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RESEARCH ARTICLE

Baseline characteristics of patients with heart failure with mildly reduced or preserved ejection fraction: The FINEARTS-HF trial

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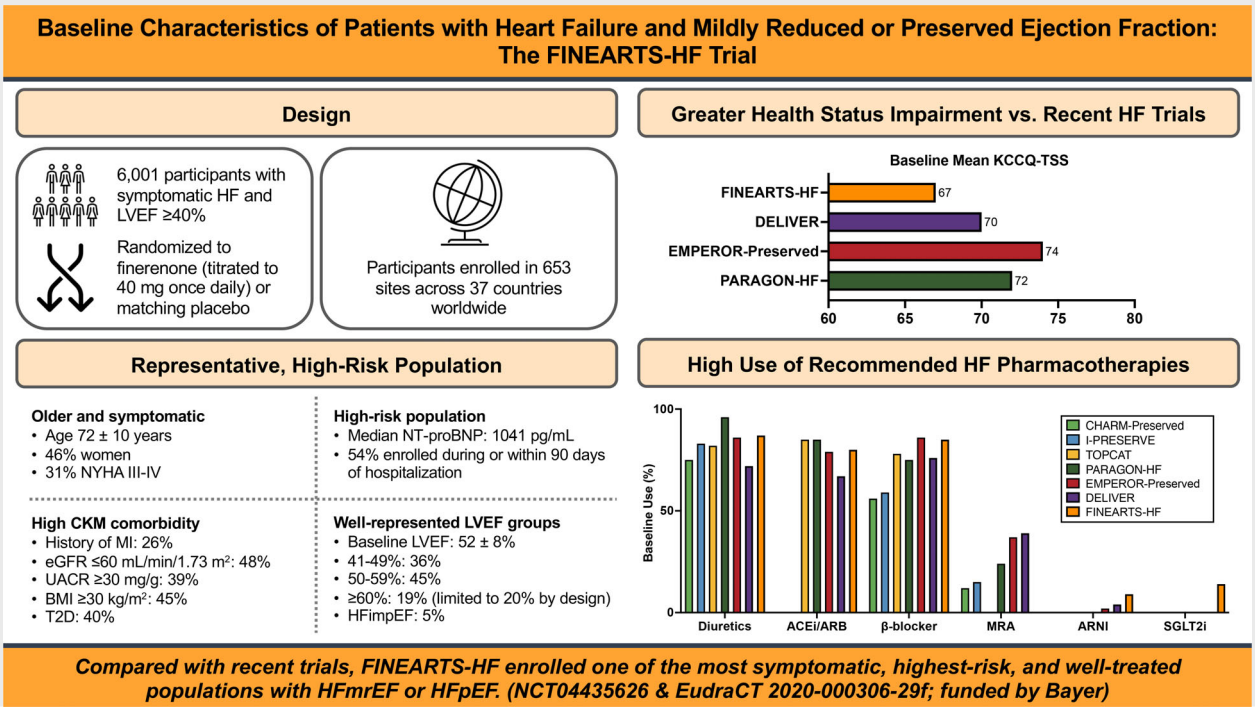
Aims To describe the baseline characteristics of participants in the FINEARTS-HF trial, contextualized with prior trials including patients with heart failure (HF) with mildly reduced and preserved ejection fraction (HFmrEF/HFpEF). The FINEARTS-HF trial is comparing the effects of the non-steroidal mineralocorticoid receptor antagonist finerenone with placebo in reducing cardiovascular death and total worsening HF events in patients with HFmrEF/HFpEF.

Methods and results Patients with symptomatic HF, left ventricular ejection fraction (LVEF) ≥40%, estimated glomerular filtration rate ≥ 25 ml/min/1.73 m^2, elevated natriuretic peptide levels and evidence of structural heart disease were enrolled and randomized to finerenone titrated to a maximum of 40 mg once daily or matching placebo. We validly randomized 6001 patients to finerenone or placebo (mean age 72 ± 10 years, 46% women). The majority were New York Heart Association functional class II (69%). The baseline mean LVEF was 53 ± 8% (range 34–84%); 36% of participants had a LVEF <50% and 64% had a LVEF ≥50%. The median N-terminal pro-B-type natriuretic peptide (NT-proBNP) was 1041 (interquartile range 449–1946) pg/ml. A total of 1219 (20%) patients were enrolled during or within 7 days of a worsening HF event, and 3247 (54%) patients were enrolled within 3 months of a worsening HF event. Compared with prior large-scale HFmrEF/HFpEF trials, FINEARTS-HF participants were more likely to have recent (within 6 months) HF hospitalization and greater symptoms and functional limitations. Further, concomitant medications included a larger percentage of sodium–glucose cotransporter 2 inhibitors and angiotensin receptor–neprilysin inhibitors than previous trials.

Conclusions FINEARTS-HF has enrolled a broad range of high-risk patients with HFmrEF and HFpEF. The trial will determine the safety and efficacy of finerenone in this population.

Graphical Abstract



Baseline characteristics of FINEARTS-HF participants. BMI, body mass index; CKM, cardiovascular-kidney-metabolic; eGFR, estimated glomerular filtration rate; FINEARTS-HF, Finerenone Trial to Investigate Efficacy and Safety Superior to Placebo in Patients with Heart Failure; HF, heart failure; HFimpEF, heart failure with improved ejection fraction; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire total symptom score; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; T2D, type 2 diabetes; UACR, urine albumin-to-creatinine ratio.

