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RESEARCH ARTICLE

Finerenone, glycaemic status, and heart failure with mildly reduced or preserved ejection fraction: A prespecified analysis of the FINEARTS-HF trial

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Aims The efficacy and safety of the non-steroidal mineralocorticoid receptor antagonist, finerenone, have not been examined in patients without diabetes. We examined the efficacy and safety of finerenone, compared with placebo, according to glycaemic status in FINEARTS-HF.

Methods and results A total of 6001 patients with heart failure (HF) with New York Heart Association functional class II–IV, left ventricular ejection fraction ≥40%, evidence of structural heart disease, and elevated N-terminal pro-B-type natriuretic peptide levels were randomized to finerenone or placebo. The effect of finerenone according to glycaemic status (i.e. normoglycaemia [no investigator-reported history of diabetes and glycated haemoglobin (HbA1c) <5.7%], pre-diabetes [no investigator-reported history of diabetes and HbA1c 5.7–6.4%] and diabetes [investigator-reported history of diabetes or HbA1c ≥6.5%]) at baseline were examined. The primary outcome was cardiovascular death and total worsening HF events. At baseline, 1243 (20.8%) patients were normoglycaemic, 1979 (33.1%) had pre-diabetes, and 2764 (46.2%) had diabetes. Compared with patients with normoglycaemia, those with diabetes, but not pre-diabetes, had a higher rate of the primary endpoint (normoglycaemia: reference; pre-diabetes: adjusted rate ratio [RR] 1.02, 95% confidence interval [CI] 0.84–1.23; diabetes: adjusted RR 1.32 [95% CI 1.11–1.58]). The benefit of finerenone on the primary outcome was consistent across glycaemic status (normoglycaemia: RR 0.85 [95% CI 0.63–1.14]; pre-diabetes: RR 0.85 [95% CI 0.66–1.08]; diabetes: RR 0.82 [95% CI 0.69–0.98]; $p_{interaction} = 0.93$). The effects of finerenone on the components of the primary outcome, all-cause death, composite kidney endpoints, and improvement in the Kansas City Cardiomyopathy Questionnaire total symptom score were not modified by glycaemic status.

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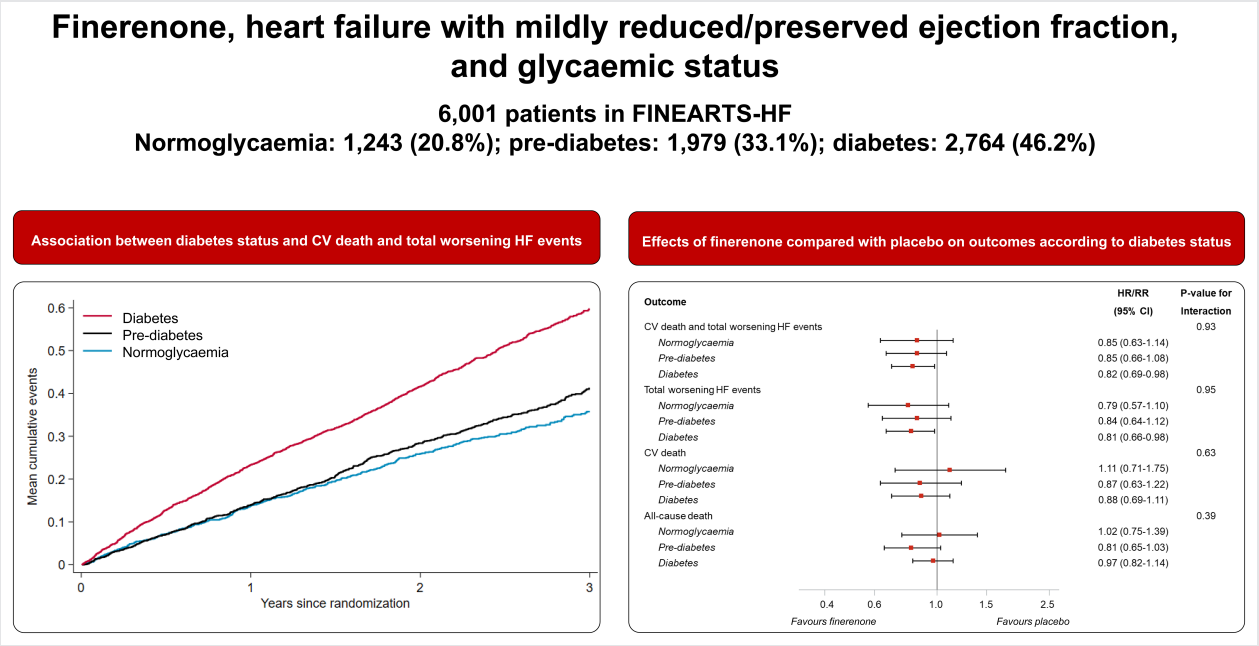
Conclusion In patients with HF with mildly reduced/preserved ejection fraction, the beneficial effects of finerenone, compared with placebo, on clinical events and symptoms, were consistent, irrespective of glycaemic status at baseline.

Graphical Abstract



Finerenone and glycaemic status in patients with heart failure with mildly reduced/preserved ejection fraction. CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; RR, rate ratio.

Keywords Heart failure with preserved ejection fraction • Mineralocorticoid receptor antagonist • Diabetes mellitus • Pre-diabetes • Glycated haemoglobin

Introduction

In two large clinical trials of patients with chronic kidney disease, the non-steroidal mineralocorticoid receptor antagonist (MRA), finerenone, led to a reduction in kidney and cardiovascular events, including hospitalizations for heart failure (HF).[1–3] In both trials, all participants had type 2 diabetes, and few had HF at baseline. Finerenone counteracts the pathophysiological consequences of mineralocorticoid receptor overactivation on the heart, vasculature, and kidney, which include myocardial hypertrophy and fibrosis, endothelial dysfunction, systemic hypertension, sodium retention, inflammation, and proteinuria.[4,5] Antagonizing these detrimental actions should benefit patients with HF and mildly reduced or preserved ejection fraction (HFmrEF/HFpEF), including those without diabetes.

In the Finerenone Trial to Investigate Efficacy and Safety Superior to Placebo in Patients with Heart Failure (FINEARTS-HF), which enrolled 6001 patients with HFmrEF/HFpEF, finerenone reduced the risk of the primary composite outcome of total (first and recurrent) worsening HF events and cardiovascular death, and improved health-related quality of life.[6–8] In FINEARTS-HF, approximately 60% of the participants did not have a history of diabetes at baseline, and this trial therefore represents the first opportunity to test the effects of finerenone in patients without diabetes. The subgroup analyses published in the main results paper for this trial demonstrated a consistent benefit of finerenone on the primary outcome. Here, we provide a detailed prespecified report of the effect of finerenone on all of the prospectively defined in FINEARTS-HF, along with a description of safety and tolerability, according to glycaemic status.

Methods

FINEARTS-HF was a randomized, double-blind, placebo-controlled trial in patients with symptomatic HFmrEF/HFpEF, investigating the

efficacy and safety of finerenone compared with matching placebo in addition to usual therapy. The design, baseline characteristics, and primary results of FINEARTS-HF are published.[6–8] The trial protocol was approved by the ethics committee at all participating institutions, and all patients provided written informed consent.

Trial patients

Key inclusion criteria were age ≥40 years, a diagnosis of HF, diuretic treatment for ≥30 days prior to randomization, New York Heart Association (NYHA) functional class II–IV, left ventricular ejection fraction (LVEF) ≥40%, evidence of structural heart disease (either left atrial enlargement or left ventricular hypertrophy), and elevated natriuretic peptide levels (N-terminal pro-B-type natriuretic peptide [NT-proBNP] ≥300 pg/ml or B-type natriuretic peptide [BNP] ≥100 pg/ml for patients in sinus rhythm; NT-proBNP ≥900 pg/ml or BNP ≥300 pg/ml for patients in atrial fibrillation), measured within 30 days prior to randomization in those without a recent worsening HF event or within 90 days in those with a recent worsening HF event. Both ambulatory and hospitalized patients were eligible for enrolment. Patients with prior LVEF <40% with subsequent improvement to ≥40% were also eligible for enrolment provided that ongoing HF symptoms were present. Key exclusion criteria were estimated glomerular filtration rate (eGFR) <25 ml/min/1.73 m^2 or serum/plasma potassium >5.0 mmol/L at screening or randomization; continuous (≥90 days) treatment with an MRA within 12 months, or treatment with an MRA within 30 days, prior to screening; systolic blood pressure ≥160 mmHg if not on treatment with ≥3 blood pressure-lowering medications; systolic blood pressure ≥180 mmHg irrespective of background antihypertensive therapy; or symptomatic hypotension with mean systolic blood pressure <90 mmHg at screening or at randomization. A complete list of exclusion criteria is provided in the design paper.[7]

Eligible participants were randomized in a 1:1 ratio to finerenone or matching placebo. Participants with an eGFR ≤60 ml/min/1.73 m^2 started 10 mg once daily with a maximum maintenance dose of 20 mg once daily, whereas participants with an eGFR >60 ml/min/1.73 m^2 started 20 mg once daily with a maximum maintenance dose of 40 mg once daily.

Glycaemic status at baseline

Data on medical conditions at baseline, including a history of diabetes, were investigator-reported and retrieved from the trial case report forms. Glycated haemoglobin (HbA1c) was measured at baseline, 1 month, 3, months, 6 months, 9 months, and 12 months, and every fourth month hereafter.

