Finerenone and new-onset diabetes in heart failure: a prespecified analysis of the FINEARTS-HF trial

Jawad H Butt, Pardeep S Jhund, Alasdair D Henderson, Brian L Claggett, Akshay S Desai, Prabhakar Viswanathan, Peter Kolkhof, Patrick Schloemer, Flaviana Amarante, Carolyn S P Lam, Michele Senni, Sanjiv J Shah, Adriaan A Voors, Faiez Zannad, Bertram Pitt, Muthiah Vaduganathan, Scott D Solomon, John J V McMurray, FINEARTS-HF Committees and Investigators

Summary

Background Data on the effect of mineralocorticoid receptor antagonist therapy on HbA_{1c} levels and new-onset diabetes are conflicting. We aimed to examine the effect of oral finerenone, compared with placebo, on incident diabetes in the Finerenone Trial to Investigate Efficacy and Safety Superior to Placebo in Patients with Heart Failure (FINEARTS-HF) trial.

Methods In this randomised, double-blind, placebo-controlled trial, 6001 participants with heart failure with New York Heart Association functional class II–IV, left ventricular ejection fraction 40% or higher, evidence of structural heart disease, and elevated N-terminal pro-B-type natriuretic peptide levels were randomly assigned to finerenone or placebo, administered orally. Randomisation was performed with concealed allocation. The primary outcome of the trial was the composite of cardiovascular death and total (first and recurrent) heart failure events (ie, heart failure hospitalisation or urgent heart failure visit). In the present analysis, participants with diabetes at baseline (investigator-reported history of diabetes or baseline HbA_{1c} ≥6·5%) were excluded. New-onset diabetes was defined as a HbA_{1c} measurement of 6·5% or higher on two consecutive follow-up visits or new initiation of glucose-lowering therapy. The full-analysis set comprised all participants randomly assigned to study treatment, analysed according to their treatment assignment irrespective of the treatment received (ie, intention to treat). The safety analysis set comprised participants randomly assigned to study treatment who took at least one dose of the investigational product, analysed according to the treatment actually received. This trial is registered with ClinicalTrials.gov, NCT04435626, and is closed to new participants.

Findings Between Sept 14, 2020, and Jan 10, 2023, 6001 participants were recruited and randomly assigned to finerenone or placebo. 3222 (53·7%) participants did not have diabetes at baseline and comprised the study population. During a median duration of follow-up of 31·3 months (IQR 21·5–36·3), 115 (7·2%) participants in the finerenone group and 147 (9·1%) in the placebo group developed new-onset diabetes, corresponding to a rate of 3·0 events per 100 person-years (95% CI 2·5–3·6) in the finerenone group and 3·9 events per 100 person-years (3·3–4·6) in the placebo group. Compared with placebo, finerenone significantly reduced the hazard of new-onset diabetes by 24% (hazard ratio [HR] 0·76 [95% CI 0·59–0·97], p=0·026). Fine–Gray competing risk analysis, accounting for the competing risk of death, yielded a similar finding (subdistribution HR 0·75 [0·59–0·96], p=0·024). Results were similar in sensitivity analyses, in which the definition of new-onset diabetes was expanded to include initiation of SGLT2 inhibitor treatment with diabetes as indication, restricted to HbA_{1c} measurements only, and restricted to new initiation of glucose-lowering drugs only (excluding SGLT2 inhibitor treatment). Findings were similar when participants treated with glucose-lowering drugs at baseline were excluded (n=15). The effect of finerenone, compared with placebo, on new-onset diabetes was consistent across key participant subgroups. Seven participants had an adverse event of new diabetes not captured by any of the definitions above.

Interpretation In participants with heart failure with mildly reduced or preserved ejection fraction without diabetes, oral finerenone reduced the hazard of new-onset diabetes, representing a meaningful additional clinical benefit of this treatment in these individuals.

Funding Bayer.

Lancet Diabetes Endocrinol 2025; 13: 107–18

Published Online January 13, 2025 https://doi.org/10.1016/S2213-8587(24)00309-7

See Comment page 78

British Heart Foundation Cardiovascular Research Centre, University of Glasgow, Glasgow, UK (J H Butt MD, Prof P S Jhund MBChB, A D Henderson PhD, Prof J J V McMurray MD); **Cardiovascular Division, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA** (B L Claggett PhD, A S Desai MD, M Vaduganathan MD, Prof S D Solomon MD); **Research & Development, Pharmaceuticals, Bayer, Whippany, NJ, USA** (P Viswanathan MBBS); **Research and Early Development, Cardiovascular, Renal and Immunology, Pharmaceuticals, Bayer, Wuppertal, Germany** (P Kolkhof PhD); **Research & Development, Pharmaceuticals, Bayer, Berlin, Germany** (P Schloemer PhD); **Research & Development, Pharmaceuticals, Bayer, São Paulo, Brazil** (F Amarante MD); **National Heart Centre Singapore and Duke-National University of Singapore, Singapore** (Prof C S P Lam MBBS PhD); **University of Milano-Bicocca ASST Papa Giovanni XXIII Hospital, Bergamo, Italy** (Prof M Senni MD); **Northwestern University Feinberg School of Medicine, Chicago, IL, USA** (Prof S J Shah MD); **University of Groningen, Groningen, Netherlands** (Prof A A Voors MD PhD); **University of Lorraine, Nancy, France** (Prof F Zannad MD); **University of Michigan, Ann Arbor, MI, USA** (Prof B Pitt MD)

Introduction

People with heart failure are at higher risk of developing new-onset diabetes than age-matched and sex-matched healthy individuals.[1,2] The development of diabetes has a detrimental effect on individuals with heart failure, as those with diabetes have worse heart failure symptoms and quality of life, more rapid decline in kidney function, higher rates of hospitalisation, and reduced survival compared with those without diabetes.[3–9] The increased risks related to diabetes have been repeatedly documented in both individuals with heart failure and reduced ejection fraction (HFrEF; ie, left ventricular ejection

Correspondence to:
Prof John J V McMurray, British Heart Foundation Cardiovascular Research Centre, University of Glasgow, Glasgow G12 8TA, UK
john.mcmurray@glasgow.ac.uk

Research in context

Evidence before this study

We searched PubMed for publications in English from database inception to Aug 1, 2024, using the search terms "heart failure", "mineralocorticoid receptor antagonists", and "diabetes". The steroidal mineralocorticoid receptor antagonist (MRA) spironolactone has consistently been associated with elevations in HbA_{1c} in individuals with and without diabetes. In the EMPHASIS-HF trial, which enrolled participants with heart failure and reduced ejection fraction, the steroidal MRA eplerenone did not reduce the risk of incident diabetes. In two large clinical trials of participants with chronic kidney disease and type 2 diabetes, the non-steroidal MRA finerenone led to a reduction in kidney and cardiovascular events, including hospitalisations for heart failure. In FINEARTS-HF, which enrolled participants with heart failure with mildly reduced or preserved ejection, with and without diabetes, finerenone reduced the hazard of the primary composite outcome of total (first and recurrent) worsening heart failure events and cardiovascular death, and improved health-related quality of life. We consider this evidence to have a low risk of bias.

Added value of this study

In participants with heart failure with mildly reduced or preserved ejection fraction, without diabetes, the non-steroidal MRA finerenone reduced the hazard of new-onset diabetes (defined as a HbA_{1c} measurement of ≥6·5% on two consecutive follow-up visits or new initiation of glucose-lowering therapy, excluding SGLT2 inhibitor treatment) by 24%. Results were similar in sensitivity analyses, in which the definition of new-onset diabetes was expanded to include initiation of SGLT2 inhibitor treatment with diabetes as indication, restricted to HbA_{1c} measurements only, and restricted to new initiation of glucose-lowering drugs only (excluding SGLT2 inhibitor treatment). The effect of finerenone, compared with placebo, on new-onset diabetes was consistent across key participant subgroups.