Keywords Clinical trials • Heart failure with mildly reduced or preserved ejection fraction • Mineralocorticoid receptor antagonists

Introduction

Heart failure (HF) with mildly reduced or preserved ejection fraction (HFmrEF/HFpEF) accounts for at least half of patients with chronic HF. Despite the success of sodium–glucose cotransporter 2 (SGLT2) inhibitors, which are now guideline-recommended in patients with HFmrEF and HFpEF,[1,2] and sacubitril/valsartan, which now has an indication in some countries for select patients with HF and left ventricular ejection fraction (LVEF) >40%, there remains substantial residual risk in this population. Steroidal mineralocorticoid receptor antagonists (MRAs), such as spironolactone and eplerenone, are disease-modifying drugs in HF with reduced ejection fraction (HFrEF) and following myocardial infarction.[3–5] In patients with HF with LVEF ≥45% in the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist) trial, spironolactone did not significantly reduce cardiovascular death, HF hospitalization, or resuscitated cardiac arrest,[6] but post hoc analyses suggested potential benefit among patients enrolled in the Americas.[7] Nevertheless, steroidal MRAs are known to increase the risk of renal dysfunction and hyperkalaemia, and post hoc analyses in TOPCAT have additionally suggested attenuated efficacy and more adverse events with spironolactone in patients with an estimated glomerular filtration rate (eGFR) under 60 ml/min/1.73 m^2.[8]

Finerenone is a non-steroidal MRA that is more selective for the mineralocorticoid receptor than spironolactone or eplerenone, and targets adverse haemodynamic (e.g. sodium retention and albuminuria) and non-haemodynamic (e.g. fibrotic and inflammatory) pathways related to mineralocorticoid receptor overactivation in the heart, kidneys, and vasculature.[9–11] In pre-clinical models, finerenone has been shown to have more pronounced anti-inflammatory/anti-fibrotic effects, as well as a more balanced distribution in heart and kidney tissue, compared with spironolactone and eplerenone (which preferentially concentrate in the kidneys).[10–13] As such, finerenone's unique pharmacological characteristics may provide a more favourable balance of risk and benefit compared with steroidal MRAs. Indeed, among patients with chronic kidney disease, proteinuria, and type 2 diabetes, finerenone has been shown to reduce the incidence of renal and cardiovascular events.[14,15]

The FINEARTS-HF (FINerenone trial to investigate Efficacy and sAfety superioR to placebo in paTientS with Heart Failure) trial is testing the hypothesis that finerenone, compared with placebo, would reduce cardiovascular death and total HF events in patients with HFmrEF or HFpEF. Herein, we describe the baseline characteristics of patients enrolled in the FINEARTS-HF trial in comparison with prior trials including patients with HFmrEF/HFpEF.

Methods

Study design

FINEARTS-HF is an ongoing, global, randomized, double-blind, parallel-group, event-driven trial comparing the efficacy and safety of finerenone with placebo in patients with chronic HFmrEF or HFpEF. The details of the FINEARTS-HF study design have been previously published,[16] and the trial is registered with ClinicalTrials.gov (NCT04435626) and EudraCT (2020-000306-29). Briefly, FINEARTS-HF enrolled patients aged 40 years or older, with signs and symptoms of HF (New York Heart Association [NYHA] functional class II–IV) and LVEF ≥40%; LVEF <50% was consistent with HFmrEF and LVEF ≥50% was consistent with HFpEF. All patients were additionally required to have elevated natriuretic peptide concentrations and evidence of structural heart disease.

Eligibility thresholds for natriuretic peptides were adjusted according to timing of recent HF events and the presence of atrial fibrillation. For patients in sinus rhythm, N-terminal pro-B-type natriuretic peptide (NT-proBNP) ≥300 pg/ml (or B-type natriuretic peptide [BNP] ≥100 pg/ml) were required, measured within 30 days (in those without a recent worsening HF event) or within 90 days (in those with a recent worsening HF event). Qualifying levels of NT-proBNP or BNP were tripled (i.e. NT-proBNP ≥900 pg/ml or BNP ≥300 pg/ml) if a patient had atrial fibrillation at screening. A worsening HF event was defined as either HF hospitalization or an urgent visit for HF. Structural heart disease was defined as either increased left atrial size (left atrial diameter ≥3.8 cm, left atrial area ≥20 cm^2, or left atrial volume index >30 ml/m^2) or left ventricular hypertrophy (left ventricular mass index ≥115 g/m^2 [if male] or ≥95 g/m^2 [if female] or either septal or posterior wall thickness ≥1.1 cm).

Patients with HF with improved ejection fraction (if previously below 40% but increased to 40% or greater by the time of enrolment) could also be included. Patients were enrolled either as outpatients or in the setting of hospitalization for worsening HF; the sample of patients without a worsening ambulatory or hospitalized HF event within 3 months was capped at approximately 50% of total enrolment. Key exclusion criteria at randomization included serum potassium >5.0 mmol/L or eGFR <25 ml/min/1.73 m^2, any MRA use within 30 days, systolic blood pressure ≥160 mmHg if not on treatment with ≥3 blood pressure-lowering medications, or systolic blood pressure ≥180 mmHg irrespective of background antihypertensive therapy.

Country	FINEARTS-HF Participants Enrolled
CHN	428
USA	355
ESP	353
UKR	327
RUS	300
JPN	286
BGR	275
HUN	267
SVK	262
POL	259
ITA	227
GRC	217
ARG	211
CZE	206
ROU	193
BRA	185
ISR	181
COL	167
TUR	159
CAN	116
LTU	100
GBR	99
PRT	88
DNK	79
MEX	78
KOR	74
AUT	73
TWN	69
LVA	65
NLD	64
MYS	57
HKG	41
NZL	40
AUS	32
IND	28
GER	20
FIN	20