For purposes of this analysis, the population was divided as prespecified in the trial's Academic Statistical Analysis Plan into the following categories based on glycaemic status at baseline, derived from the most recent criteria of the American Diabetes Association and investigator-reported history of diabetes:[9] (1) normoglycaemia (no investigator-reported history of diabetes and baseline HbA1c <5.7% [<39 mmol/mol]); (2) pre-diabetes (no investigator-reported history of diabetes and baseline HbA1c 5.7–6.4% [39–47 mmol/mol]); and (3) diabetes (investigator-reported history of diabetes or baseline HbA1c ≥6.5% [48 mmol/mol]). Patients without a HbA1c measurement at baseline were categorized into either the normoglycaemic group or the diabetes group based on the investigator-reported history of diabetes.

Trial outcomes

The primary outcome in FINEARTS-HF was the composite of cardiovascular death and total (first and recurrent) HF events (i.e. HF hospitalization or urgent HF visit). The secondary outcomes were total (first and recurrent) HF events; improvement in NYHA class from baseline to 12 months; change in the Kansas City Cardiomyopathy Questionnaire (KCCQ) total symptom score (KCCQ-TSS) from baseline to 6, 9, and 12 months; composite kidney endpoint (defined as sustained decrease in eGFR ≥50% relative to baseline over at least 4 weeks, or sustained eGFR decline <15 ml/min/1.73 m^2, or initiation of dialysis or renal transplantation); and all-cause death. In the present analysis, we also examined major adverse cardiovascular events (defined as a composite of stroke, myocardial infarction, or cardiovascular death), a second composite kidney endpoint (defined as sustained decrease in eGFR ≥57%, sustained eGFR decline <15 ml/min/1.73 m^2, initiation of dialysis, or renal transplantation), a third composite kidney endpoint (defined as sustained decrease in eGFR ≥40%, sustained eGFR decline <15 ml/min/1.73 m^2, initiation of dialysis, or renal transplantation), new-onset micro- or macroalbuminuria (urine albumin-to-creatinine ratio [UACR] ≥30 mg/g; only patients with a UACR <30 mg/g at baseline were included), and new-onset macroalbuminuria (UACR ≥300 mg/g; only patients with a UACR <300 mg/g at baseline were included). All deaths and potential primary non-fatal events were adjudicated by an independent clinical events committee.

As prespecified in the Academic Statistical Analysis Plan, the primary outcome and secondary outcomes were analysed by investigator-reported history of diabetes, glycaemic status at baseline, and across baseline HbA1c levels as a continuous measure.

Prespecified safety analyses included hyperkalaemia, hypokalaemia, hypotension, and elevations in serum creatinine levels. Safety analyses were only performed in patients who had received at least one dose of either finerenone or placebo.

Statistical analyses

Baseline characteristics were summarized as frequencies with percentages, means with standard deviations, or medians with interquartile ranges, and differences were tested using the chi-square test for binary or categorical variables and the Wilcoxon test and two-sample *t*-test for non-normal and normally distributed continuous variables, respectively.

The association between glycaemic status and clinical outcomes was evaluated using Cox proportional-hazards models for time-to-event data and semiparametric proportional-rates models for total (first and recurrent) events,[10] and hazard ratios (HR) and rate ratios (RR), respectively, were stratified according to geographic region and LVEF stratification (<60%, ≥60%) and adjusted for treatment assignment. In addition, HRs and RRs, stratified by geographic region and LVEF stratification and adjusted for treatment assignment, age, sex, systolic blood pressure, heart rate, body mass index, log of NT-proBNP, eGFR, LVEF, NYHA functional class, prior HF hospitalization, myocardial infarction or coronary revascularization, and atrial fibrillation/flutter were reported.

To compare the effects of finerenone versus placebo on clinical outcomes according to glycaemic status, time-to-event data and total events were evaluated with Cox proportional-hazards models and semiparametric proportional-rates models, respectively, and these models were stratified according to geographic region and LVEF stratification. The effect of finerenone was also examined according to continuous HbA1c at baseline as a fractional polynomial. The proportion of

patients with improvement in NYHA class from baseline to 12 months was analysed using a logistic regression model, adjusted for geographic region and LVEF stratification, and odds ratios were reported.

The change in KCCQ-TSS from baseline to 12 months was summarized as means and standard deviations within each subgroup at 12 months, and the effect of finerenone versus placebo on the change in KCCQ-TSS from baseline to 12 months was estimated using a linear regression model within each subgroup, adjusted for baseline KCCQ-TSS, geographic region, and LVEF stratification. Interaction was tested for using a likelihood ratio test.

All analyses were conducted using STATA version 18.0 (StataCorp., College Station, TX, USA).

Results

Of the 6001 patients randomized in FINEARTS-HF, 15 patients had an investigator-reported history of type 1 diabetes at baseline and were excluded from the analysis. The remaining 5986 patients comprised our study population, of whom 2439 (40.7%) had an investigator-reported history of diabetes and 3547 (59.3%) did not.

A HbA1c measurement at baseline was available in 5873 (98.1%) patients. The distribution of HbA1c levels is shown in online supplementary *Figure S1*. At baseline, 1243 (20.8%) patients were normoglycaemic (i.e. no investigator-reported history of diabetes and HbA1c <5.7%), 1979 (33.1%) had pre-diabetes (i.e. no investigator-reported history of diabetes and HbA1c 5.7–6.4%), and 2764 (46.2%) had diabetes (i.e. investigator-reported history of diabetes [$n = 2439$; 40.7%] or HbA1c ≥6.5% [$n = 325$; 5.4%]). The median HbA1c level at baseline was 6.1% (interquartile range [IQR] 5.7–6.7%) overall and 5.4% (IQR 5.2–5.6%) in patients without diabetes, 5.9% (IQR 5.8–6.1%) in participants with pre-diabetes and 6.8% (IQR 6.4–7.7%) in people with diabetes.

Patient characteristics according to glycaemic status

Investigator-reported history of diabetes

The baseline characteristics of patients according to a history of diabetes are shown in online supplementary *Table S1*. Compared to patients without a history of diabetes, those with diabetes were younger, more often male, and more likely to be current/former smokers, and they had a higher systolic blood pressure, body mass index, blood urea nitrogen, and UACR levels, but lower eGFR. Although there were no significant differences in LVEF and NT-proBNP levels between patients with and without a history of diabetes, those with diabetes had a more advanced NYHA functional class and lower (worse) KCCQ scores, and they were more likely to have a prior HF hospitalization, ischaemic heart disease, peripheral artery disease, hypertension, and sleep apnoea, but were less likely to have atrial fibrillation/flutter.

Regarding pharmacological therapy, patients with diabetes were more frequently treated with an angiotensin receptor blocker, sodium–glucose co-transporter 2 (SGLT2) inhibitor, and loop diuretic compared with individuals without diabetes (online supplementary *Table S1*). Of patients with diabetes, 28% were treated with insulin.

Glycaemic status at baseline (normoglycaemia, pre-diabetes, diabetes)

The baseline characteristics of patients according to glycaemic status at baseline are shown in *Table 1*. In general, patients with pre-diabetes had a phenotypic picture intermediate between those with normoglycaemia and diabetes, except for age (oldest in pre-diabetes), sex (more women in pre-diabetes), atrial fibrillation/flutter (highest prevalence in pre-diabetes), and sleep apnoea (lowest prevalence in pre-diabetes) (*Table 1*).

Clinical outcomes according to glycaemic status

Investigator-reported history of diabetes

Patients with a history of diabetes had a significantly higher risk of all clinical outcomes compared with those without (online supplementary *Table S2*, *Figure 1*, and *graphical abstract*). After adjustment for other recognized prognostic variables, these associations persisted (online supplementary *Table S2*).

Glycaemic status at baseline (normoglycaemia, pre-diabetes, diabetes)

Compared with patients with normoglycaemia, patients with diabetes, but not pre-diabetes, had a significantly higher risk of all clinical outcomes (*Table 2*, *Figure 1* and *graphical abstract*). After adjustment for prognostic variables, these associations persisted (*Table 2*).

Effects of finerenone on clinical outcomes according to glycaemic status

Investigator-reported history of diabetes

Finerenone, compared with placebo, reduced the risk of total (first and recurrent) worsening HF events and cardiovascular death in the overall trial population (RR 0.84 [95% CI 0.74–0.95], $p = 0.007$). The reduction in risk was consistent in patients with (RR 0.83 [95% CI, 0.69–1.00], $p = 0.06$) and without a history of diabetes (RR 0.84 [0.70–1.00], $p = 0.05$), with no interaction between diabetes and effect of treatment ($p_{interaction} = 0.91$) (online supplementary *Table S3*, *Figure 2*). The effects of finerenone on secondary clinical outcomes were consistent regardless of a history of diabetes (online supplementary *Table S3*, *Figure 2*). The effect of finerenone on the main kidney composite endpoint was not modified by a history of diabetes ($p_{interaction} = 0.31$). Finerenone reduced the risk of both new-onset micro- and macroalbuminuria, regardless of a history of diabetes ($p_{interaction} = 0.68$ and 0.99, respectively).

The mean increase in KCCQ-TSS from baseline to 12 months was greater with finerenone compared with placebo in both patients with and without a history of diabetes ($p_{interaction} = 0.58$) (online supplementary *Table S3*). The effect of finerenone on improvement in NYHA class from baseline to 12 months was not modified by a history of diabetes ($p_{interaction} = 0.64$).