Implications of all the available evidence

In participants with heart failure with mildly reduced or preserved ejection fraction, without diabetes, finerenone reduced the hazard of new-onset diabetes, representing a meaningful additional clinical benefit of this treatment in these individuals.

fraction [LVEF] ≤40%) and those with mildly reduced (HFmrEF; ie, LVEF of 41–49%) or preserved (HFpEF; ie, LVEF ≥50%) ejection fraction,[3–9] and these risks might be greater in individuals with HFmrEF or HFpEF compared with those with HFrEF.[3–9] Individuals with HFmrEF or HFpEF might also have a higher incidence diabetes than those with HFrEF, because obesity is more prevalent in the former.[3–9]

The reasons for the increased incidence of diabetes in heart failure are uncertain, but heart failure is a state of insulin resistance, and activation of the renin–angiotensin–aldosterone system appears to contribute to this.[10,11] Angiotensin receptor blockers (ARBs), and possibly angiotensin-converting enzyme inhibitors, reduce the incidence of diabetes in individuals with heart failure (and in individuals with hypertension and impaired glucose tolerance as well).[12–14] Therefore, it is of interest to know whether mineralocorticoid receptor antagonists (MRAs) also affect the incidence of diabetes in individuals with heart failure. This question was addressed in the Finerenone Trial to Investigate Efficacy and Safety Superior to Placebo in Patients with Heart Failure trial (FINEARTS-HF), which enrolled 6001 participants with HFmrEF or HFpEF, with and without diabetes.[15,16] Finerenone is a non-steroidal MRA that counteracts the pathophysiological effects 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.[17,18] Antagonising these detrimental actions might also counteract several of the causes of glucose intolerance and reduce the incidence of new-onset diabetes.

See Online for appendix 1

In the overall FINEARTS-HF population, finerenone reduced the risk of the primary composite outcome of total (first and repeat) worsening heart failure events and cardiovascular death, and improved health-related quality of life.[19] In this analysis, we examined the efficacy of finerenone compared with placebo in preventing new-onset diabetes, which was a prespecified exploratory endpoint in FINEARTS-HF.

Methods

Study design

FINEARTS-HF was a randomised, double-blind, placebo-controlled trial in participants with symptomatic HFmrEF or 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.[15,16,19] The trial protocol (appendix 1 pp 1–284) was approved by the ethics committees at all participating institutions, and all participants provided written informed consent.

Trial participants

Key inclusion criteria were age 40 years or older, diuretic treatment for 30 days or more before randomisation, New York Heart Association (NYHA) functional class II–IV, LVEF 40% or higher, evidence of structural heart disease, and elevated natriuretic peptide levels. Both individuals who were ambulatory and hospitalised were eligible for enrolment. Individuals with previous LVEF lower than 40% with subsequent improvement to 40% or higher were also eligible for enrolment provided that ongoing heart failure symptoms were

present. Key exclusion criteria were estimated glomerular filtration rate (eGFR) lower than 25 mL/min/1·73 m² or serum or plasma potassium higher than 5·0 mmol/L at screening or randomisation. A complete list of exclusion criteria is provided in the design paper.[16]

For the purposes of this analysis, participants with diabetes at baseline (investigator-reported history of diabetes or baseline HbA_{1c} ≥6·5% [48 mmol/mol]) were excluded. The remaining participants, constituting our study population, were divided into the following categories based on glycaemic status at baseline, derived from the criteria of the American Diabetes Association:[20] normoglycaemia (no investigator-reported history of diabetes and baseline HbA_{1c} <5·7% [<39 mmol/mol]) and prediabetes (no investigator-reported history of diabetes and baseline HbA_{1c} 5·7–6·4% [39–47 mmol/mol]).

Randomisation and masking

Eligible participants were randomly assigned (1:1) to finerenone or matching placebo. Block randomisation was performed using block sizes of six and stratified according to geographic region (Western Europe and Oceania, Southwestern Europe, Central Europe, Southeastern Europe, Northeastern Europe, Asia, North America, or Latin America) and LVEF (<60% or ≥60%). Randomisation was performed with concealed allocation as detailed in the protocol (appendix 1 pp 1–284) and statistical analysis plan (appendix 1 pp 285–337).

Procedures

Participants with an eGFR of 60 mL/min/1·73 m² or lower started 10 mg of the assigned treatment once daily with a maximum maintenance dose of 20 mg once daily, whereas participants with an eGFR higher than 60 mL/min/1·73 m² started 20 mg once daily with a maximum maintenance dose of 40 mg once daily.

We measured HbA_{1c} at baseline, 1 month, 3, months, 6 months, 9 months, 12 months, and every fourth month thereafter.

Outcomes

The primary outcome was the composite of cardiovascular death and total (first and recurrent) heart failure events (ie, heart failure hospitalisation or urgent heart failure visit). The secondary outcomes were: total (first and recurrent) heart failure events; improvement in NYHA class from baseline to 12 months; change in the Kansas City Cardiomyopathy Questionnaire total symptom score (KCCQ-TSS) from baseline to 6, 9, and 12 months; composite kidney endpoint (defined as sustained decline in eGFR ≥50% relative to baseline over at least 4 weeks, sustained eGFR decline <15 mL/min/1·73 m², or initiation of dialysis or renal transplantation); and all-cause death. All deaths and potential primary non-fatal events were adjudicated by an independent clinical events committee.

The incidence of a new diagnosis of diabetes in participants without this condition at baseline was prespecified as an exploratory endpoint in the academic statistical analysis plan (appendix 1 pp 285–337) and is the focus of this report. We defined new-onset diabetes as a HbA_{1c} measurement of 6·5% or higher on two consecutive follow-up visits or the initiation of a glucose-lowering agent (ie, insulin, biguanides, sulfonylurea, DPP-4 inhibitors, GLP-1 analogues, glitazones, glinides, and alpha-glucosidase inhibitors). In the main analysis, initiation of SGLT2 inhibitor treatment was not included in the definition of new-onset diabetes because these agents were shown to be of benefit in participants with HFmrEF or HFpEF during the conduct of FINEARTS-HF.

In sensitivity analyses, we expanded the new-onset diabetes endpoint to include: initiation of SGLT2 inhibitor treatment, if the investigator-reported indication was diabetes; and adverse event reports, where diabetes was recorded as an adverse event.

We also examined the change in HbA_{1c} levels from baseline to 12 months.

Statistical analysis

We summarised baseline characteristics as frequency (%), mean (SD), or median (IQR), and we tested differences in baseline characteristics between participants who developed new-onset diabetes versus those who did not using the Fisher exact test or χ^2 test for binary or categorical variables, the Wilcoxon rank sum test for non-normally distributed continuous variables, and the two-sample *t* test for normally distributed continuous variables. We assessed normal distribution by graphical assessment (ie, histograms, boxplots, and quantile–quantile plots).