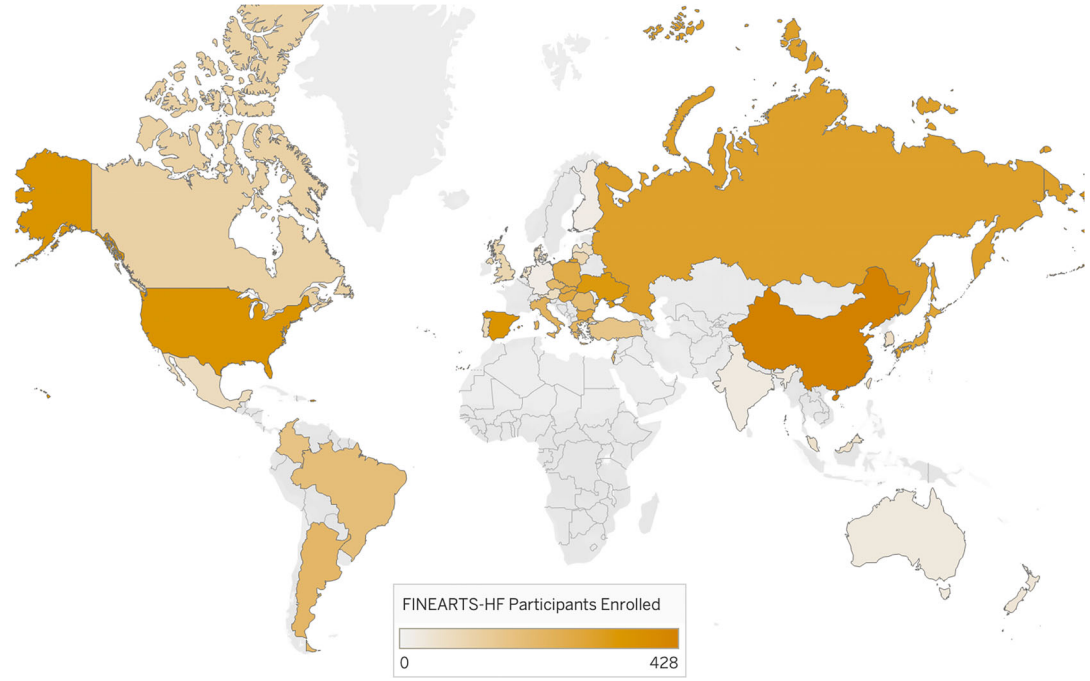


Figure 1 Enrolment in the FINEARTS-HF trial, by country. This global geographical map displays country-specific enrolment in FINEARTS-HF. Countries coloured in grey did not participate.

The primary endpoint for the trial is a composite of cardiovascular death and total worsening HF events (either a HF hospitalization or an urgent HF visit) with all primary endpoints confirmed through centralized adjudication by a clinical events committee. The trial is event-driven and will stop when approximately 2375 total adjudicated events have been reached. The study was approved by institutional review boards or ethics committees at each individual study site prior to enrolment of the first patient, and regulatory authorities according to national and international regulations. All participants provided written informed consent.

Concomitant medical therapies

Study investigators were encouraged to treat patients according to local recommendations except for MRAs, which were prohibited during the trial. In response to changes in guidelines for SGLT2 inhibitors during the trial, investigators were encouraged to treat patients with SGLT2 inhibitors unless contraindicated.

Baseline data collection and analysis

We collected detailed baseline data before randomization, including demographics, medical history, concomitant medications, cardiac procedures, physical exam, vital signs, quality of life, electrocardiography, and specific laboratory assessments. To describe patient-level characteristics, we categorized patients based on recency of a prior worsening HF event relative to randomization: within 7 days of a HF event, between 7 days and 3 months of a HF event, and after 3 months of a HF event or in the absence of a prior HF event. We further divided patients into three distinct LVEF groups (<50%, ≥50% to <60%, and ≥60%). All between-group comparisons were made using Student's *t*-tests or ANOVA for continuous variables and χ^2 tests for categorical variables. Statistical analyses were performed using STATA version 18.1 (StataCorp LLC; College Station, TX, USA).

Comparison with other contemporary heart failure trials

Baseline characteristics in FINEARTS-HF were described alongside other trials enrolling patients with HFmrEF or HFpEF, including CHARM-Preserved (Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity), I-Preserve (Irbesartan in Heart Failure With Preserved Ejection Fraction), TOPCAT Americas, PARAGON-HF (Prospective Comparison of ARNI with ARB Global Outcomes in Heart Failure with Preserved Ejection Fraction), EMPEROR-Preserved (Empagliflozin Outcome Trial in Patients With Chronic Heart Failure with Preserved Ejection Fraction), and DELIVER (Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure).[7,17–21] To enable comparison across trials, we evaluated the proportion of FINEARTS-HF participants with most recent HF hospitalization ≤6 months, most recent HF hospitalization ≤12 months, or any prior HF hospitalization prior to randomization. HF hospitalization within 6 months of randomization was defined as recent.

Results

Between 14 September 2020 and 10 January 2023, we screened 7463 patients from 653 sites across 37 countries for enrolment.

Table 1 Baseline characteristics by recency of worsening heart failure event before randomization

