are the minority (around one quarter of patients) but account for around half of patients with heart failure and preserved ejection fraction.
Race or ethnic group	In the United States, heart failure with preserved ejection fraction is rising in prevalence in Black patients[1].
Geography	Heart failure with mildly reduced or preserved ejection fraction affects patients globally, with some differences in phenotypic presentation in different locations[2].
Other considerations	Patients with heart failure and mildly reduced ejection fraction (LVEF between 40 and 49%) have a phenotype intermediate between that of heart failure with reduced ejection fraction and heart failure with preserved ejection fraction.
Overall representativeness of this trial	The participants in the present trial demonstrated the expected ratio of men to women based on the ejection fraction distribution. The proportion of women is expectedly slightly lower than in prior HFpEF trials in which the LVEF inclusion criteria were higher. Biologic sex was reported by the participants. The age distribution in this trial is typical for heart failure with mildly reduced or preserved ejection fraction, and similar to other trials in this population. The proportion of Black patients who underwent randomization overall was small (1.5%), primarily because FINEARTS-HF was a global trial and the proportion of Black people in the population of the majority of countries in which FINEARTS-HF enrolled was very low. Among patients enrolled in the United States, 12.4% were Black, which is exactly the population distribution of Black people in the United States (12.4%). The causes of heart failure and the coexisting conditions, including kidney dysfunction, were consistent with the epidemiology and registry data available from participating countries. No patients were enrolled in Africa.

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