We analysed the change in HbA_{1c} levels from baseline to 12 months using mixed-effect models for repeated measurements and adjusted for baseline value, visit, treatment-by-visit interaction, geographic region, and

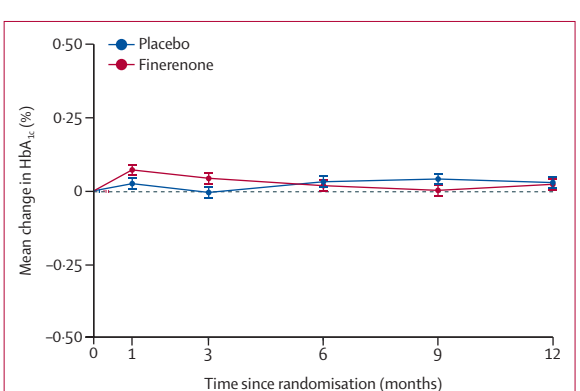

Figure 1: **Effect of finerenone compared with placebo on change in HbA_{1c} from baseline to 12 months in participants without diabetes at baseline**
Error bars represent 95% CIs. The mixed-effects model was adjusted for baseline value, visit, treatment-by-visit interaction, geographic region, and baseline LVEF.

See Online for appendix 2

	No new-onset diabetes (n=2960)	New-onset diabetes (n=262)	p value
Age, years	72·5 (9·9)	70·6 (10·4)	0·0025
Sex	..	..	0·24
Male	1548 (52·3%)	147 (56%)	..
Female	1412 (47·7%)	115 (44%)	..
Race	..	..	0·19
White	2331 (78·8%)	195 (74%)	..
Black	40 (1·4%)	2 (<1%)	..
Asian	489 (16·5%)	57 (22%)	..
Other	100 (3·4%)	8 (3%)	..
Geographic region	..	..	0·019
Western Europe, Oceania and Others	638 (21·6%)	55 (21%)	..
Eastern Europe	1305 (44·1%)	124 (47%)	..
Asia	486 (16·4%)	55 (21%)	..
North America	213 (7·2%)	8 (3%)	..
Latin America	318 (10·7%)	20 (8%)	..
Systolic blood pressure, mm Hg	128·9 (15·5)	129·3 (14·4)	0·66
Diastolic blood pressure, mm Hg	75·8 (10·3)	77·5 (9·2)	0·013
Heart rate, bpm	70·8 (11·8)	72·0 (11·1)	0·11
BMI	28·9 (5·9)	30·5 (6·2)	<0·0001
<18·5	49/2953 (1·7%)	1 (<1%)	0·0037
18·5–24·9	744/2953 (25·2%)	49 (19%)	0·0037
25·0–29·9	1048/2953 (35·5%)	85 (32%)	0·0037
30–34·9	670/2953 (22·7%)	71 (27%)	0·0037
≥35·0	442/2953 (15·0%)	56 (21%)	0·0037
Atrial fibrillation or flutter on ECG	1194/2950 (40·5%)	130 (50%)	0·0040
NT-proBNP, pg/mL	1067 (458–1885)	1075 (486–1937)	0·96
Atrial fibrillation or flutter on ECG	1685 (1196–2741)	1433 (1019–2339)	0·0019
No atrial fibrillation or flutter on ECG	570 (322–1196)	530 (257–1422)	0·61
HbA_{1c}, %	5·7% (0·4)	6·0% (0·4)	<0·0001
HbA_{1c}, mmol/mol	39·1 (4·0)	41·7 (4·2)	<0·0001
Creatinine, µmol/L	95·9 (27·7)	94·9 (26·6)	0·60
eGFR, mL/min/1·73m²	63·6 (19·2)	65·7 (19·1)	0·093
≥60	1648 (55·7%)	158 (60%)	0·15
<60	1312 (44·3%)	104 (40%)	0·15
Urine albumin-to-creatinine ratio, mg/g	13·0 (5·2–37·0)	21·0 (7·0–62·5)	<0·0001
<30	2018/2859 (70·6%)	149/252 (59%)	0·0001
30–299	717/2859 (25·1%)	81/252 (32%)	0·0001
≥300	124/2859 (4·3%)	22/252 (9%)	0·0001
Potassium, mmol/L	4·4 (0·5)	4·3 (0·5)	0·042
Sodium, mmol/L	140·9 (2·9)	141·1 (2·4)	0·21
Haemoglobin, g/L	135·1 (15·7)	137·5 (17·0)	0·021
Blood urea nitrogen, mg/dL	21·5 (8·5)	21·5 (9·0)	0·95
Platelet count, 10^9/L	218·2 (66·4)	213·7 (70·5)	0·31
White blood cell count, 10^9/L	6·5 (2·0)	6·8 (2·0)	0·017
Smoking status			
Never	1877 (63·4%)	161 (61%)	0·25
Former	853 (28·8%)	73 (28%)	0·25
Current	230 (7·8%)	28 (11%)	0·25
LVEF, %	52·7% (8·0)	51·7% (7·7)	0·052
<50	1055/2956 (35·7%)	116 (44%)	0·022

(Table 1 continues on next page)

baseline LVEF. We reported least-squares mean differences with 95% CIs between treatment groups.[21] For each treatment group, we estimated a separate covariance pattern on the basis of an unstructured covariance to adjust for within-subject variance. The assumption of normality, homogeneity of variance of residuals, and linearity of continuous predictors was fulfilled.

We calculated the incidence rate of new-onset diabetes as number of events per 100 person-years, and we estimated 95% CIs with Poisson regression with robust SEs. We calculated the cumulative incidence of new-onset diabetes using the Aalen–Johansen estimator to account for the competing risk of death, and we assessed the difference between treatment groups with the Gray test. We evaluated the effect of finerenone versus placebo on new-onset diabetes with Cox proportional hazards models, stratified according to geographic region (Western Europe and Oceania, Southwestern Europe, Central Europe, Southeastern Europe, Northeastern Europe, Asia, North America, or Latin America) and baseline LVEF (<60% or ≥60%), and adjusted for HbA_{1c} level at baseline, and we reported hazard ratios (HRs) with 95% CIs.[22] We stratified models according to the randomisation stratification variables as prespecified in the statistical analysis plan (appendix 1 pp 285–337). The proportional hazards assumption was examined with scaled Schoenfeld residuals and log(–log[survival]) curves and was not violated (appendix 2 p 11). The assumption of linearity was assessed by plotting the observed Martingale residuals against the values of continuous predictors and was not violated. We also performed a Fine–Gray competing risk analysis, with all-cause death considered a competing risk, and reported subdistribution HRs (ie, the instantaneous risk of the outcome of interest given that a participant has not already died for any reason) with 95% CIs.[23] In all models, we set both the origin and start time at the date of randomisation and followed participants until the date of development of diabetes (ie, the date of the first HbA_{1c} measurement of ≥6·5% or the initiation of a glucose-lowering agent), death, or last contact. In a sensitivity analysis, we used the date of the second (confirmatory) HbA_{1c} measurement of ≥6·5% (or the date of initiation of a glucose-lowering agent) as the time of new-onset diabetes.

We evaluated the association between new-onset diabetes and clinical outcomes using Cox proportional-hazards models for time-to-event data and semiparametric proportional-rates models for total (first and recurrent) events,[24] where an indicator of a new diabetes diagnosis was entered into the model as a time-updated covariate (with follow-up time starting at randomisation).[25] We attributed the period of risk before a new diagnosis of diabetes to the group with no diagnosis of diabetes for the calculation of incidence rates. We reported HRs for time-to-event data and rate

ratios (RRs) for total events, stratified according to geographic region and baseline LVEF and adjusted for treatment assignment. In addition, we reported HRs and RRs stratified by geographic region and baseline LVEF and adjusted for treatment assignment, age, sex, systolic blood pressure, heart rate, BMI, log of N-terminal pro-B-type natriuretic peptide (NT-proBNP), eGFR, LVEF, NYHA class, previous heart failure hospitalisation, ischaemic heart disease (ie, previous myocardial infarction or coronary revascularisation), and atrial fibrillation or flutter. We selected these covariates before analysis, and only included those we considered most relevant based on previous knowledge and literature.[26–29] In all models, we set both the origin and start time at the date of randomisation. In the time-to-event models, we followed participants until the date of the outcome of interest, death, or last contact; in the total events models, we followed participants until death or last contact.