Patients with diabetes were at greater risk of hyperkalaemia than those without. Participants in the finerenone treatment arm were

Table 1 Baseline characteristics according to glycaemic status at baseline (normoglycaemia, pre-diabetes, diabetes)

	Normoglycaemia ($n = 1243$)	Pre-diabetes ($n = 1979$)	Diabetes ($n = 2764$)	*p*-value
Age (years), mean ± SD	71.8 ± 10.1	72.8 ± 9.9	71.5 ± 9.2	<0.001
Sex, *n* (%)				0.005
Men	663 (53.3)	1032 (52.1)	1567 (56.7)	
Women	580 (46.7)	947 (47.9)	1197 (43.3)	
Race, *n* (%)				0.007
White	1015 (81.7)	1511 (76.4)	2195 (79.4)	
Black	16 (1.3)	26 (1.3)	46 (1.7)	
Asian	176 (14.2)	370 (18.7)	449 (16.2)	
Other	36 (2.9)	72 (3.6)	74 (2.7)	
Geographic region, *n* (%)				<0.001
Western Europe, Oceania and others	278 (22.4)	415 (21.0)	558 (20.2)	
Eastern Europe	552 (44.4)	877 (44.3)	1216 (44.0)	
Asia	171 (13.8)	370 (18.7)	441 (16.0)	
North America	100 (8.0)	121 (6.1)	246 (8.9)	
Latin America	142 (11.4)	196 (9.9)	303 (11.0)	
Physiological measures				
Systolic blood pressure (mmHg), mean (SD)	129.4 ± 15.4	128.6 ± 15.4	130.0 ± 15.2	0.013
Diastolic blood pressure (mmHg), mean (SD)	75.8 ± 10.2	76.1 ± 10.3	74.9 ± 10.5	<0.001
Heart rate (bpm), mean ± SD	70.2 ± 11.5	71.3 ± 11.8	72.1 ± 11.9	<0.001
Body mass index (kg/m^2), mean ± SD	29.0 ± 5.8	29.1 ± 6.0	31.0 ± 6.2	<0.001
Body mass index, *n* (%)				<0.001
<18.5	16 (1.3)	34 (1.7)	15 (0.5)	
18.5–24.9	307 (24.8)	486 (24.6)	441 (16.0)	
25.0–29.9	449 (36.2)	684 (34.6)	854 (31.0)	
30–34.9	284 (22.9)	457 (23.1)	802 (29.1)	
≥35.0	184 (14.8)	314 (15.9)	646 (23.4)	
Atrial fibrillation/flutter on ECG, *n* (%)	447 (36.0)	877 (44.5)	988 (35.9)	<0.001
Left bundle branch block on ECG, *n* (%)	56 (4.5)	75 (3.8)	107 (3.9)	0.57
NT-proBNP (pg/ml), median (IQR)	980 (410–1781)	1138 (490–1956)	1014 (438–2015)	0.001
Atrial fibrillation/flutter on ECG	1734 (1214–2772)	1613 (1146–2610)	1833 (1133–2928)	0.058
No atrial fibrillation/flutter on ECG	549 (300–1099)	576 (329–1309)	603 (303–1292)	0.10
HbA1c (%), mean ± SD	5.4 ± 0.3	6.0 ± 0.2	7.2 ± 1.3	<0.001
Creatinine (μmol/L), mean ± SD	94.8 ± 27.7	96.4 ± 27.6	104.3 ± 36.8	<0.001
eGFR (ml/min/1.73 m^2), mean ± SD	65.2 ± 19.6	63.0 ± 18.9	60.2 ± 20.2	<0.001
eGFR (ml/min/1.73 m^2), *n* (%)				<0.001
≥60	730 (58.7)	1076 (54.4)	1299 (47.0)	
<60	513 (41.3)	903 (45.6)	1465 (53.0)	
Urine albumin-to-creatinine ratio (mg/g), median (IQR)	11.0 (5.0–32.0)	15.0 (6.0–45.0)	29.5 (10.0–131.0)	<0.001
Urine albumin-to-creatinine ratio (mg/g), *n* (%)				<0.001
<30	870 (73.4)	1297 (67.4)	1336 (50.0)	
30–299	265 (22.3)	533 (27.7)	908 (34.0)	
≥300	51 (4.3)	95 (4.9)	428 (16.0)	
Potassium (mmol/L), mean ± SD	4.3 ± 0.5	4.4 ± 0.5	4.4 ± 0.5	0.004
Sodium (mmol/L), mean ± SD	141.0 ± 3.0	140.9 ± 2.8	140.4 ± 3.1	<0.001
Haemoglobin (g/L), mean ± SD	134.6 ± 16.2	135.7 ± 15.6	132.3 ± 17.2	<0.001
Alanine aminotransferase (U/L), mean (SD)	20.5 ± 13.9	20.9 ± 15.1	20.5 ± 12.4	0.52
Bilirubin (mg/dl), mean ± SD	0.7 ± 0.4	0.7 ± 0.4	0.6 ± 0.4	<0.001
Alkaline phosphatase (U/L), mean ± SD	84.3 ± 31.0	85.2 ± 30.7	87.3 ± 37.1	0.018
Blood urea nitrogen (mg/dl), mean ± SD	21.0 ± 8.7	21.8 ± 8.4	24.1 ± 10.5	<0.001
Platelet count (10^9/L), mean ± SD	216.6 ± 66.4	218.5 ± 67.0	222.5 ± 70.6	0.029
White blood cell count (10^9/L), mean ± SD	6.3 ± 1.8	6.7 ± 2.1	7.3 ± 5.8	<0.001
Smoking status, *n* (%)				0.044
Never	783 (63.0)	1255 (63.4)	1647 (59.6)	
Former	367 (29.5)	559 (28.2)	864 (31.3)	
Current	93 (7.5)	165 (8.3)	253 (9.2)	

Table 1 (Continued)

	Normoglycaemia ($n = 1243$)	Pre-diabetes ($n = 1979$)	Diabetes ($n = 2764$)	*p*-value
LVEF (%), mean ± SD	53.1 ± 8.1	52.3 ± 7.8	52.5 ± 7.6	0.012
LVEF (%), *n* (%)				0.008
<50%	419 (33.8)	752 (38.0)	1000 (36.2)	
50–59%	547 (44.1)	884 (44.7)	1238 (44.9)	
≥60%	275 (22.2)	341 (17.2)	522 (18.9)	
NYHA class, *n* (%)				<0.001
II	921 (74.2)	1376 (69.5)	1840 (66.6)	
III	314 (25.3)	594 (30.0)	899 (32.5)	
IV	7 (0.6)	9 (0.5)	25 (0.9)	
KCCQ-TSS, mean ± SD	68.7 ± 22.9	68.8 ± 22.9	65.0 ± 24.9	<0.001
KCCQ-CSS, mean ± SD	67.1 ± 21.5	67.5 ± 21.5	63.1 ± 23.3	<0.001
KCCQ-OSS, mean ± SD	64.4 ± 21.5	64.6 ± 21.5	60.8 ± 22.9	<0.001
Medical history, *n* (%)				
Hospitalization for HF	701 (56.4)	1173 (59.3)	1737 (62.8)	<0.001
Time from last HF hospitalization				0.001
No prior HF hospitalization	542 (43.6)	806 (40.7)	1027 (37.2)	
0–7 days	202 (16.3)	331 (16.7)	470 (17.0)	
8 days–3 months	299 (24.1)	549 (27.7)	769 (27.8)	
3–12 months	91 (7.3)	109 (5.5)	202 (7.3)	
>1 year	109 (8.8)	184 (9.3)	296 (10.7)	
Atrial fibrillation/flutter	707 (56.9)	1184 (59.8)	1423 (51.5)	<0.001
Stroke	166 (13.4)	271 (13.7)	393 (14.2)	0.74
Myocardial infarction	268 (21.6)	448 (22.6)	821 (29.7)	<0.001
PCI or CABG	342 (27.5)	617 (31.2)	1075 (38.9)	<0.001
Peripheral arterial occlusive disease	67 (5.4)	159 (8.0)	307 (11.1)	<0.001
Hypertension	1073 (86.3)	1690 (85.4)	2549 (92.2)	<0.001
Chronic obstructive pulmonary disease	130 (10.5)	263 (13.3)	378 (13.7)	0.015
Sleep apnoea	70 (5.6)	86 (4.3)	243 (8.8)	<0.001
History of LVEF <40%	50 (4.0)	96 (4.9)	125 (4.5)	0.55
Treatment, *n* (%)				
ACEi	460 (37.0)	704 (35.6)	986 (35.7)	0.67
ARB	400 (32.2)	676 (34.2)	1018 (36.8)	0.011
ARNI	94 (7.6)	172 (8.7)	247 (8.9)	0.35
Beta-blocker	1017 (81.8)	1678 (84.8)	2387 (86.4)	<0.001
SGLT2 inhibitor	70 (5.6)	107 (5.4)	639 (23.1)	<0.001
Loop diuretic	1066 (85.8)	1714 (86.6)	2445 (88.5)	0.033
Any diuretic	1231 (99.0)	1954 (98.7)	2730 (98.8)	0.72
Digoxin	94 (7.6)	178 (9.0)	199 (7.2)	0.070
Pacemaker/CRT/ICD	83 (6.7)	144 (7.3)	185 (6.7)	0.70
Insulin	0 (0.0)	1 (0.1)	676 (24.5)	<0.001
Biguanide	6 (0.5)	6 (0.3)	1400 (50.7)	<0.001
Sulfonylurea	0 (0.0)	0 (0.0)	425 (15.4)	<0.001
DPP-4 inhibitor	0 (0.0)	0 (0.0)	440 (15.9)	<0.001
GLP-1 analogue	1 (0.1)	1 (0.1)	164 (5.9)	<0.001
Glitazone	0 (0.0)	0 (0.0)	31 (1.1)	<0.001
Glinide	0 (0.0)	0 (0.0)	39 (1.4)	<0.001
Alpha glucosidase inhibitor	0 (0.0)	0 (0.0)	61 (2.2)	<0.001

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor–neprilysin inhibitor; CABG, coronary artery bypass graft; CSS, clinical summary score; CRT, cardiac resynchronization therapy; DPP-4, dipeptidyl peptidase 4; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide-1; HbA1c, glycated haemoglobin; HF, heart failure; ICD, implantable cardioverter-defibrillator; IQR, interquartile range; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; NT-proBNP, N-terminal pro-B-type natriuretic peptide; OSS, overall summary score; PCI, percutaneous coronary intervention; SD, standard deviation; SGLT2, sodium–glucose co-transporter 2; TSS, total symptom score.