Characteristic	All FINEARTS-HF participants ($n = 6001$)	Recency of worsening HF event			*p*-value*
		≤7 days ($n = 1219$)	>7 days to ≤3 months ($n = 2028$)	>3 months or no event ($n = 2754$)	
Age, years	72.0 ± 9.6	72.2 ± 9.7	71.3 ± 10.3	72.4 ± 9.1	<0.001
Women	2731 (45.5)	583 (47.8)	936 (46.2)	1212 (44.0)	0.06
Race					<0.001
Asian	996 (16.6)	74 (6.1)	507 (25.1)	415 (15.1)	
Black	88 (1.5)	7 (0.6)	34 (1.7)	47 (1.7)	
Other	165 (2.8)	29 (2.4)	70 (3.5)	66 (2.4)	
White	4735 (79.1)	1106 (91.0)	1412 (69.8)	2217 (80.8)	
Geographic region					<0.001
Asia	983 (16.4)	74 (6.1)	505 (25.0)	404 (14.7)	
Eastern Europe	2650 (44.2)	759 (62.3)	665 (32.8)	1226 (44.5)	
Latin America	641 (10.7)	122 (10.0)	297 (14.7)	222 (8.0)	
North America	471 (7.8)	16 (1.3)	120 (5.9)	335 (12.2)	
Western Europe, Oceania, Other	1256 (20.9)	248 (20.3)	441 (21.7)	567 (20.6)	
History of chronic obstructive pulmonary disease	770 (12.8)	181 (14.8)	251 (12.4)	338 (12.3)	0.06
History of type 2 diabetes	2438 (40.6)	510 (41.8)	829 (40.9)	1099 (39.9)	0.50
History of hypertension	5323 (88.7)	1117 (91.6)	1761 (86.8)	2445 (88.8)	<0.001
History of myocardial infarction	1539 (25.6)	269 (22.1)	435 (21.4)	835 (30.3)	<0.001
History of stroke	707 (11.8)	148 (12.1)	272 (13.4)	287 (10.4)	=0.006
History of LVEF <40%	271 (4.5)	36 (3.0)	96 (4.7)	139 (5.0)	0.012
Smoking status					0.020
Current	509 (8.5)	104 (8.5)	176 (8.7)	229 (8.3)	
Former	1793 (29.9)	343 (28.1)	567 (28.0)	883 (32.1)	
Never	3699 (61.6)	772 (63.3)	1285 (63.4)	1642 (59.6)	
Body mass index, kg/m^2	29.9 ± 6.1	30.5 ± 6.2	29.4 ± 6.3	30.1 ± 5.9	<0.001
Body mass index groups, kg/m^2					<0.001
<18.5 (underweight)	65 (1.1)	13 (1.1)	37 (1.8)	15 (0.5)	
18.5–<25 (normal weight)	1241 (20.7)	222 (18.3)	502 (24.8)	517 (18.8)	
25–<30 (overweight)	1990 (33.2)	397 (32.6)	646 (31.9)	947 (34.5)	
30–<35 (class I obesity)	1546 (25.8)	319 (26.2)	489 (24.1)	738 (26.9)	
≥35 (class II–III obesity)	1146 (19.1)	265 (21.8)	351 (17.3)	530 (19.3)	
Any prior HF hospitalization	3618 (60.3)	1065 (87.4)	1685 (83.1)	868 (31.5)	<0.001
Prior HF hospitalization (≤6 months)	2827 (47.1)	1024 (84.0)	1623 (80.0)	180 (6.5)	<0.001
Prior HF hospitalization (≤1 year)	3027 (50.4)	1034 (84.8)	1644 (81.1)	349 (12.7)	<0.001
KCCQ total symptom score	67.0 ± 23.9	52.9 ± 23.9	70.2 ± 23.3	71.0 ± 22.0	<0.001
NYHA functional class					<0.001
II	4145 (69.1)	618 (50.7)	1455 (71.8)	2072 (75.2)	
III	1814 (30.2)	578 (47.4)	559 (27.6)	677 (24.6)	
IV	41 (0.7)	23 (1.9)	13 (0.6)	5 (0.2)	
LVEF, %	52.6 ± 7.8	51.7 ± 7.7	51.8 ± 7.3	53.5 ± 8.1	<0.001
Pooled LVEF groups					<0.001
<50%	2172 (36.2)	483 (39.6)	792 (39.2)	897 (32.6)	
≥50% to <60%	2674 (44.6)	549 (45.0)	943 (46.6)	1182 (43.0)	
≥60%	1147 (19.1)	187 (15.3)	290 (14.3)	670 (24.4)	
HbA1c, %	6.4 ± 1.2	6.4 ± 1.2	6.4 ± 1.2	6.4 ± 1.2	0.13
NT-proBNP, pg/ml	1041 [449–1946]	1168 [474–2451]	1119 [473–2113]	952 [426–1718]	<0.001
ECG AF	2293 (38.2)	534 (43.8)	783 (38.6)	976 (35.4)	<0.001
Heart rate, bpm	71.5 ± 11.8	72.5 ± 11.5	72.0 ± 12.2	70.6 ± 11.6	<0.001
Heart rate (AF), bpm	76.5 ± 12.4	76.6 ± 11.9	77.0 ± 13.0	76.0 ± 12.3	0.20
Heart rate (non-AF), bpm	68.3 ± 10.3	69.3 ± 10.1	68.8 ± 10.5	67.7 ± 10.1	<0.001

Table 1 (Continued)

Characteristic	All FINEARTS-HF participants (*n* = 6001)	Recency of worsening HF event			*p*-value*
		≤7 days (*n* = 1219)	>7 days to ≤3 months (*n* = 2028)	>3 months or no event (*n* = 2754)	
Systolic blood pressure, mmHg	129.4 ± 15.3	127.1 ± 13.9	128.6 ± 15.9	131.0 ± 15.3	<0.001
eGFR, ml/min/1.73 m^2	62.1 ± 19.7	60.2 ± 20.0	63.3 ± 20.2	62.1 ± 19.2	<0.001
eGFR <60 ml/min/1.73 m^2	2888 (48.1)	637 (52.3)	918 (45.3)	1333 (48.4)	<0.001
Potassium, mmol/L	4.4 ± 0.5	4.4 ± 0.5	4.4 ± 0.5	4.4 ± 0.4	0.06
UACR, mg/g	18 [7–67]	19 [7–73]	19 [7–72]	18 [7–58]	0.05
UACR category, mg/g[a]					0.30
<30	3511 (60.6)	711 (60.7)	1152 (59.1)	1648 (61.5)	
30 to <300	1712 (29.5)	347 (29.6)	582 (29.9)	783 (29.2)	
≥300	574 (9.9)	113 (9.6)	214 (11.0)	247 (9.2)	
Pharmacotherapy					
β-blocker	5096 (84.9)	1017 (83.4)	1701 (83.9)	2378 (86.3)	0.016
ACEi	2154 (35.9)	474 (38.9)	638 (31.5)	1042 (37.8)	<0.001
ARB	2610 (43.5)	486 (39.9)	948 (46.7)	1176 (42.7)	<0.001
ARNI	509 (8.5)	76 (6.2)	251 (12.4)	182 (6.6)	<0.001
SGLT2i	816 (13.6)	188 (15.4)	370 (18.2)	258 (9.4)	<0.001
Loop diuretic	5240 (87.3)	1075 (88.2)	1880 (92.7)	2285 (83.0)	<0.001
CCB	1970 (32.8)	427 (35.0)	615 (30.3)	928 (33.7)	0.009

Values are mean ± standard deviation, *n* (%), or median [interquartile range].
ACEi, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; CCB, calcium channel blocker; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; HF, heart failure; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SGLT2i, sodium–glucose cotransporter 2 inhibitor; UACR, urine albumin-to-creatinine ratio.
[a]Baseline UACR unavailable in 204 participants, hence percentages are expressed as the number of participants out of 5797.
**P*-value reflects global comparison across subgroups defined by recency of HF event before randomization.