We performed all analyses according to the intention-to-treat principle (ie, participants were analysed according to their randomly allocated treatment assignment, irrespective of the treatment received). We conducted all analyses using Stata version 18.0.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, writing of the report, or the decision to submit for publication.

Results

Of the 6001 participants randomly assigned, 1243 (20·7%) were normoglycaemic (ie, no investigator-reported history of diabetes and HbA_{1c} <5·7%), 1979 (33·0%) had prediabetes (ie, no investigator-reported history of diabetes and HbA_{1c} 5·7–6·4%), and 2779 (46·3%) had diabetes (ie, investigator-reported history of diabetes [including 15 participants with type 1 diabetes] or HbA_{1c} ≥6·5%). A HbA_{1c} measurement at baseline was available for 5888 (98·1%) participants, and the median HbA_{1c} level at baseline was 6·1% (IQR 5·7–6·7).

The baseline characteristics of participants according to glycaemic status are shown in appendix 2 (pp 2–3). Compared with participants with diabetes, those with normoglycaemia or prediabetes were older, more likely to be female, and less likely to be current or former smokers, and they had lower systolic blood pressure, heart rate, BMI, HbA_{1c}, blood urea nitrogen, and urine albumin-to-creatinine ratio but higher eGFR. Although there were no significant differences in LVEF and NT-proBNP levels between participants with and without diabetes, those with normoglycaemia or prediabetes had less advanced NYHA functional class and higher (better) KCCQ-TSS, and they were less likely to have a previous heart failure hospitalisation, ischaemic heart disease, peripheral artery disease, hypertension, and sleep apnoea, but were more likely to have atrial fibrillation or

	No new-onset diabetes (n=2960)	New-onset diabetes (n=262)	p value
(Continued from previous page)			
50-59	1329/2956 (45·0%)	102 (39%)	0·022
≥60	572/2956 (19·4%)	44 (17%)	0·022
New York Heart Association class			
II	2110 (71·3%)	187 (71%)	1·00
III	834 (28·2%)	74 (28%)	1·00
IV	15 (0·5%)	1 (<1%)	1·00
KCCQ-TSS	69·0 (22·8)	66·8 (23·8)	0·15
KCCQ-CSS	67·5 (21·5)	65·7 (22·4)	0·20
KCCQ-OSS	64·6 (21·4)	63·6 (22·2)	0·47
Medical history			
Prediabetes	1769 (59·8%)	210 (80%)	<0·0001
Hospitalisation for heart failure	1704 (57·6%)	170 (65%)	0·021
Time from last heart failure hospitalisation			
No previous heart failure hospitalisation	1256 (42·4%)	92 (35%)	0·010
0–7 days	480 (16·2%)	53 (20%)	0·010
8 days–3 months	781 (26·4%)	67 (26%)	0·010
3–12 months	173 (5·8%)	27 (10%)	0·010
>1 year	270 (9·1%)	23 (9%)	0·010
Atrial fibrillation or flutter	1718 (58·0%)	173 (66%)	0·012
Stroke	390 (13·2%)	47 (18%)	0·031
Myocardial infarction	650 (22·0%)	66 (25%)	0·23
PCI or CABG	866 (29·3%)	93 (35%)	0·034
Peripheral arterial occlusive disease	202 (6·8%)	24 (9%)	0·16
Hypertension	2528 (85·4%)	235 (90%)	0·057
Chronic obstructive pulmonary disease	363 (12·3%)	30 (11%)	0·70
Sleep apnoea	142 (4·8%)	14 (5%)	0·69
History of LVEF <40%	135 (4·6%)	11 (4%)	0·79
Treatment			
Angiotensin-converting enzyme inhibitor	1074 (36·3%)	90 (34%)	0·53
Angiotensin receptor blocker	976 (33·0%)	100 (38%)	0·087
Angiotensin receptor–neprilysin inhibitor	252 (8·5%)	14 (5%)	0·074
β-blocker	2467 (83·3%)	228 (87%)	0·12
SGLT2 inhibitor	164 (5·5%)	13 (5%)	0·69
Loop diuretic	2545 (86·0%)	235 (90%)	0·094
Any diuretic	2927 (98·9%)	258 (98%)	0·55
Digoxin	234 (7·9%)	38 (15%)	0·0002
Pacemaker/CRT/ICD	208 (7·0%)	19 (7%)	0·89
Insulin	1 (<0·1%)	0	1·00
Biguanide	12 (0·4%)	0	0·62
Sulfonylurea	0	0	1·00
DPP-4 inhibitor	0	0	1·00
GLP-1 receptor agonist	2 (<0·1%)	0	1·00
Glitazone	0	0	1·00
Glinide	0	0	1·00
Alpha-glucosidase inhibitor	0	0	1·00

Data are mean (SD), n (%), n/N (%), median (IQR), or p. ECG=electrocardiogram. NT-proBNP=N-terminal pro-B-type natriuretic peptide. eGFR=estimated glomerular filtration rate. LVEF=left ventricular ejection fraction. KCCQ=Kansas City Cardiomyopathy Questionnaire. TSS=total symptom score. CSS=clinical summary score. OSS=overall summary score. PCI=percutaneous coronary intervention. CABG=coronary artery bypass graft surgery. CRT=cardiac resynchronisation therapy. ICD=implantable cardioverter-defibrillator.

Table 1: **Baseline characteristics according to development of new-onset diabetes in participants without diabetes at baseline**

flutter. Regarding pharmacological therapy, participants with normoglycaemia or prediabetes were less frequently treated with an ARB, β-blocker, SGLT2 inhibitor, and loop diuretic compared with individuals with diabetes. One participant with prediabetes (baseline HbA_{1c} 6·3%) was treated with insulin (which can be used in individuals with prediabetes).

The population for these analyses comprised 3222 participants who did not have diabetes at baseline, of whom 1979 (61·4%) had prediabetes. A HbA_{1c} measurement at baseline was available in 3151 (97·8%) participants, and the median HbA_{1c} level was 5·8% (IQR 5·5–6·0%). The baseline characteristics according to treatment assignment in participants without diabetes at baseline are shown in appendix 2 (pp 4–5). The baseline characteristics were well balanced between participants assigned to receive finerenone or placebo.

In participants without diabetes at baseline, HbA_{1c} levels changed little during follow-up in either treatment group. Compared with placebo, finerenone did not affect HbA_{1c} levels (placebo-corrected mean change at 12 months –0·01 [95% CI –0·03 to 0·02], p=0·67; figure 1).

During a median follow-up of 31·3 months (IQR 21·5–36·3), 262 (8·1%) participants developed new-onset diabetes, of whom 176 fulfilled the HbA_{1c} criterion for new-onset diabetes. Among these 176 participants, 35 (20%) initiated glucose-lowering treatment excluding SGLT2 inhibitor treatment, and 45 (26%) initiated glucose-lowering treatment including SGLT2 inhibitor treatment.