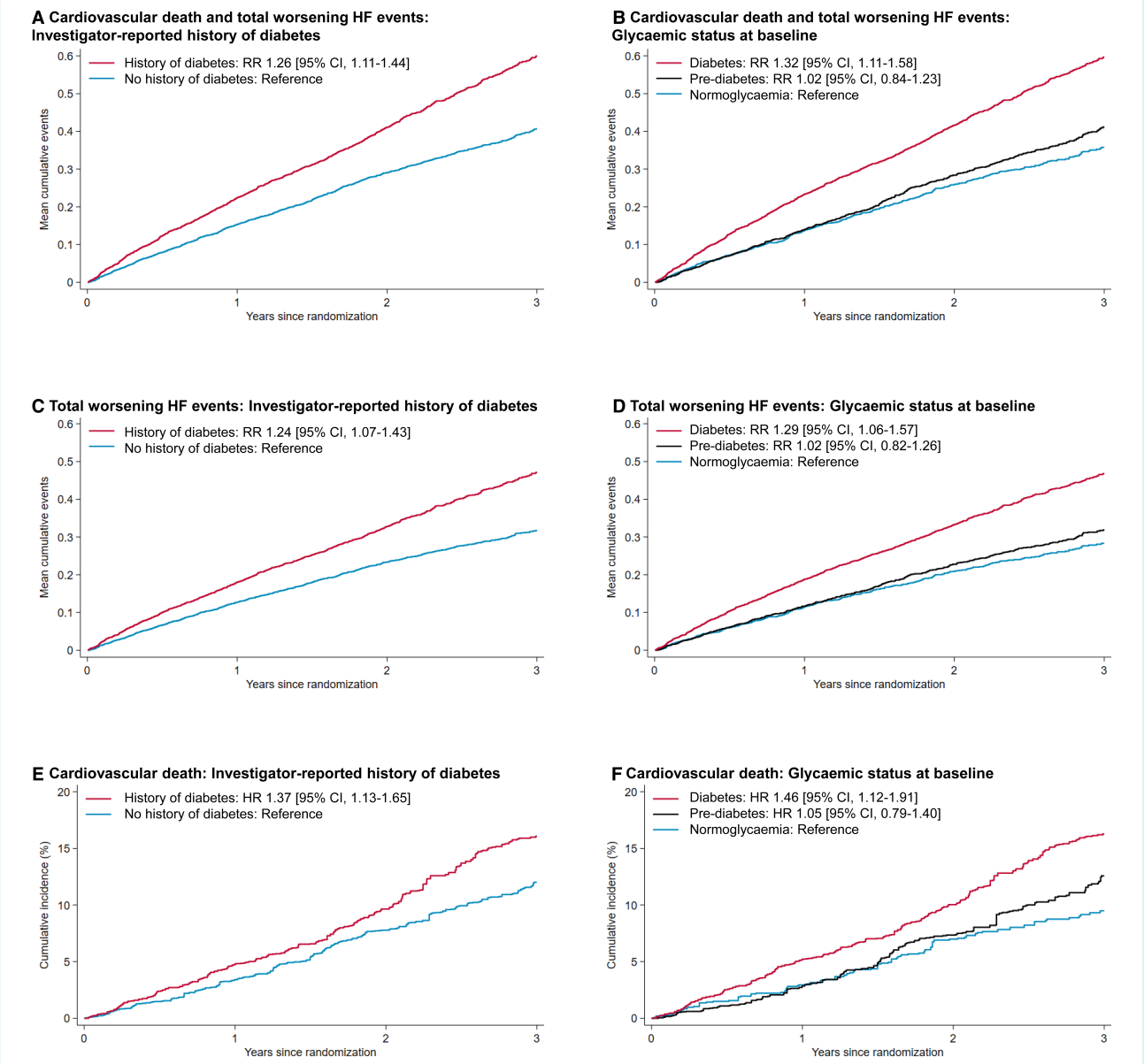


Figure 1 Outcomes according to diabetes history and glycaemic status. (*A*) Cardiovascular death and total worsening heart failure (HF) events: investigator-reported history of diabetes. (*B*) Cardiovascular death and total worsening HF events: glycaemic status at baseline. (*C*) Total worsening HF events: investigator-reported history of diabetes. (*D*) Total worsening HF events: glycaemic status at baseline. (*E*) Cardiovascular death: investigator-reported history of diabetes. (*F*) Cardiovascular death: glycaemic status at baseline. CI, confidence interval; HR, hazard ratio; RR, rate ratio. HRs and RRs were stratified by geographic region and left ventricular ejection fraction stratification and adjusted for treatment assignment, age, sex, systolic blood pressure, heart rate, body mass index, log of N-terminal pro-B-type natriuretic peptide, estimated glomerular filtration rate, left ventricular ejection fraction, New York Heart Association functional class, prior HF hospitalization, myocardial infarction or coronary revascularization, and atrial fibrillation/flutter.

more likely to experience increases in potassium and creatinine levels, and a decrease in systolic blood pressure (to <100 mmHg), compared to participants in the placebo arm. These findings were similar in patients with and without a history of diabetes (online supplementary *Table S4*). Conversely, finerenone reduced the risk of hypokalaemia compared to placebo (online supplementary *Table S4*).

Glycaemic status at baseline (normoglycaemia, pre-diabetes, diabetes)

Finerenone, compared with placebo, reduced the risk of total worsening HF events and cardiovascular death in the overall trial population (RR 0.84 [95% CI, 0.74–0.95], $p = 0.007$). The reduction in risk was consistent, irrespective of glycaemic status at baseline, with no interaction between diabetes and the effect

Table 2 Outcomes according to glycaemic status at baseline (normoglycaemia, pre-diabetes, diabetes)

	Normoglycaemia ($n = 1243$)	Pre-diabetes ($n = 1979$)	Diabetes ($n = 2764$)
Cardiovascular death and total worsening HF events			
No. of events	381	662	1318
Event rate per 100 person-years (95% CI)	12.2 (10.5–14.2)	13.6 (12.1–15.4)	20.2 (18.5–22.1)
RR (95% CI)[a]	Reference	1.12 (0.93–1.36)	1.66 (1.40–1.97)
RR (95% CI)[b]	Reference	1.02 (0.84–1.23)	1.32 (1.11–1.58)
Total worsening HF events			
No. of events	305	521	1038
Event rate per 100 person-years (95% CI)	9.8 (8.3–11.6)	10.7 (9.3–12.3)	15.9 (14.4–17.6)
RR (95% CI)[a]	Reference	1.10 (0.89–1.37)	1.63 (1.34–1.98)
RR (95% CI)[b]	Reference	1.02 (0.82–1.26)	1.29 (1.06–1.57)
Cardiovascular death or first worsening HF event			
No. of events (%)	229 (18.4)	388 (19.6)	722 (26.1)
Event rate per 100 person-years (95% CI)	7.9 (6.9–9.0)	8.7 (7.8–9.6)	12.4 (11.5–13.4)
HR (95% CI)[a]	Reference	1.10 (0.93–1.30)	1.56 (1.34–1.81)
HR (95% CI)[b]	Reference	1.01 (0.85–1.19)	1.29 (1.11–1.51)
First worsening HF event			
No. of events (%)	183 (14.7)	303 (15.3)	565 (20.4)
Event rate per 100 person-years (95% CI)	6.3 (5.5–7.3)	6.8 (6.0–7.6)	9.7 (8.9–10.6)
HR (95% CI)[a]	Reference	1.07 (0.89–1.29)	1.52 (1.28–1.80)
HR (95% CI)[b]	Reference	1.00 (0.83–1.21)	1.25 (1.05–1.49)
Cardiovascular death			
No. of events (%)	76 (6.1)	142 (7.2)	281 (10.2)
Event rate per 100 person-years (95% CI)	2.4 (1.9–3.1)	2.9 (2.5–3.4)	4.3 (3.8–4.8)
HR (95% CI)[a]	Reference	1.22 (0.92–1.61)	1.80 (1.40–2.33)
HR (95% CI)[b]	Reference	1.05 (0.79–1.40)	1.46 (1.12–1.91)
All-cause death			
No. of events (%)	163 (13.1)	290 (14.7)	556 (20.1)
Event rate per 100 person-years (95% CI)	5.2 (4.5–6.1)	5.9 (5.3–6.7)	8.5 (7.8–9.2)
HR (95% CI)[a]	Reference	1.17 (0.96–1.42)	1.65 (1.38–1.96)
HR (95% CI)[b]	Reference	1.03 (0.85–1.26)	1.42 (1.18–1.70)
Sustained decrease in eGFR ≥50%, sustained eGFR decline <15 ml/min/1.73 m^2, initiation of dialysis, or renal transplantation			
No. of events (%)	19 (1.5)	30 (1.5)	81 (2.9)
Event rate per 100 person-years (95% CI)	0.7 (0.4–1.1)	0.7 (0.5–1.0)	1.4 (1.1–1.7)
HR (95% CI)[a]	Reference	1.00 (0.56–1.78)	2.12 (1.28–3.50)
HR (95% CI)[b]	Reference	1.10 (0.60–2.02)	1.96 (1.14–3.37)
Sustained decrease in eGFR ≥57%, sustained eGFR decline <15 ml/min/1.73 m^2, initiation of dialysis, or renal transplantation			
No. of events (%)	7 (0.6)	19 (1.0)	46 (1.7)
Event rate per 100 person-years (95% CI)	0.2 (0.1–0.5)	0.4 (0.3–0.7)	0.8 (0.6–1.1)
HR (95% CI)[a]	Reference	1.74 (0.73–4.19)	3.31 (1.49–7.36)
HR (95% CI)[b]	Reference	1.68 (0.69–4.06)	2.43 (1.08–5.50)
Sustained decrease in eGFR ≥40%, sustained eGFR decline <15 ml/min/1.73 m^2, initiation of dialysis, or renal transplantation			
No. of events (%)	49 (3.9)	83 (4.2)	178 (6.4)
Event rate per 100 person-years (95% CI)	1.8 (1.3–2.3)	1.9 (1.6–2.4)	3.2 (2.7–3.6)
HR (95% CI)[a]	Reference	1.09 (0.76–1.55)	1.79 (1.31–2.46)
HR (95% CI)[b]	Reference	1.11 (0.77–1.61)	1.75 (1.24–2.46)
Micro- or macroalbuminuria (patients without microalbuminuria at baseline)			
No. of events (%)	345/870 (39.7)	570/1297 (43.9)	706/1336 (52.8)
Event rate per 100 person-years (95% CI)	20.9 (18.8–23.2)	25.7 (23.6–27.9)	34.3 (31.9–37.0)
HR (95% CI)[a]	Reference	1.19 (1.04–1.36)	1.57 (1.38–1.79)
HR (95% CI)[b]	Reference	1.12 (0.98–1.29)	1.51 (1.32–1.73)