Details of individual country enrolment are shown in *Figure 1*. The primary reason (90%) for screen failure was not meeting ≥1 inclusion or exclusion criterion; 53% had sub-threshold natriuretic peptide levels, 9% had a serum potassium level >5.0 mmol/L, and 28% did not meet other inclusion or exclusion criteria. Overall, 6016 randomizations to receive finerenone or placebo occurred. Two of these randomizations were identified in connection to the same patient, and both entries were excluded. In addition, 13 patients from a single site were excluded from the primary analysis due to significant Good Clinical Practice violations. In total, 6001 patients were validly randomized and included in subsequent analyses.

Baseline characteristics of randomized patients are described for the entire population and by recency of a prior HF event in *Table 1*. Patients had a mean age of 72 ± 10 years; 46% were women, and 79% were White. Sixty-nine percent of patients were NYHA class II and 31% NYHA class III or IV; 41% had a history of diabetes and 26% had a history of myocardial infarction. The mean eGFR was 62 ml/min/1.73 m^2, and 48% had a baseline eGFR <60 ml/min/1.73 m^2. Overall, 60% of patients had a prior HF hospitalization. The baseline LVEF was 53 ± 8% and 271 (4.5%) patients had a history of LVEF <40%. The median baseline NT-proBNP in the overall randomized trial population

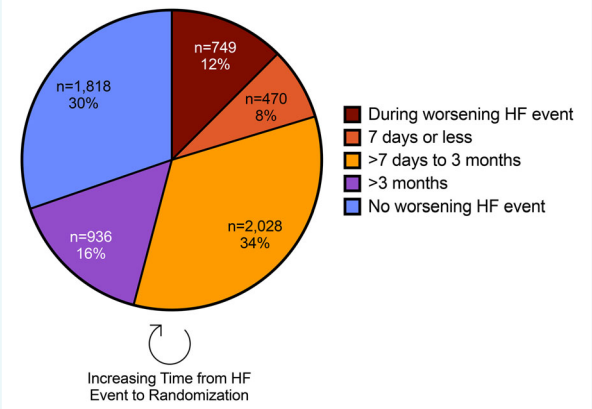


Figure 2 Recency of worsening heart failure (HF) events prior to randomization in FINEARTS-HF. Pie chart displays the FINEARTS-HF trial population, segmented according to timing from most recent worsening HF event (HF hospitalization or urgent HF visit) prior to trial enrolment.

Table 2 Baseline characteristics by left ventricular ejection fraction group

Characteristic	LVEF group			*p*-value
	<50% (*n* = 2172)	≥50% to <60% (*n* = 2674)	≥60% (*n* = 1147)	
Age, years	69.6 ± 10.1	73.3 ± 9.1	73.5 ± 9.2	<0.001
Women	679 (31.3)	1367 (51.1)	679 (59.2)	<0.001
Race				<0.001
Asian	432 (20.0)	359 (13.5)	205 (17.9)	
Black	23 (1.1)	36 (1.3)	29 (2.5)	
Other	50 (2.3)	88 (3.3)	27 (2.4)	
White	1659 (76.7)	2185 (81.9)	883 (77.2)	
Geographic region				<0.001
Asia	429 (19.8)	355 (13.3)	199 (17.3)	
Eastern Europe	1007 (46.4)	1140 (42.6)	503 (43.9)	
Latin America	255 (11.7)	281 (10.5)	105 (9.2)	
North America	125 (5.8)	218 (8.2)	123 (10.7)	
Western Europe, Oceania, Other	356 (16.4)	680 (25.4)	217 (18.9)	
History of chronic obstructive pulmonary disease	265 (12.2)	346 (12.9)	158 (13.8)	0.42
History of type 2 diabetes	866 (39.9)	1096 (41.0)	472 (41.2)	0.67
History of hypertension	1858 (85.5)	2411 (90.2)	1046 (91.2)	<0.001
History of myocardial infarction	804 (37.0)	569 (21.3)	163 (14.2)	<0.001
History of stroke	264 (12.2)	320 (12.0)	122 (10.6)	0.40
History of LVEF <40%	195 (9.0)	67 (2.5)	9 (0.8)	<0.001
Smoking status				<0.001
Current	235 (10.8)	188 (7.0)	84 (7.3)	
Former	713 (32.8)	748 (28.0)	331 (28.9)	
Never	1224 (56.4)	1738 (65.0)	732 (63.8)	
Body mass index, kg/m^2	29.3 ± 5.9	30.3 ± 6.2	30.4 ± 6.2	<0.001
Body mass index groups, kg/m^2				<0.001
<18.5 (underweight)	30 (1.4)	21 (0.8)	14 (1.2)	
18.5–<25 (normal weight)	509 (23.5)	515 (19.3)	217 (19.0)	
25–<30 (overweight)	755 (34.8)	874 (32.8)	360 (31.4)	
30–<35 (class I obesity)	532 (24.5)	697 (26.2)	314 (27.4)	
≥35 (class II–III obesity)	344 (15.9)	558 (20.9)	240 (21.0)	
Any prior HF hospitalization	1449 (66.7)	1582 (59.2)	583 (50.8)	<0.001
Prior HF hospitalization (≤6 months)	1143 (52.6)	1247 (46.6)	435 (37.9)	<0.001
Prior HF hospitalization (≤1 year)	1216 (56.0)	1339 (50.1)	469 (40.9)	<0.001
Recency of worsening HF event[a]				<0.001
≤7 days	483 (22.2)	549 (20.5)	187 (16.3)	
>7 days to ≤3 months	792 (36.5)	943 (35.3)	290 (25.3)	
>3 months or no worsening HF event	897 (41.3)	1182 (44.2)	670 (58.4)	
KCCQ total symptom score	69.2 ± 23.9	65.9 ± 23.8	65.5 ± 23.9	<0.001
NYHA functional class				0.31
II	1499 (69.0)	1827 (68.3)	815 (71.1)	
III	661 (30.4)	824 (30.8)	325 (28.4)	
IV	12 (0.6)	23 (0.9)	6 (0.5)	
LVEF, %	44.4 ± 2.8	54.2 ± 2.9	64.0 ± 4.6	<0.001
HbA1c, %	6.5 ± 1.2	6.4 ± 1.2	6.4 ± 1.2	0.014
NT-proBNP, pg/mL	1139 [506–2205]	1008 [426–1880]	941 [406–1776]	<0.001
ECG AF	771 (35.5)	1099 (41.1)	421 (36.7)	<0.001
Heart rate, bpm	72.1 ± 11.8	71.5 ± 11.7	70.4 ± 11.8	<0.001
Heart rate (AF), bpm	77.4 ± 12.4	76.2 ± 12.3	75.5 ± 12.8	0.024
Heart rate (non-AF), bpm	69.1 ± 10.4	68.1 ± 10.1	67.4 ± 10.1	<0.001
Systolic blood pressure, mmHg	127.5 ± 14.9	130.2 ± 15.5	131.2 ± 15.3	<0.001
eGFR, ml/min/1.73 m^2	64.8 ± 20.1	61.0 ± 19.3	59.6 ± 19.4	<0.001
eGFR <60 ml/min/1.73 m^2	929 (42.8)	1345 (50.3)	610 (53.2)	<0.001