Baseline characteristics according to the development of new-onset diabetes are shown in table 1. Compared with participants who did not develop diabetes, those who did were younger and more likely to have prediabetes, and they had higher BMI, urine albumin-to-creatinine ratio, and HbA_{1c} levels. They also had lower LVEF, but similar KCCQ-TSS and NYHA functional class. Participants who developed diabetes were more likely to have a previous heart failure hospitalisation, ischaemic heart disease, atrial fibrillation or flutter, and stroke than those who did not.

Data on the numbers and proportions of participants at risk and participants censored during follow-up according to treatment assignment are shown in appendix 2 (p 6). Overall, 115 (7·2%) participants in the finerenone group and 147 (9·1%) in the placebo group developed new-onset diabetes, corresponding to a rate of 3·0 events per 100 person-years (95% CI, 2·5–3·6) in the finerenone group and 3·9 events per 100 person-years

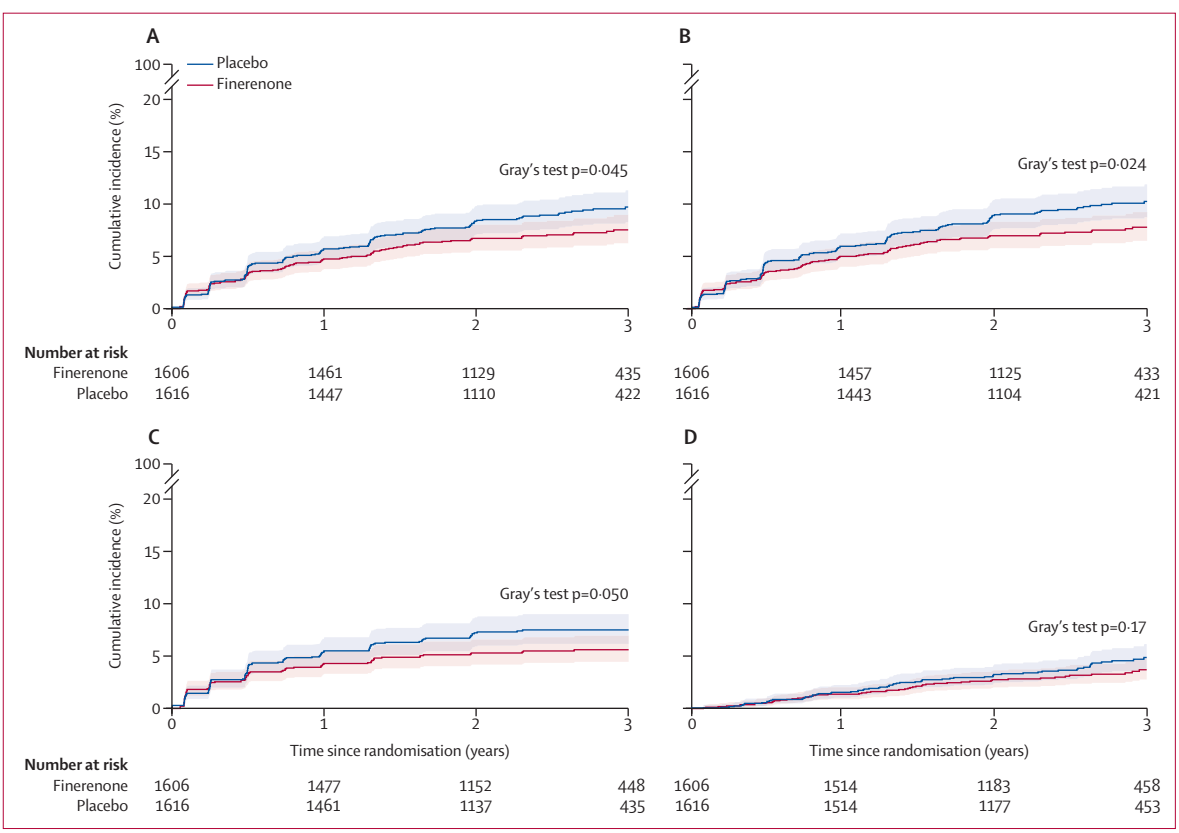

Figure 2: **Effect of finerenone compared with placebo on new-onset diabetes in participants without diabetes at baseline**
HbA_{1c} measurements or initiation of glucose-lowering drugs excluding (A) and including (B) SGLT2 inhibitors, HbA_{1c} measurements only (C), and initiation of glucose-lowering drugs excluding SGLT2 inhibitors (D). Shaded area represents 95% CI.

(3·3–4·6) in the placebo group (figure 2). Compared with placebo, finerenone significantly reduced the hazard of new-onset diabetes by 24% (HR 0·76 [95% CI 0·59–0·97], p=0·026). Fine–Gray competing risk analysis, accounting for the competing risk of death, yielded a similar finding (subdistribution HR 0·75 [0·59–0·96], p=0·024). Results were similar in sensitivity analyses, in which the definition of new-onset diabetes was expanded to include initiation of SGLT2 inhibitor treatment with diabetes as the indication, restricted to HbA_{1c} measurements only, and restricted to new initiation of glucose-lowering drugs only (excluding SGLT2 inhibitor treatment; table 2, figure 2). Data on the type of glucose-lowering drugs initiated during follow-up are shown in appendix 2 (p 7). The findings were similar when participants treated with glucose-lowering drugs at baseline were excluded (n=15; appendix 2 p 8). Similar findings were also yielded when the date of the second (confirmatory) HbA_{1c} measurement of 6·5% or higher was used as the time of new-onset diabetes (appendix 2 p 9). Analysis of adverse events identified seven participants reported as possible cases of new diabetes not captured by any of the definitions above. Four of these participants had a HbA_{1c} measurement of 6·5% or higher as the final measurement in the trial (of whom one initiated an SGLT2 inhibitor with heart failure as the indication), and therefore did not have a confirmatory measurement; two had a single HbA_{1c} measurement of 6·5% or higher not confirmed on a subsequent measurement (of whom one initiated an SGLT2 inhibitor with heart failure as the indication); and one participant did not have an elevated HbA_{1c} at any point (or initiate any glucose-lowering therapy). The inclusion of these seven participants in the analysis of new-onset diabetes defined by HbA_{1c} measurements and new initiation of glucose-lowering drugs (including initiation of SGLT2 inhibitor treatment with diabetes as the indication) did not change the findings (table 2).

The effect of finerenone, compared with placebo, on new-onset diabetes was consistent in both participants with normoglycaemia and those with prediabetes at baseline, regardless of the definition of new-onset diabetes (appendix 2 p 10). The effect of finerenone, compared with placebo, on new-onset diabetes was also consistent across other key subgroups, including age, sex, race, BMI, smoking status, NYHA class, KCCQ-TSS, LVEF, NT-proBNP, eGFR, and baseline medication (figure 3).

Data on the association between new-onset diabetes (as a time-updated covariate) and clinical outcomes are shown in table 3. The event rates associated with the development of new-onset diabetes were 23·5 events per 100 person-years for the primary composite endpoint, 18·0 events per 100 person-years for total worsening heart failure events, 5·5 events per 100 person-years for cardiovascular death, and 8·5 events per 100 person-years for all-cause death. For comparison, the corresponding event rates in the full FINEARTS-HF population were 16·3, 12·8, 3·5, and 6·9 events per 100 person-years. New-onset diabetes was associated with a higher risk of cardiovascular death and total worsening heart failure events and each of its components, as well as all-cause death, and these associations persisted after adjustment for other recognised prognostic variables. There was no interaction between new-onset diabetes and randomised treatment for any of the outcomes ($p_{interaction}$=0·90 for the primary outcome, 0·68 for total worsening heart failure events, 0·44 for cardiovascular death, and 0·26 for all-cause death), suggesting that the development of diabetes is associated with worse outcomes, regardless of treatment assignment.