Table 2 (Continued)

	Normoglycaemia ($n = 1243$)	Pre-diabetes ($n = 1979$)	Diabetes ($n = 2764$)
Macroalbuminuria (patients without macroalbuminuria at baseline)			
No. of events (%)	92/1135 (8.1)	181/1830 (9.9)	361/2244 (16.1)
Event rate per 100 person-years (95% CI)	3.4 (2.7–4.1)	4.3 (3.7–5.0)	7.4 (6.7–8.2)
HR (95% CI)[a]	Reference	1.25 (0.97–1.61)	2.16 (1.71–2.71)
HR (95% CI)[b]	Reference	1.17 (0.91–1.51)	1.98 (1.56–2.51)
Stroke, myocardial infarction, or cardiovascular death			
No. of events (%)	125 (10.1)	211 (10.7)	421 (15.2)
Event rate per 100 person-years (95% CI)	4.1 (3.4–4.9)	4.4 (3.9–5.1)	6.7 (6.1–7.3)
HR (95% CI)[a]	Reference	1.09 (0.87–1.36)	1.64 (1.34–2.00)
HR (95% CI)[b]	Reference	0.97 (0.77–1.22)	1.32 (1.07–1.63)

CI, confidence interval; eGFR, estimated glomerular filtration rate; HF, heart failure; HR, hazard ratio; RR, rate ratio.
[a]Models were stratified by geographic region and left ventricular ejection fraction stratification and adjusted for treatment assignment.
[b]Models were stratified by geographic region and left ventricular ejection fraction stratification and adjusted for treatment assignment, age, sex, systolic blood pressure, heart rate, body mass index, log of N-terminal pro-B-type natriuretic peptide, eGFR, left ventricular ejection fraction, New York Heart Association functional class, prior HF hospitalization, myocardial infarction or coronary revascularization, and atrial fibrillation/flutter.

of treatment ($p_{interaction} = 0.93$) (*Table 3*, *Figure 2*). The RRs were (0.85 [95% CI 0.63–1.14], $p = 0.27$), (0.85 [0.66–1.08], $p = 0.19$), and (0.82 [0.69–0.98], $p = 0.03$) in patients with normoglycaemia, pre-diabetes, and diabetes at baseline, respectively. The effects of finerenone on secondary outcomes were not modified by glycaemic status at baseline (*Table 3*, *Figure 2* and *graphical abstract*).

The effects of finerenone, compared with placebo, on the incidence of abnormal laboratory measurements and vital signs were consistent, regardless of glycaemic status at baseline (*Table 4*).

Effect of finerenone according to glycated haemoglobin level at baseline

The effect of finerenone, compared with placebo, on the primary outcome, and each of its components, according to HbA1c levels at baseline analysed as a continuous variable are illustrated in *Figure 3*. The effects of finerenone were consistent, regardless of HbA1c level at baseline.

Discussion

The main finding from this prespecified analysis of FINEARTS-HF was that the effect of the non-steroidal MRA, finerenone, on the primary and key secondary outcomes did not differ in individuals with and without diabetes (or pre-diabetes) (*Graphical Abstract*). These data highlight the substantial and clinically meaningful benefits of finerenone in HFmrEF/HFpEF, irrespective of glycaemic status and provide evidence that finerenone is a new treatment option for patients with HFmrEF/HFpEF with and without diabetes.

Characteristics and outcomes according to glycaemic status

The proportions of patients with pre-diabetes and diabetes enrolled in FINEARTS-HF were similar to those in recent HFmrEF/HFpEF trials.[11–14] Also consistent with these other trials, the proportion of patients with undiagnosed diabetes was relatively high in FINEARTS-HF (5.6% of all participants; 9.5% of patients without a history of diabetes).[11–14] This finding underscores the importance of increased awareness among cardiologists about the possibility of comorbid diabetes in their patients and, perhaps, highlights the difficulty in diagnosing diabetes in individuals who may already experience fatigue and, due to treatment with diuretics, frequent urination and thirst.

The present analysis demonstrated substantial differences in the clinical profile across glycaemic status (and according to a history of diabetes), confirming findings from other contemporary trials.[11–14] In FINEARTS-HF, patients with diabetes were younger, more often male, and more obese, and they had a more advanced NYHA functional class and worse KCCQ scores. They also had worse kidney function and a higher prevalence of atherosclerotic disease, hypertension, and sleep apnoea, but a lower prevalence of atrial fibrillation/flutter. Therefore, it is not surprising that patients with diabetes had a substantially higher risk of worsening HF events and death compared to those without this condition, even after comprehensive adjustment for potential confounders. Although individuals with pre-diabetes had a phenotypic picture intermediate between those with normoglycaemia and diabetes, interestingly they did not have a significantly higher risk of these outcomes compared to normoglycaemic individuals, in keeping with previous reports in patients with HFmrEF/HFpEF.[11,12,14] The difference in risk associated with pre-diabetes and diabetes may be related to the duration and degree, of hyperglycaemia. The diagnosis of diabetes also leads to the initiation of glucose-lowering therapy and the safety of some types of anti-hyperglycaemic treatment, including insulin, is uncertain in patients with HF.

In FINEARTS-HF, 14% of study participants were treated with an SGLT2 inhibitor at baseline. The substantially higher rate of use of this therapy in patients with diabetes (23%), compared with normoglycaemic individuals (6%), was expected, since SGLT2