Table 2 (Continued)

Characteristic	LVEF group			*p*-value
	<50% (*n* = 2172)	≥50% to <60% (*n* = 2674)	≥60% (*n* = 1147)	
Potassium, mmol/L	4.4 ± 0.5	4.4 ± 0.5	4.3 ± 0.4	<0.001
UACR, mg/g	18 [7–68]	19 [7–67]	19 [7–62]	0.82
UACR category[b], mg/g				0.98
<30	1274 (60.5)	1559 (60/8)	674 (60.2)	
30 to <300	619 (29.4)	753 (29.4)	338 (30.2)	
≥300	213 (10.1)	253 (9.9)	108 (9.6)	
Pharmacotherapy				
β-blocker	1919 (88.4)	2243 (83.9)	927 (80.8)	<0.001
ACEi	870 (40.1)	889 (33.2)	392 (34.2)	<0.001
ARB	955 (44.0)	1159 (43.3)	492 (42.9)	0.82
ARNI	339 (15.6)	143 (5.3)	27 (2.4)	<0.001
SGLT2i	335 (15.4)	366 (13.7)	113 (9.9)	<0.001
Loop diuretic	1973 (90.8)	2318 (86.7)	943 (82.2)	<0.001
CCB	516 (23.8)	946 (35.4)	504 (43.9)	<0.001

Values are mean ± standard deviation, *n* (%), or median [interquartile range].
ACEi, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; CCB, calcium channel blocker; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; HF, heart failure; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SGLT2i, sodium–glucose cotransporter 2 inhibitor; UACR, urine albumin-to-creatinine ratio.
[a]Measured relative to randomization.
[b]Baseline UACR unavailable in 204 participants, hence percentages are expressed as the number of participants out of 5797.

was 1041 [449-1946] pg/ml. Among patients with known atrial fibrillation, the median NT-proBNP was 1714 [1152–2807] pg/ml; the median NT-proBNP was 588 [313–1255] pg/ml in patients without atrial fibrillation. The mean Kansas City Cardiomyopathy Questionnaire (KCCQ) total symptom score (TSS) was 67 ± 24. The majority of patients (61%) had a urine albumin-to-creatinine ratio (UACR) <30 mg/g, 30% had UACR between 30 and 300 mg/g, and 10% had UACR >300 mg/g. Concomitant medications at baseline included β-blockers (85%), angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB) (79%), an angiotensin receptor–neprilysin inhibitor (ARNI) (9%), SGLT2 inhibitors (14%), and loop diuretics (87%).

A total of 1219 patients (20%) had a worsening HF event within 7 days before randomization, with 749 (12%) patients enrolled during the index event. Of those enrolled during a worsening HF event, 652 (87%) were enrolled during a HF hospitalization and 97 (13%) were enrolled during an outpatient HF visit. A total of 2028 (34%) patients had a worsening HF event between 7 days and 3 months before randomization, 936 (16%) patients had had a worsening HF event more than 3 months before randomization, and 1818 (30%) patients had never had a prior worsening HF event (*Figure 2*). There were notable baseline differences between patients based on the recency of a HF event before randomization. Patients randomized within 7 days of a worsening HF event had higher NYHA functional class, lower KCCQ-TSS, higher baseline NT-proBNP levels, and lower baseline eGFR. The use of SGLT2 inhibitors and ARNIs was also notably higher in those within ≤3 months of a worsening HF event compared with the residual randomized population.

A total of 2172 (36%) patients had LVEF <50%, 2674 (45%) patients had LVEF ≥50% to <60%, and 1147 (19%) patients had LVEF ≥60% (*Table 2*). Participants with a higher LVEF were more likely to be women compared with men. Those with lower LVEF were more likely to have younger age, had a prior myocardial infarction, a prior history of LVEF <40%, a prior HF hospitalization, elevated NT-proBNP levels, and be treated with β-blockers, SGLT2 inhibitors, or an ARNI.