	Finerenone (n=1606)	Placebo (n=1616)	p value
HbA_{1c} measurements or initiation of glucose-lowering drugs excluding SGLT2 inhibitors			
Events	115 (7·2%)	147 (9·1%)	..
Event rate per 100 person-years	3·0 (2·5 to 3·6)	3·9 (3·3 to 4·6)	..
Rate difference	–0·89 (–1·74 to –0·05)	..	..
HR*	0·76 (0·59 to 0·97)	..	0·026
Subdistribution HR†	0·75 (0·59 to 0·96)	..	0·024
HbA_{1c} measurements or initiation of glucose-lowering drugs including SGLT2 inhibitors			
Events	119 (7·4%)	156 (9·7%)	..
Event rate per 100 person-years	3·1 (2·6 to 3·8)	4·2 (3·6 to 4·9)	..
Rate difference	–1·03 (–1·90 to –0·17)	..	..
HR*	0·74 (0·58 to 0·94)	..	0·013
Subdistribution HR†	0·73 (0·58 to 0·93)	..	0·012
HbA_{1c} measurements, initiation of glucose-lowering drugs including SGLT2 inhibitors, or adverse events			
Events	123 (7·7%)	159 (9·8%)	..
Event rate per 100 person-years	3·2 (2·7 to 3·9)	4·3 (3·6 to 5·0)	..
Rate difference	–1·01 (–1·89 to –0·13)	..	..
HR*	0·74 (0·59 to 0·94)	..	0·015
Subdistribution HR†	0·74 (0·59 to 0·94)	..	0·015
HbA_{1c} measurements only			
Events	75 (4·7%)	101 (6·3%)	..
Event rate per 100 person-years	1·9 (1·5 to 2·4)	2·7 (2·2 to 3·2)	..
Rate difference	–0·71 (–1·39 to –0·02)	..	..
HR*	0·71 (0·52 to 0·96)	..	0·027
Subdistribution HR†	0·70 (0·52 to 0·95)	..	0·023
Initiation of glucose-lowering drugs excluding SGLT2 inhibitors			
Events	53 (3·3%)	68 (4·2%)	..
Event rate per 100 person-years	1·3 (1·0 to 1·8)	1·7 (1·4 to 2·2)	..
Rate difference	–0·39 (–0·94 to 0·16)	..	..
HR*	0·77 (0·54 to 1·11)	..	0·16
Subdistribution HR†	0·78 (0·54 to 1·11)	..	0·17

Data are n (%), effect size (95% CI), or p. HR=hazard ratio. *Models were stratified by geographic region and baseline LVEF and adjusted for HbA_{1c} levels at baseline. †Models were adjusted for geographic region baseline LVEF, and HbA_{1c} levels at baseline.

Table 2: **Effect of finerenone compared with placebo on new-onset diabetes in participants without diabetes at baseline**

Discussion

In this prespecified analysis of FINEARTS-HF, we confirmed that individuals with HFmrEF or HFpEF have

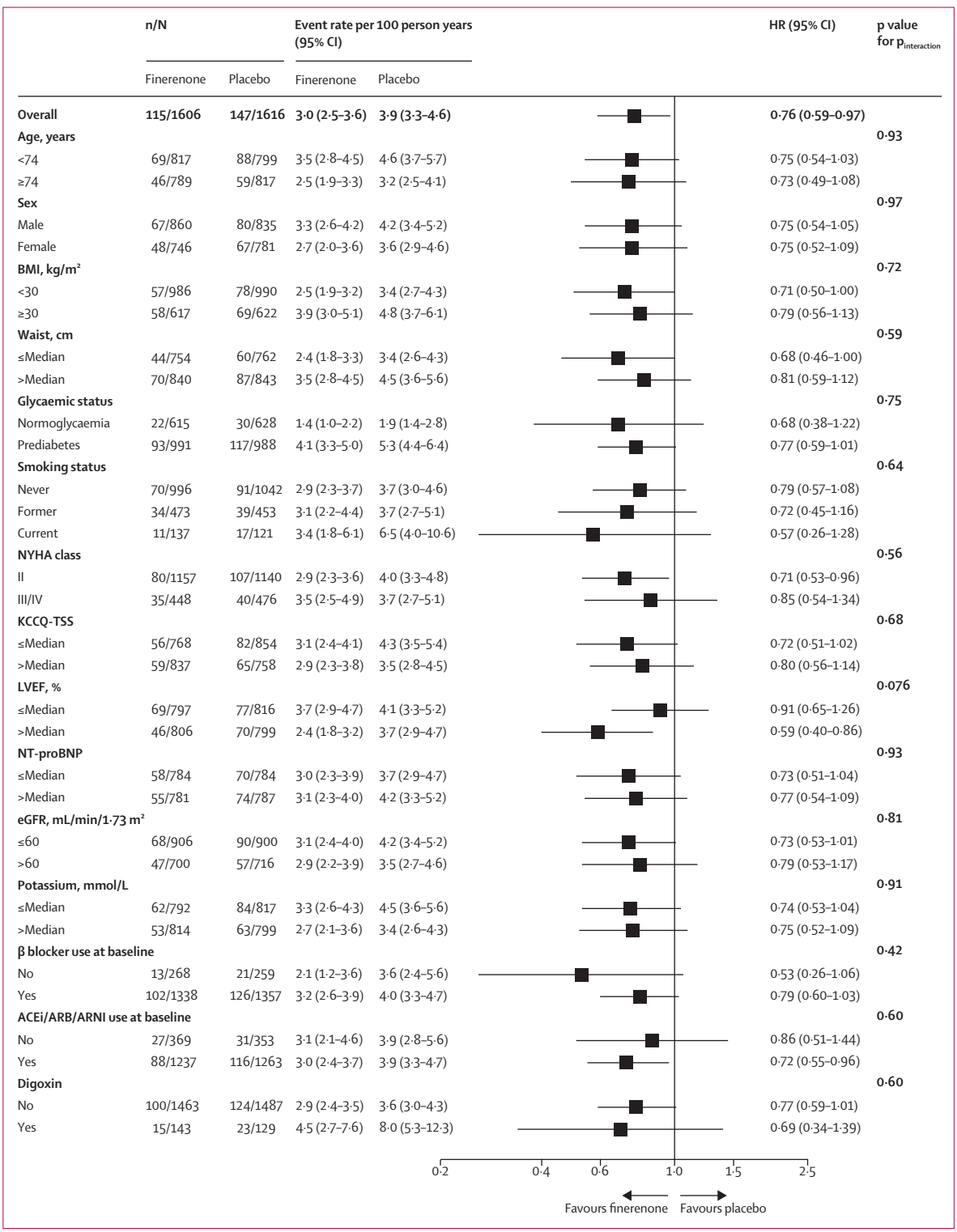

Figure 3: **Effect of finerenone compared with placebo on new-onset diabetes in participants without diabetes at baseline according to subgroups**
Models were stratified by geographic region and baseline LVEF and adjusted for HbA_{1c} levels at baseline. New-onset diabetes was defined based on HbA_{1c} measurements or initiation of glucose-lowering drugs (excluding SGLT2 inhibitors). ACEi=angiotensin-converting enzyme inhibitor. ARB=angiotensin receptor blocker. ARNI=angiotensin receptor–neprilysin inhibitor. eGFR=estimated glomerular filtration rate. KCCQ-TSS=Kansas City Cardiomyopathy Questionnaire total symptom score. LVEF=left ventricular ejection fraction. NT-proBNP=N-terminal pro-B-type natriuretic peptide. NYHA=New York Heart Association.

a high incidence of diabetes, of whom more than 80% had prediabetes at baseline, and showed that the non-steroidal MRA finerenone reduces this hazard by 24%, representing a meaningful additional clinical benefit of this treatment in individuals with HFmrEF or HFpEF.