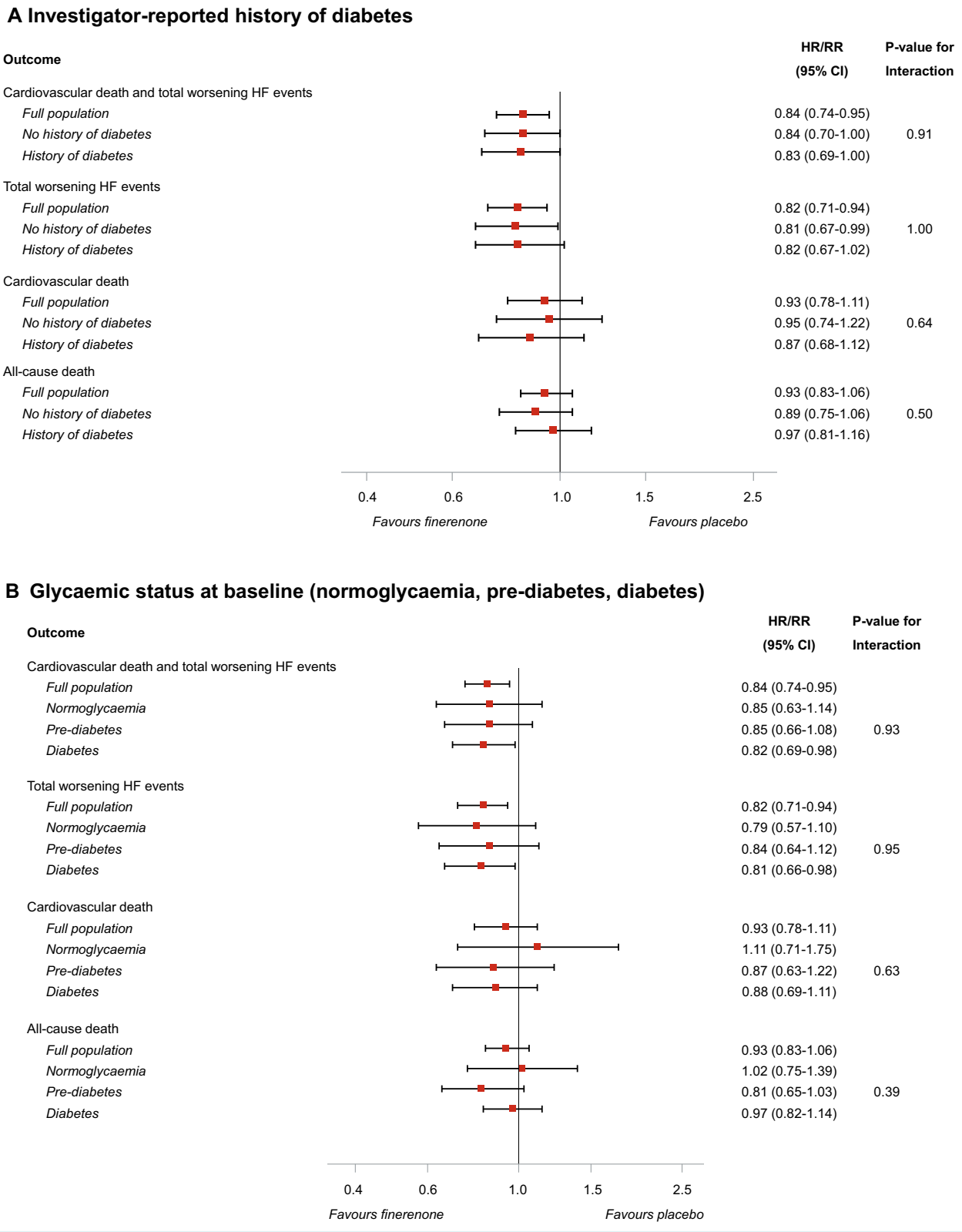


Figure 2 Effects of finerenone compared with placebo on outcomes according to diabetes history and glycaemic status. (*A*) Investigator-reported history of diabetes. (*B*) Glycaemic status at baseline (normoglycaemia, pre-diabetes, diabetes). CI, confidence interval; HF, heart failure; HR, hazard ratio; RR, rate ratio.

Table 3 Effects of finerenone compared with placebo on outcomes according to glycaemic status at baseline (normoglycaemia, pre-diabetes, diabetes)

	Full population ($n = 6001$)		Normoglycaemia ($n = 1243$)		Pre-diabetes ($n = 1979$)		Diabetes ($n = 2764$)		*p*-value for interaction
	Finerenone ($n = 3003$)	Placebo ($n = 2998$)	Finerenone ($n = 615$)	Placebo ($n = 628$)	Finerenone ($n = 991$)	Placebo ($n = 988$)	Finerenone ($n = 1389$)	Placebo ($n = 1375$)	
Cardiovascular death and total worsening HF events									0.93
No. of events	1083	1283	177	204	310	352	591	727	
Event rate per 100 person-years (95% CI)	14.9 (13.5–16.4)	17.7 (16.2–19.3)	11.5 (9.2–14.3)	13.0 (10.6–15.9)	12.7 (10.5–15.3)	14.6 (12.5–17)	18.1 (15.9–20.5)	22.4 (19.8–25.3)	
Rate ratio (95% CI)[a]	0.84 (0.74–0.95)		0.85 (0.63–1.14)		0.85 (0.66–1.08)		0.82 (0.69–0.98)		
Total worsening HF events									0.95
No. of events	842	1024	137	168	244	277	459	579	
Event rate per 100 person-years (95% CI)	11.6 (10.4–12.9)	14.1 (12.8–15.6)	8.9 (6.9–11.4)	10.7 (8.5–13.4)	10.0 (8.0–12.4)	11.5 (9.6–13.7)	14.0 (12.1–16.2)	17.8 (15.5–20.5)	
Rate ratio (95% CI)[a]	0.82 (0.71–0.94)		0.79 (0.57–1.10)		0.84 (0.64–1.12)		0.81 (0.66–0.98)		
Cardiovascular death or worsening HF event									0.74
No. of events (%)	624 (20.8)	719 (24.0)	110 (17.9)	119 (18.9)	176 (17.8)	212 (21.5)	334 (24.0)	388 (28.2)	
Event rate per 100 person-years (95% CI)	9.3 (8.6–10.1)	11.0 (10.2–11.8)	7.6 (6.3–9.2)	8.2 (6.8–9.9)	7.8 (6.7–9.0)	9.6 (8.4–11.0)	11.2 (10.1–12.5)	13.6 (12.3–15.1)	
Hazard ratio (95% CI)[a]	0.84 (0.76–0.94)		0.89 (0.69–1.16)		0.79 (0.65–0.97)		0.84 (0.72–0.97)		
First worsening HF event									0.93
No. of events (%)	479 (16.0)	573 (19.1)	85 (13.8)	98 (15.6)	138 (13.9)	165 (16.7)	255 (18.4)	310 (22.5)	
Event rate per 100 person-years (95% CI)	7.1 (6.5–7.8)	8.8 (8.1–9.5)	5.9 (4.8–7.3)	6.8 (5.5–8.3)	6.1 (5.1–7.2)	7.5 (6.4–8.7)	8.6 (7.6–9.7)	10.9 (9.7–12.2)	
Hazard ratio (95% CI)[a]	0.81 (0.72–0.92)		0.83 (0.62–1.12)		0.80 (0.64–1.00)		0.81 (0.68–0.95)		
Cardiovascular death									0.63
No. of events (%)	242 (8.1)	260 (8.7)	40 (6.5)	36 (5.7)	67 (6.8)	75 (7.6)	132 (9.5)	149 (10.8)	
Event rate per 100 person-years (95% CI)	3.3 (2.9–3.8)	3.6 (3.2–4.0)	2.6 (1.9–3.5)	2.3 (1.7–3.2)	2.7 (2.2–3.5)	3.1 (2.5–3.9)	4.0 (3.4–4.8)	4.6 (3.9–5.4)	
Hazard ratio (95% CI)[a]	0.93 (0.78–1.11)		1.11 (0.71–1.75)		0.87 (0.63–1.22)		0.88 (0.69–1.11)		
All-cause death									0.39
No. of events (%)	491 (16.4)	522 (17.4)	82 (13.3)	81 (12.9)	131 (13.2)	159 (16.1)	275 (19.8)	281 (20.4)	
Event rate per 100 person-years (95% CI)	6.7 (6.1–7.3)	7.2 (6.6–7.8)	5.3 (4.3–6.6)	5.1 (4.1–6.4)	5.3 (4.5–6.3)	6.6 (5.6–7.6)	8.3 (7.4–9.4)	8.6 (7.7–9.7)	
Hazard ratio (95% CI)[a]	0.93 (0.83–1.06)		1.02 (0.75–1.39)		0.81 (0.65–1.03)		0.97 (0.82–1.14)		
Sustained decrease in eGFR ≥50%, sustained eGFR decline <15 ml/min/1.73 m^2, initiation of dialysis, or renal transplantation									0.54
No. of events (%)	75 (2.5)	55 (1.8)	9 (1.5)	10 (1.6)	17 (1.7)	13 (1.3)	49 (3.5)	32 (2.3)	
Event rate per 100 person-years (95% CI)	1.2 (0.9–1.5)	0.9 (0.7–1.1)	0.7 (0.3–1.3)	0.7 (0.4–1.3)	0.8 (0.5–1.3)	0.6 (0.4–1.0)	1.7 (1.3–2.2)	1.1 (0.8–1.6)	
Hazard ratio (95% CI)[a]	1.33 (0.94–1.89)		0.89 (0.36–2.20)		1.20 (0.57–2.49)		1.54 (0.99–2.41)		
Sustained decrease in eGFR ≥57%, sustained eGFR decline <15 ml/min/1.73 m^2, initiation of dialysis, or renal transplantation									0.27
No. of events (%)	41 (1.4)	31 (1.0)	2 (0.3)	5 (0.8)	11 (1.1)	8 (0.8)	28 (2.0)	18 (1.3)	
Event rate per 100 person-years (95% CI)	0.6 (0.5–0.9)	0.5 (0.3–0.7)	0.1 (0.04–0.6)	0.3 (0.1–0.8)	0.5 (0.3–0.9)	0.4 (0.2–0.7)	1.0 (0.7–1.4)	0.6 (0.4–1.0)	
Hazard ratio (95% CI)[a]	1.28 (0.80–2.05)		0.40 (0.08–2.06)		1.21 (0.48–3.08)		1.59 (0.88–2.89)		
Sustained decrease in eGFR ≥40%, sustained eGFR decline <15 ml/min/1.73 m^2, initiation of dialysis, or renal transplantation									0.29
No. of events (%)	188 (6.3)	122 (4.1)	30 (4.9)	19 (3.0)	56 (5.7)	27 (2.7)	102 (7.3)	76 (5.5)	
Event rate per 100 person-years (95% CI)	3.0 (2.6–3.4)	1.9 (1.6–2.3)	2.2 (1.5–3.2)	1.3 (0.9–2.1)	2.6 (2.0–3.4)	1.3 (0.9–1.8)	3.6 (3.0–4.4)	2.7 (2.2–3.4)	
Hazard ratio (95% CI)[a]	1.55 (1.23–1.94)		1.66 (0.93–2.96)		2.17 (1.37–3.45)		1.34 (0.99–1.80)		
Micro- or macroalbuminuria (patients without microalbuminuria at baseline)									0.88
No. of events (%)	742/1765 (42.0)	884/1746 (50.6)	159/440 (36.1)	186/430 (43.4)	257/649 (39.6)	313/648 (48.3)	323/670 (48.2)	383/666 (57.5)	
Event rate per 100 person-years (95% CI)	23.4 (21.8–25.2)	31.9 (29.8–34.0)	18.2 (15.6–21.3)	23.8 (20.6–27.5)	21.9 (19.4–24.8)	29.9 (26.7–33.4)	29.0 (26.0–32.4)	40.6 (36.7–44.9)	
Hazard ratio (95% CI)[a]	0.76 (0.68–0.83)		0.78 (0.63–0.97)		0.73 (0.62–0.87)		0.76 (0.66–0.89)		
Macroalbuminuria (patients without macroalbuminuria at baseline)									0.34
No. of events (%)	250/2609 (9.6)	386/2614 (14.8)	30/561 (5.3)	62/574 (10.8)	76/925 (8.2)	105/905 (11.6)	143/1115 (12.8)	218/1129 (19.3)	
Event rate per 100 person-years (95% CI)	4.1 (3.6–4.7)	6.7 (6.0–7.4)	2.2 (1.5–3.1)	4.6 (3.6–5.9)	3.5 (2.8–4.4)	5.1 (4.2–6.2)	5.7 (4.9–6.8)	9.2 (8.0–10.5)	
Hazard ratio (95% CI)[a]	0.62 (0.53–0.73)		0.47 (0.30–0.72)		0.67 (0.50–0.90)		0.63 (0.51–0.78)		