The baseline characteristics of patients in FINEARTS-HF were similar to those in prior trials of patients with HFmrEF/HFpEF, in particular the two most recent trials, EMPEROR-Preserved and DELIVER, which had similar LVEF inclusion criteria (*Table 3*). FINEARTS-HF, by design, enrolled a higher percentage of patients with a recent (within 6 months) HF hospitalization, resulting in a higher proportion of patients with NYHA functional class III or IV, worse patient-reported health status (as reflected by a lower mean KCCQ score at baseline), and a higher proportion of patients treated with SGLT2 inhibitors and an ARNI (*Figure 3*). The prevalence of moderate (UACR 30 to <300 mg/g) or severe (UACR ≥300 mg/g) albuminuria among FINEARTS-HF participants at baseline was similar to that observed in the EMPEROR programme (*Figure 4*).[22]

Discussion

FINEARTS-HF, a large, contemporary trial of HFmrEF or HFpEF with broad inclusion criteria, will test the hypothesis that finerenone compared with placebo will reduce cardiovascular

Table 3 Comparison of baseline characteristics across major outcomes trials in heart failure with mildly reduced or preserved ejection fraction

Characteristic	FINEARTS-HF ($n = 6001$)	DELIVER ($n = 6263$)	EMPEROR-Preserved ($n = 5988$)	PARAGON-HF ($n = 4822$)	TOPCAT-Americas ($n = 1767$)	I-Preserve ($n = 4128$)	CHARM-Preserved ($n = 3023$)
Age, years	72 ± 10	72 ± 10	72 ± 9	73 ± 8	72 [64–79]	72 ± 7	67 ± 11
Women, %	46	44	45	52	50	60	40
KCCQ total symptom score	67	70	74	72	–	–	–
NYHA functional class, %							
II	69	75	82	77	59	22	61
III	30	25	18	27	35	77	38
IV	1	0.3	0.3	0.6	1	3	2
Active smoking, %	9	8	7	7	7	18	14
History of COPD, %	13	11	13	14	–	–	–
History of hypertension, %	89	89	90	96	90	89	64
History of myocardial infarction, %	26	26	29	22	20	24	44
History of stroke, %	12	9 (stroke/TIA)	10	10	9	10	9
History of type 2 diabetes, %	41	45	49	43	45	27	28
Body mass index, kg/m^2	30	30	30	30	32	30	29
AFF at screening, %	38 (AF only)	42	35	32	34	29	29
Prior HF hospitalization, %							
Any prior HF hospitalization	60	40	–	48	59	–	68
Within 6 months	47	–	–	34	–	44	–
Within 12 months	50	26	23	48	–	–	–
LVEF, mean, %	53	54	54	58	58	60	54
eGFR, ml/min/1.73 m^2, mean	62	61	61	62	61	73	72
NT-proBNP, pg/ml, median	1041	1011	974	885	900	339	–
β-blocker, %	85	76	86	75	79	59	56
ACEi, %	36	33	40	40	50	26	19
ARB, %	44	34	39	45	31	–	–
ARNI, %	9	4	2	–	–	–	–
MRA, %	–	39	37	24	–	15	12
SGLT2i, %	14	–	–	–	–	–	–
Diuretic, %	Loop: 87	Loop: 72	86	96	89	Loop: 83 Thiazide: 52	75

Values are mean ± standard deviation, or median [IQR], unless otherwise indicated.
ACEi, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; AFF, atrial fibrillation or flutter; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; CHARM-Preserved, Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity; COPD, chronic obstructive pulmonary disease; DELIVER, Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure; eGFR, estimated glomerular filtration rate; EMPEROR-Preserved, Empagliflozin Outcome Trial in Patients With Chronic Heart Failure with Preserved Ejection Fraction; FINEARTS-HF, Finerenone Trial to Investigate Efficacy and Safety Superior to Placebo in Patients with Heart Failure; HF, heart failure; I-Preserve, Irbesartan in Heart Failure With Preserved Ejection Fraction; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PARAGON-HF, Prospective Comparison of ARNI with ARB Global Outcomes in Heart Failure with Preserved Ejection Fraction; SGLT2i, sodium–glucose cotransporter 2 inhibitor; TIA, transient ischaemic attack; TOPCAT, Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist.

death and total (first and recurrent) worsening HF events in this population. The inclusion criteria for FINEARTS-HF were similar to several contemporary trials in the same population, and thus the baseline characteristics were largely comparable. However, the overall clinical profile of FINEARTS-HF participants was relatively higher-risk, defined by a larger proportion of patients with recent worsening HF events and greater symptoms and functional limitations. In addition, FINEARTS-HF participants were more commonly treated with background medical therapies at baseline (*Graphical Abstract*).

Nearly all recent trials of HFmrEF or HFpEF have required elevated natriuretic peptides for enrolment, the levels of which may depend on the presence of a recent HF hospitalization. However, no prior trial of HFmrEF/HFpEF has specifically targeted those with a recent worsening HF event, a strategy for enrichment of clinical event rates that has been employed in HFrEF[23] and will enable assessment of the safety and efficacy of finerenone when initiated during this unstable phase. In FINEARTS-HF, the proportion of patients without a worsening HF event in the 3 months before enrolment was prospectively planned to account for no more than approximately half of the trial population. Indeed, 54% of all participants in FINEARTS-HF had a worsening HF event within 3 months of enrolment. This resulted in a comparatively higher-risk population than seen in prior trials of HFmrEF/HFpEF, as