Among participants without diabetes at baseline assigned to placebo, the incidence of new diabetes was 3·9 cases per 100 person-years of follow-up. This incidence rate is similar to those reported in other clinical trials in participants with heart failure,[12,30–32] but considerably higher than expected in the general population; for example, the incidence of self-reported physician diagnosis of diabetes was around 0·7 cases per 100 person-years in American adults aged 65 years or older.[33]

Previous data on the effect of steroidal MRAs on glycaemic indices are conflicting. Spironolactone has consistently been associated with elevations in HbA_{1c} in individuals with and without diabetes.[34–37] This could reflect the relatively non-selective action of spironolactone leading to an increase in cortisol levels, mediated through binding to glucocorticoid receptors.[34] Less is known about eplerenone, although, in an analysis similar to the present one, eplerenone did not reduce the incidence of diabetes in the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure trial (EMPHASIS-HF).[26] Finerenone, a non-steroidal MRA, did not change HbA_{1c} levels in participants with chronic kidney disease and type 2 diabetes,[38] consistent with the observations in the present study which included participants without diabetes, although we do not know whether these findings can be generalised to individuals who are non-diabetic without heart failure.

There is evidence that ARBs and angiotensin-converting enzyme inhibitors might also reduce the incidence of diabetes.[12,13] In FINEARTS-HF, almost 80% of participants were treated with one of these agents at baseline, showing that the reduction in new-onset diabetes with finerenone was additional to any effect of these other agents (and larger than observed with ARBs).[12,13] More recently, the SGLT2 inhibitor dapagliflozin was shown to reduce the incidence of diabetes in participants with HFrEF in the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure trial (DAPA-HF).[32] Because enrolment and much of the follow-up in FINEARTS-HF occurred before SGLT2 inhibitors were shown to be of benefit in HFmrEF or HFpEF, baseline use of these agents was low (5·5% in participants with normoglycaemia or prediabetes: 4·8% in the finerenone group and 6·2% in the placebo group). Importantly, fewer participants in the finerenone group (12·4%) initiated an SGLT2 inhibitor after randomisation than in the placebo group (16·5%); ie, a differential drop-in of SGLT2 inhibitor did not account for the lower incidence of diabetes in the finerenone group.

	No new-onset diabetes (n=2960)	New-onset diabetes (n=262)	p value
Cardiovascular death and total worsening heart failure events			
Event rate per 100 person-years	12·4 (11·7–13·3)	23·5 (19·4–28·3)	..
RR*	..	2·04 (1·42–2·95)	0·0001
RR†	..	1·88 (1·33–2·67)	0·0004
Total worsening heart failure events			
Event rate per 100 person-years	9·9 (9·2–10·6)	18·0 (14·5–22·3)	..
RR*	..	2·04 (1·34–3·12)	0·0009
RR†	..	1·84 (1·23–2·75)	0·0029
Cardiovascular death			
Event rate per 100 person-years	2·6 (2·2–3·0)	5·5 (3·7–8·1)	..
HR*	..	2·05 (1·34–3·13)	0·0009
HR†	..	2·00 (1·30–3·09)	0·0016
All-cause death			
Event rate per 100 person-years	5·5 (5·0–6·0)	8·5 (6·2–11·7)	..
HR*	..	1·48 (1·06–2·06)	0·022
HR†	..	1·55 (1·10–2·17)	0·011

Data are effect size (95% CI) or p. One participant had missing data for systolic blood pressure, one for heart rate, one for New York Heart Association functional class, seven for BMI, four for LVEF, and 86 for N-terminal pro-B-type natriuretic peptide. In total, 97 (3·0%) participants had at least one missing variable. RR=rate ratio. HR=hazard ratio. LVEF=left ventricular ejection fraction. *Models were stratified by geographic region and baseline LVEF. †Models were stratified by geographic region and baseline LVEF and adjusted for age, sex, systolic blood pressure, heart rate, BMI, log of N-terminal pro-B-type natriuretic peptide, estimated glomerular filtration rate, LVEF, New York Heart Association functional class, previous hospitalisation with heart failure, ischaemic heart disease (ie, previous myocardial infarction or coronary revascularisation), and atrial fibrillation or flutter.

Table 3: **Association between new-onset diabetes as a time-updated covariate and outcomes**

A 24% reduction in the hazard of new-onset diabetes with finerenone is clinically meaningful and represents an additional clinical benefit of this treatment in individuals with HFmrEF or HFpEF. Although the 95% CI suggests that the true effect of this treatment could range from a large reduction of 41% to a small reduction of 3%, any reduction in the hazard of new diabetes in individuals with heart failure is important, given that the development of diabetes is associated with substantial morbidity and mortality in these high-risk individuals, as also shown in the present study.

The beneficial effect of finerenone in reducing new-onset diabetes was generally consistent across key participant subgroups, although participants with higher LVEF appeared to derive a greater benefit compared with those with lower LVEF ($p_{interaction}$=0·076). However, subgroup analyses like these should be interpreted carefully because the interaction tests were not sufficiently powered and, more importantly, were not adjusted for multiple comparisons (ie, 15 subgroups were evaluated), and therefore could constitute chance findings.

The absence of a significant difference in HbA_{1c} levels between treatment arms, despite a reduction in new-onset diabetes with finerenone, is likely to reflect variation in individual changes in HbA_{1c}. Although the treatment might have effectively prevented HbA_{1c} from crossing the threshold for diabetes in high-risk

individuals (ie, individuals with prediabetes), the variation in individual changes could have diluted this effect when examining the mean changes across the entire population.

The mechanism underlying the reduction in the hazard of new diabetes observed in FINEARTS-HF is uncertain. Primary hyperaldosteronism is a state of insulin resistance, and higher plasma aldosterone levels are associated with greater insulin resistance in normotensive and hypertensive individuals.[39] However, as discussed earlier, steroidal MRAs do not improve glycaemic control, although this could be due to off-target effects not shared by finerenone. Diuretic use in heart failure frequently causes hypokalaemia, which is known to cause impaired glucose tolerance by reducing insulin secretion,[40] and finerenone halved the risk of hypokalaemia in FINEARTS-HF. Reducing progressive worsening of heart failure might reduce the use (and doses) of diuretic agents and decrease neurohumoral activation, which promotes insulin resistance.[10,11] Finerenone does not directly reduce blood glucose or weight.[41,42] We do not know whether it could have enhanced pancreatic β-cell function or improved insulin sensitivity because we could not investigate these in FINEARTS-HF, which was designed as a large phase 3 morbidity and mortality trial. Finerenone did improve participant-reported health status as measured by the KCCQ-TSS in FINEARTS-HF, and if this translated into increased physical activity, it could have contributed to a reduction in incident diabetes. Other more speculative mechanisms include a reduction in inflammation and oxidative stress (effects shown experimentally following blockade of the mineralocorticoid receptor), improvement of glucose tolerance through recruitment of brown adipose tissue, and other direct effects of renin–angiotensin–aldosterone system inhibition not related to insulin resistance, eg, enhancement of pancreatic β-cell function, increase in skeletal muscle blood flow, inhibition of adipocyte maturation, and reduction in diuretic use.[17,18,43]

The findings of this study should be viewed in the context of potential limitations. First, participants enrolled in clinical trials are selected according to specific inclusion and exclusion criteria, and our results might not be generalisable to all individuals with heart failure in the general population. In particular, the proportion of non-White participants recruited was not globally representative. Second, because this is a HFmrEF or HFpEF trial, these data cannot necessarily be extrapolated to a population without HFmrEF or HFpEF, including those with HFrEF or those without heart failure. Third, we did not have measurements of plasma insulin or glucometabolic investigations that might have helped better understand the salutary effects of finerenone on new-onset diabetes. Fourth, since some of the glucose-lowering therapies have indications beyond diabetes (eg, GLP-1 receptor agonists for the treatment of obesity), we cannot rule out that some participants might have initiated these drugs during follow-up for reasons other than diabetes. Fifth, in the analyses of the association between new-onset diabetes (as a time-updated covariate) and outcomes, the risk of residual confounding cannot be excluded, despite comprehensive adjustment for potential confounders. In addition, the CIs of the point estimates in these analyses were wide, and the associations should therefore be interpreted with caution.