Table 3 (Continued)

	Full population ($n = 6001$)		Normoglycaemia ($n = 1243$)		Pre-diabetes ($n = 1979$)		Diabetes ($n = 2764$)		*p*-value for interaction
	Finerenone ($n = 3003$)	Placebo ($n = 2998$)	Finerenone ($n = 615$)	Placebo ($n = 628$)	Finerenone ($n = 991$)	Placebo ($n = 988$)	Finerenone ($n = 1389$)	Placebo ($n = 1375$)	
Stroke, myocardial infarction, or cardiovascular death									0.14
No. of events (%)	388 (12.9)	373 (12.4)	72 (11.7)	53 (8.4)	101 (10.2)	110 (11.1)	211 (15.2)	210 (15.3)	
Event rate per 100 person-years (95% CI)	5.5 (5.0–6.1)	5.2 (4.7–5.8)	4.8 (3.8–6.1)	3.4 (2.6–4.5)	4.2 (3.5–5.1)	4.6 (3.8–5.6)	6.7 (5.8–7.7)	6.6 (5.8–7.6)	
Hazard ratio (95% CI)[a]	1.05 (0.91–1.21)		1.41 (0.99–2.02)		0.89 (0.68–1.16)		1.02 (0.84–1.23)		
Improvement in NYHA class from baseline to 12 months									0.20
No. (%)	557 (18.6)	553 (18.4)	117 (19)	108 (17)	170 (17)	192 (19)	270 (19)	251 (18)	
Odds ratio (95% CI)[b]	1.01 (0.88–1.15)		1.13 (0.85–1.52)		0.86 (0.68–1.08)		1.09 (0.90–1.31)		
Change in KCCQ-TSS from baseline to 12 months									0.93
Mean change (SD)	8.86 (21.28)	7.81 (21.26)	8.20 (19.94)	7.62 (21.00)	7.59 (19.65)	6.77 (19.73)	10.10 (22.95)	8.68 (22.42)	
Difference in mean (95% CI)[c]	1.66 (0.71–2.61)		1.82 (−0.11 to 3.75)		1.76 (0.19 to 3.33)		1.44 (−0.08 to 2.95)		

CI, confidence interval; eGFR, estimated glomerular filtration rate; HF, heart failure; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire total symptom score; NYHA, New York Heart Association; SD, standard deviation.
[a]Models were stratified by geographic region and left ventricular ejection fraction stratification.
[b]Models were adjusted for geographic region and left ventricular ejection fraction stratification.
[c]Models were adjusted for baseline value, geographic region, and left ventricular ejection fraction stratification.

inhibitors were originally developed as a treatment for individuals with type 2 diabetes, and the two clinical trials demonstrating benefits of SGLT2 inhibitors in HFmrEF/HFpEF were only published during the conduct of FINEARTS-HF.[15,16] However, despite that the use of SGLT2 inhibitors increased during the course of the trial (i.e. among patients who were not treated with an SGLT2 inhibitor at baseline, 13.0%, 15.3%, and 25.3% initiated this treatment in the normoglycaemic, pre-diabetic, and diabetic group, respectively), patients with diabetes remained at much higher risk than those without.

Effects of finerenone on clinical outcomes according to glycaemic status

The effects of steroidal MRAs according to glycaemic status have been examined in both patients with HF with reduced ejection fraction (HFrEF) and HFpEF. In two HFrEF trials, RALES and EMPHASIS-HF, the beneficial effects of steroidal MRAs spironolactone and eplerenone, respectively, on clinical outcomes, including HF hospitalizations and mortality, were evident in both patients with and without diabetes at baseline.[17–19]

Before FINEARTS-HF, the effects of the non-steroidal MRA, finerenone, had not been evaluated in large clinical trials of patients without diabetes, since both FIDELIO-DKD and FIGARO-DKD tested finerenone in individuals with type 2 diabetes across the spectrum of chronic kidney disease.[1–3] In this prespecified analysis of FINEARTS-HF, we demonstrated that the efficacy of finerenone on a range of clinical outcomes was not modified by a history of diabetes or glycaemic status at baseline. Specifically, finerenone, compared with placebo, reduced the risk of the primary composite outcome of cardiovascular death and total worsening HF events, as well as first and total worsening HF events, regardless of glycaemic status. Because patients with diabetes were at higher absolute risk, their absolute benefit was greater. Moreover, the benefits of finerenone were similar in participants with diabetes despite a relatively high rate of background SGLT2 inhibitor use in these individuals. Conversely, in TOPCAT, spironolactone did not show a significant reduction in the primary endpoint in patients with HFpEF although in a post hoc analysis restricted to patients enrolled in North and South America, there was a benefit, and this was consistent in patients with and without diabetes.[13]

In a combined analysis of FIDELIO-DKD and FIGARO-DKD (FIDELITY), finerenone reduced the risk of a composite kidney outcome (i.e. kidney failure, sustained decline in eGFR of ≥57%, or renal death) and end-stage kidney disease in patients with type 2 diabetes across the spectrum of chronic kidney disease and independently of HbA1c level.[3,20,21] In FINEARTS-HF, finerenone did not reduce the risk of kidney outcomes compared with placebo, and glycaemic status did not significantly modify the effect of finerenone on this outcome. While these findings appear to contrast with those of the FIDELITY meta-analysis, the rate of kidney events was substantially lower in FINEARTS-HF because the population was not specifically enriched for kidney risk. A similar disparity has been noted for renin–angiotensin system blockers in diabetic kidney disease and HF.[22–25] Importantly, finerenone did reduce the risk of new-onset micro- and macroalbuminuria

Table 4 Effects of finerenone compared with placebo on laboratory measures and systolic blood pressure according to glycaemic status at baseline (normoglycaemia, pre-diabetes, diabetes)

	Normoglycaemia *n* = 1241		Pre-diabetes *n* = 1974		Diabetes *n* = 2756		*p*-value for interaction
	Finerenone *n* = 614	Placebo *n* = 627	Finerenone *n* = 987	Placebo *n* = 987	Finerenone *n* = 1384	Placebo *n* = 1372	
Creatinine ≥2.5 mg/dL							0.84
No. of events (%)	19/592 (3.21)	11/606 (1.82)	32/956 (3.35)	22/950 (2.32)	90/1342 (6.71)	54/1325 (4.08)	
Odds ratio (95% CI)[a]	1.75 (0.82–3.73)		1.47 (0.85–2.55)		1.73 (1.22–2.45)		
Creatinine ≥3 mg/dL							0.40
No. of events (%)	10/592 (1.69)	3/606 (0.5)	8/956 (0.84)	7/950 (0.74)	39/1342 (2.91)	24/1325 (1.81)	
Odds ratio (95% CI)[a]	3.32 (0.91–12.17)		1.17 (0.42–3.24)		1.64 (0.98–2.75)		
Potassium >5.5 mmol/L							0.55
No. of events (%)	59/592 (9.97)	34/605 (5.62)	114/956 (11.92)	54/949 (5.69)	239/1343 (17.80)	107/1328 (8.06)	
Odds ratio (95% CI)[a]	1.89 (1.21–2.94)		2.39 (1.70–3.38)		2.47 (1.93–3.14)		
Potassium >6 mmol/L							0.89
No. of events (%)	13/592 (2.2)	6/605 (0.99)	23/956 (2.41)	13/949 (1.37)	50/1343 (3.72)	22/1328 (1.66)	
Odds ratio (95% CI)[a]	2.22 (0.83–5.91)		1.86 (0.93–3.71)		2.28 (1.37–3.80)		
Potassium <3.5 mmol/L							0.32
No. of events (%)	36/592 (6.08)	71/605 (11.74)	45/956 (4.71)	84/949 (8.85)	46/1343 (3.43)	126/1328 (9.49)	
Odds ratio (95% CI)[a]	0.48 (0.31–0.73)		0.48 (0.33–0.71)		0.34 (0.24–0.48)		
Systolic blood pressure <100 mmHg							0.96
No. of events (%)	116/597 (19.43)	77/609 (12.64)	204/961 (21.23)	129/955 (13.51)	215/1346 (15.97)	152/1333 (11.40)	
Odds ratio (95% CI)[a]	1.72 (1.24–2.40)		1.72 (1.33–2.23)		1.64 (1.30–2.07)		

CI, confidence interval.
A total of 15 randomized patients were excluded from the safety analysis, as these were performed in patients who had undergone randomization and received at least one dose of finerenone or placebo.
[a]Models were adjusted for geographic region and left ventricular ejection fraction stratification.