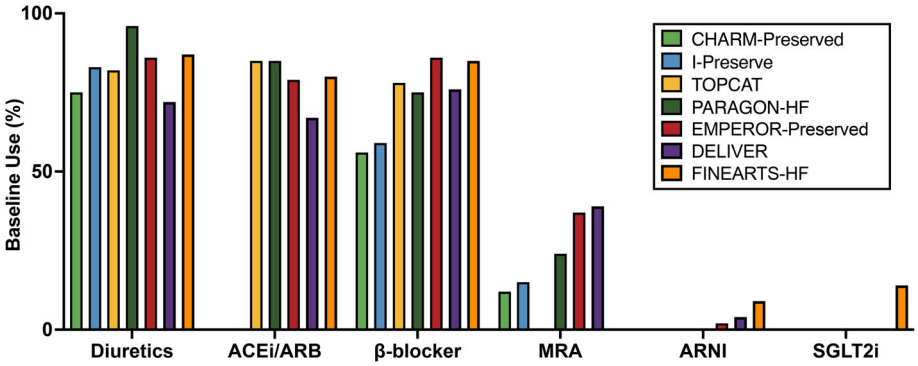


Figure 3 Background pharmacotherapy in FINEARTS-HF compared with major outcomes trials in heart failure with mildly reduced or preserved ejection fraction. Angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEi/ARB) were not permitted initially, and the proportion of users was restricted in CHARM-Preserved and I-Preserve. A mineralocorticoid receptor antagonist (MRA) was not permitted in TOPCAT and FINEARTS-HF. A sodium–glucose cotransporter 2 inhibitor (SGLT2i) was not permitted in EMPEROR-Preserved and DELIVER. ARNI, angiotensin receptor–neprilysin inhibitor; CHARM-Preserved, Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity; DELIVER, Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure; EMPEROR-Preserved, Empagliflozin Outcome Trial in Patients With Chronic Heart Failure with Preserved Ejection Fraction; FINEARTS-HF, Finerenone Trial to Investigate Efficacy and Safety Superior to Placebo in Patients with Heart Failure; I-Preserve, Irbesartan in Heart Failure With Preserved Ejection Fraction; PARAGON-HF, Prospective Comparison of ARNI with ARB Global Outcomes in Heart Failure with Preserved Ejection Fraction; TOPCAT, Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist.

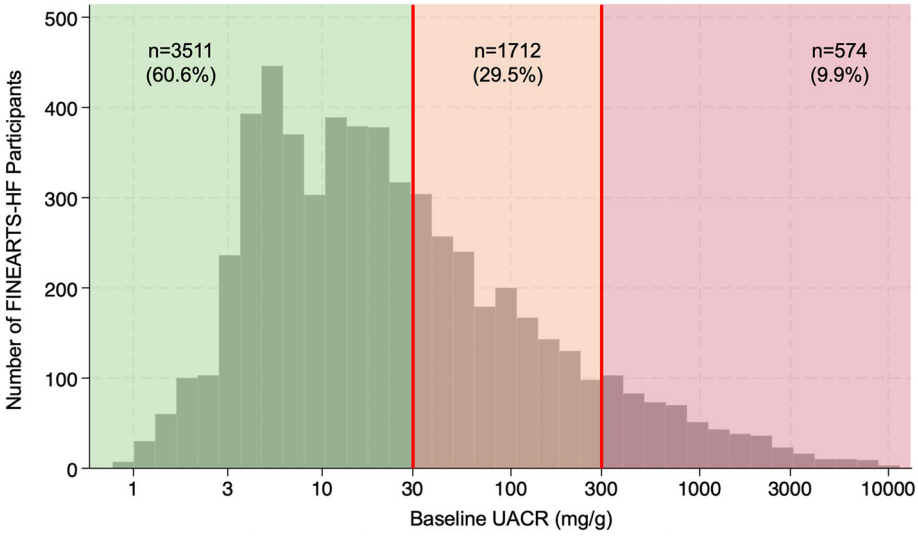


Figure 4 Distribution of baseline urine albumin-to-creatinine ratio (UACR) in FINEARTS-HF participants. UACR available at baseline in 5797 (97%) FINEARTS-HF participants. The vertical red lines at UACR = 30 mg/g and UACR = 300 mg/g represent contemporary thresholds recommended by Kidney Disease: Improving Global Outcomes (KDIGO) for defining severity of albuminuria: <30 mg/g refers to normal or mildly increased albuminuria, 30–300 mg/g refers to moderately increased albuminuria, and >300 mg/g refers to severely increased albuminuria.

evidenced by relatively high NYHA class and low average baseline KCCQ-TSS. Participants with recent worsening HF events are anticipated to face relatively higher event rates. In addition, 12% of FINEARTS-HF participants were enrolled during a hospitalization or urgent HF visit for worsening HF. Recent data have suggested that rapid implementation of guideline-directed medical therapies including MRAs is safe and highly effective after a hospitalization for HF.[24] FINEARTS-HF will provide placebo-controlled prospective data informing the safety and efficacy of in-hospital initiation of non-steroidal MRAs.

FINEARTS-HF is targeting a high-risk population at the intersection of cardiovascular, kidney, and metabolic diseases. Despite an average eGFR >60 ml/min/1.73 m^2, nearly 40% of participants had evidence of moderately or severely increased levels of albuminuria.

The high prevalence of albuminuria among FINEARTS-HF participants mirrors the EMPEROR programme and emphasizes the key role of UACR screening in patients with HF to diagnose chronic kidney disease at earlier stages and to estimate risk of kidney disease progression.[25] Finerenone has also previously been shown to safely ameliorate cardiovascular-kidney risk in patients with type 2 diabetes and chronic kidney disease with or without a history of HF[14,15,26,27]; FINEARTS-HF will clarify whether finerenone will show similar safety and efficacy in patients with HF, with or without diabetes and with or without chronic kidney disease.

Participants in FINEARTS-HF are also well-treated with contemporary pharmacotherapies. During the conduct of the FINEARTS-HF trial, clinical trials demonstrated benefits with the use of SGLT2 inhibitors in this same target population, and investigators were encouraged to implement this new treatment once approved and available. Rates of use of SGLT2 inhibitors (14%) and an ARNI (9%) at baseline, while still modest, were the highest among contemporary HFmrEF/HFpEF trials, and these rates are expected to increase during the course of the trial. It is noteworthy that the high-risk patients with more recent worsening HF events were relatively better treated with background medical therapies. Analyses evaluating the effects of finerenone on patients who are enrolled at various time points following a HF event, and on various background medical regimens, including in the >800 participants co-treated with an SGLT2 inhibitor and >500 participants co-treated with an ARNI at baseline, are pre-specified.

In summary, FINEARTS-HF has enrolled a contemporary, well-treated, and high-risk population of patients with HFmrEF/HFpEF. This study will determine the safety and efficacy of finerenone in reducing cardiovascular death and worsening HF in this population.

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