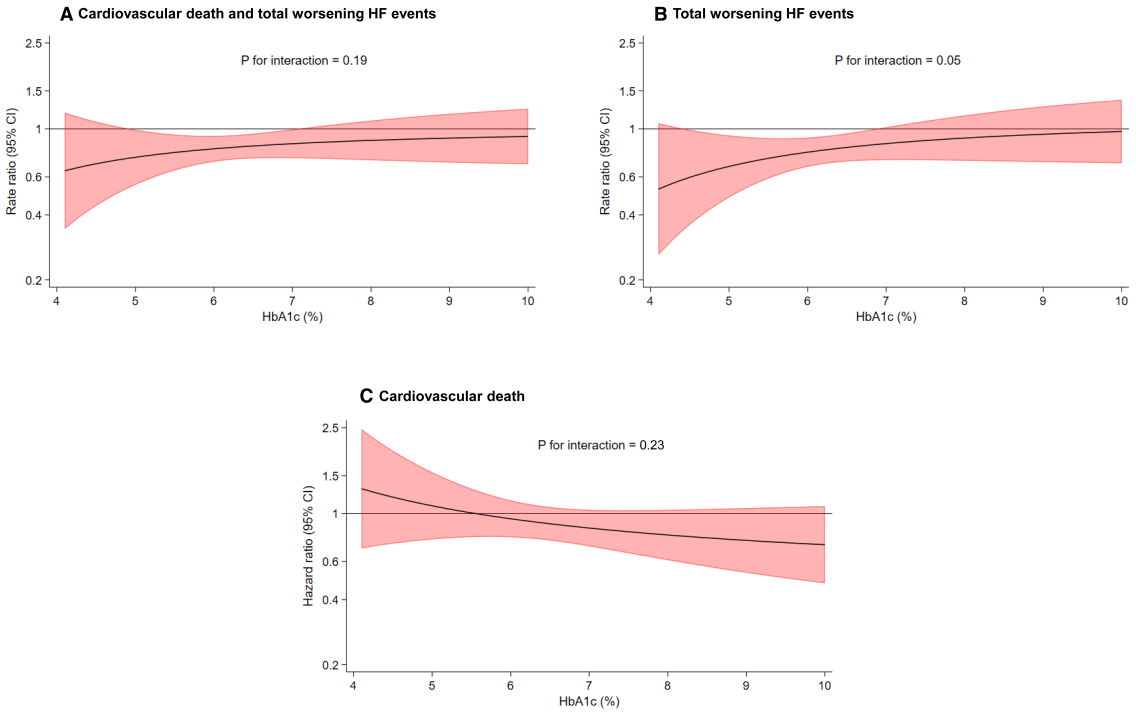


Figure 3 Effects of finerenone compared with placebo on outcomes according to continuous glycated haemoglobin (HbA1c) at baseline. (*A*) Cardiovascular death and total worsening heart failure (HF) events. (*B*) Total worsening HF events. (*C*) Cardiovascular death. CI, confidence interval.

in FINEARTS-HF, and this beneficial effect was evident across all glycaemic groups. The effect of finerenone on renal and cardiovascular outcomes in patients with chronic kidney disease but without diabetes is being investigated further in the FIND-CKD trial (NCT05047263).

A fundamental goal of the management of patients with HF is to reduce symptoms and improve physical function and quality of life.[26,27] Despite patients without diabetes having a lower symptom burden and better quality of life than those with diabetes, as confirmed by the KCCQ scores and NYHA functional class at baseline, finerenone improved the mean KCCQ-TSS after 12 months of treatment to a similar extent in both patients with and without diabetes (or pre-diabetes).

As anticipated, renal dysfunction and hyperkalaemia were more common among patients with diabetes, compared to no diabetes. Renal dysfunction and hyperkalaemia were also relatively more common with finerenone treatment compared to placebo, but the difference between therapies was similar in patients with normoglycaemia, pre-diabetes, and diabetes. Hypokalaemia occurred in a similar proportion of patients with and without diabetes (and pre-diabetes), and this risk was reduced by finerenone to a similar extent regardless of glycaemic status.

Limitations

The findings of this study should be viewed in the context of potential limitations. First, although this analysis was prespecified, the results reported in this study are based on subgroup analysis. The FINEARTS-HF trial was powered for the primary outcome in the overall population and was not adequately powered to investigate any subgroup. Second, a history of diabetes was determined by a question on the trial case report forms. Third, the diagnosis of previously unknown diabetes and pre-diabetes was based on only one measurement of HbA1c and not at least two measurements or supplementary analyses of non-fasting glucose, fasting glucose, and oral glucose tolerance, as recommended, which might have recategorized some patients. In addition, the lack of these supplementary analyses also limited the ability to differentiate between subtypes of pre-diabetes (i.e. impaired fasting glucose and impaired glucose tolerance). Fourth, a new diagnosis of diabetes or pre-diabetes during follow-up was not accounted for. Fifth, patients enrolled in clinical trials are selected according to specific inclusion and exclusion criteria, and our results may not be generalizable to all patients with HF in the general population. To date, finerenone has been studied in few patients with type 1 diabetes, and this population is being addressed further in the ongoing FINE-ONE trial (NCT05901831).

Conclusions

In this prespecified analysis of a randomized clinical trial of patients with HFmrEF/HFpEF, the non-steroidal MRA, finerenone, compared with placebo, reduced the risk of cardiovascular death and total worsening HF events, and was well-tolerated, independent of glycaemic status.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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Conflict of interest: J.H.B. reports advisory board honoraria from AstraZeneca and Bayer; consultant honoraria from Novartis and AstraZeneca; travel grants from AstraZeneca. P.S.J. reports speakers' fees from AstraZeneca, Novartis, Alkem Metabolics, ProAdWise Communications, Sun Pharmaceuticals; advisory board fees from AstraZeneca, Boehringer Ingelheim, Novartis; research funding from AstraZeneca, Boehringer Ingelheim, Analog Devices Inc, Roche Diagnostics. P.S.J.'s employer the University of Glasgow has been remunerated for clinical trial work from AstraZeneca, Bayer AG, Novartis and Novo Nordisk. A.D.H. has nothing to disclose. Director GCTP Ltd., B.L.C. has received personal consulting fees from Alnylam, Bristol Myers Squibb, Cardior, Cardurion, Corvia, CVRx, Eli Lilly, Intellia, Rocket, and has served on a data safety monitoring board for Novo Nordisk. A.S.D. has received institutional research grants (to Brigham and Women's Hospital) from Abbott, Alnylam, AstraZeneca, Bayer, Novartis, and Pfizer as well as personal consulting fees from Abbott, Alnylam, AstraZeneca, Bayer, Biofourmis, Boston Scientific, Medpace, Medtronic, Merck, Novartis, Parexel, Porter Health, Regeneron, River2Renal, Roche, Veristat, Verily, Zydus. C.S.P.L. has received research support from NovoNordisk and Roche Diagnostics; consulting fees from Alleviant Medical, Allysta Pharma, AnaCardio AB, Applied Therapeutics, AstraZeneca, Bayer, Biopeutics, Boehringer Ingelheim, Boston Scientific, Bristol Myers Squibb, CardioRenal, CPC Clinical Research, Eli Lilly, Impulse Dynamics, Intellia Therapeutics, Ionis Pharmaceutical, Janssen Research & Development LLC, Medscape/WebMD Global LLC, Merck, Novartis, Novo Nordisk, Prosciento Inc, Quidel Corporation, Radcliffe Group Ltd., Recardio Inc, ReCor Medical, Roche Diagnostics, Sanofi, Siemens Healthcare Diagnostics and Us2.ai; and is a co-founder and non-executive director of Us2.ai. M.B., P.S., P.V., A.L., and K.R. are employees of Bayer. M.S. has served on Advisory Boards, Consultancy and Honoraria for Novartis, Abbott, Merck, MSD, Vifor, AstraZeneca, Cardurion, Novonordisk, Bayer, Boehringer Ingelheim. S.J.S. has received research grants from NIH (U54 HL160273, X01 HL169712, R01 HL140731, R01 HL149423), AHA (24SFRNPCN1291224), AstraZeneca, Corvia, and Pfizer and consulting fees from Abbott, Alleviant, AstraZeneca, Amgen, Aria CV, Axon Therapies, Bayer, Boehringer Ingelheim, Boston Scientific, Bristol Myers Squibb, Cyclerion, Cytokinetics, Edwards Lifesciences, Eidos, Imara, Impulse Dynamics, Intellia, Ionis, Lilly, Merck, MyoKardia, Novartis, Novo Nordisk, Pfizer, Prothena, Regeneron, Rivus, Sardocor, Shifamed, Tenax, Tenaya, and Ultromics. A.A.V.'s employer received consultancy fees and/or research support from Adrenomed, Anacardio, AstraZeneca, Bayer AG, BMS, Boehringer Ingelheim, Corteria, EliLilly, Merck, Moderna, Novartis, Novo Nordisk, Roche diagnostics, SalubrisBio. F.Z. reports personal fees from 89Bio, Abbott, Acceleron, Applied Therapeutics, Bayer, Betagenon, Boehringer, BMS, CVRx, Cambrian, Cardior, Cereno pharmaceutical, Cellprothera, CEVA, Inventiva, KBP, Merck, NovoNordisk, Owkin, Otsuka, Roche Diagnostics, Northsea, USa2, having stock options at G3Pharmaceutical and equities at Cereno, Cardiorenal, Eshmoun Clinical research, and being the founder of Cardiovascular Clinical Trialists. B.P. is a consultant for Bayer, AstraZeneca, Boehringer Ingelheim, Lexicon,

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