In conclusion, in this prespecified analysis of a randomised clinical trial of participants with HFmrEF or HFpEF, more than 80% of the participants who developed diabetes had prediabetes at baseline. The non-steroidal MRA finerenone reduced the hazard of diabetes by approximately 25%, representing a meaningful additional clinical benefit of this treatment in participants with HFmrEF or HFpEF.

Contributors

JHB, PSJ, SDS, and JJVM conceptualised and designed the study. JHB and ADH did the analysis. JHB and JJVM drafted the manuscript. All authors contributed to data interpretation and writing of the final version of the manuscript. JHB, PSJ, ADH, and JJVM accessed and verified the data. All authors had full access to the study data and were responsible for the decision to submit for publication.

Declaration of interests

JHB reports advisory board honoraria from AstraZeneca and Bayer; consultant honoraria from Novartis and AstraZeneca; and travel grants from AstraZeneca. PSJ reports speakers' fees from AstraZeneca, Novartis, Alkem Metabolics, ProAdWise Communications, and Sun Pharmaceuticals; advisory board fees from AstraZeneca, Boehringer Ingelheim, and Novartis; research funding from AstraZeneca, Boehringer Ingelheim, Analog Devices, and Roche; remuneration to employer for clinical trial work from AstraZeneca, Bayer, Novartis, and Novo Nordisk; and directorship at Global Clinical Trial Partners. BLC reports personal consulting fees from Alnylam, Bristol Myers Squibb, Cardior, Cardurion, Corvia, CVRx, Eli Lilly, Intellia, and Rocket; and participation on a data safety monitoring board for Novo Nordisk. ASD reports institutional research grants from Abbott, Alnylam, AstraZeneca, Bayer, Novartis, and Pfizer; and personal consulting fees from Abbott, Alnylam, AstraZeneca, Bayer, Biofourmis, Boston Scientific, Medpace, Medtronic, Merck, Novartis, Parexel, Porter Health, Regeneron, River 2 Renal, Roche, Veristat, Verily, and Zydus. PV, PK, PS, and FA are employees of Bayer. CSPL reports research support from Novo Nordisk and Roche; consulting fees from Alleviant, Allysta, AnaCardio, Applied Therapeutics, AstraZeneca, Bayer, Biopeutics, Boehringer Ingelheim, Boston Scientific, Bristol Myers Squibb, CardioRenal, CPC Clinical Research, Eli Lilly, Impulse Dynamics, Intellia, Ionis, Janssen, Medscape, Merck, Novartis, Novo Nordisk, ProSciento, Quidel, Radcliffe Group, Recardio, Recor Medical, Roche, Sanofi, Siemens Healthcare Diagnostics, and Us2.ai; and being a cofounder and non-executive director of Us2.ai. MS reports participation on advisory boards, consultancy, and honoraria for Novartis, Abbott, Merck, MSD, Vifor, AstraZeneca, Cardurion, Novo Nordisk, Bayer, and Boehringer Ingelheim. SJS reports research grants from the National Institutes of Health, the American Heart Association, 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. AAV reports consultancy fees and research support to employer from Adrenomed, AnaCardio, AstraZeneca, Bayer, Bristol Myers Squibb, Boehringer Ingelheim, Corteria, Eli Lilly, Merck, Moderna, Novartis, Novo Nordisk, Roche, and SalubrisBio. FZ reports personal fees from 89bio, Abbott, Acceleron, Applied Therapeutics,

Bayer, Betagenon, Boehringer Ingelheim, Bristol Myers Squibb, CVRx, Cambrian, Cardior, Cereno, CellProthera, CEVA, Inventiva, KBP, Merck, Novo Nordisk, Owkin, Otsuka, Roche, NorthSea, and UsA2; stock options at G3 Pharmaceuticals; equities at Cereno, CardioRenal, and Eshmoun Clinical Research; and being the founder of Cardiovascular Clinical Trialists. BP reports consultancy for Bayer, AstraZeneca, Boehringer Ingelheim, Lexicon, Bristol Myers Squibb, KBP, Sarfez Pharmaceuticals, SQ Innovation, G3 Pharmaceuticals, SeaStar Medical, Vifor, ProIntel, and Brainstorm Medical; stock or stock options for KBP Biosciences, Sarfez Pharmaceuticals, SQ Innovation, Sea Star Medical, Vifor, ProIntel, and Brainstorm Medical; and patents US 9931412 (site specific delivery of eplerenone to the myocardium) and US pending 63/045,783 (histone modulating agents for the prevention and treatment of organ failure). MV reports research grant support from, participation on advisory boards for, or speaker engagements with American Regent, Amgen, AstraZeneca, Bayer, Baxter Healthcare, Bristol Myers Squibb, Boehringer Ingelheim, Chiesi, Cytokinetics, Fresenius Medical Care, Idorsia Pharmaceuticals, Lexicon Pharmaceuticals, Merck, Milestone Pharmaceuticals, Novartis, Novo Nordisk, Pharmacosmos, Relypsa, Roche, Sanofi, and Tricog Health; and participation on clinical trial committees for studies sponsored by AstraZeneca, Galmed, Novartis, Bayer, Occlutech, and Impulse Dynamics. SDS reports research grants from Alexion, Alnylam, AstraZeneca, Bellerophon, Bayer, Bristol Myers Squibb, Boston Scientific, Cytokinetics, Edgewise, Eidos, Gossamer, GSK, Ionis, Lilly, MyoKardia, the National Institutes of Health National Heart, Lung, and Blood Institute, Novartis, Novo Nordisk, Respicardia, Sanofi Pasteur, Theracos, and Us2.ai; and consultancy for Abbott, Action, Akros, Alexion, Alnylam, Amgen, Arena, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Cardior, Cardurion, Corvia, Cytokinetics, Daiichi Sankyo, GSK, Lilly, Merck, MyoKardia, Novartis, Roche, Theracos, Quantum Genomics, Janssen, Cardiac Dimensions, Tenaya, Sanofi Pasteur, DiNAQOR, Tremeau, CellProthera, Moderna, American Regent, Sarepta, Lexicon, AnaCardio, Akros, and Valo. JVVM reports institutional payments, consultancy fees, and grants from Amgen, AstraZeneca, Bayer, Cardurion, Cytokinetics, GSK, Novartis, the British Heart Foundation, the National Institutes of Health National Heart, Lung, and Blood Institute, Boehringer Ingelheim, SQ Innovation, and Catalyze Group; personal consultancy fees from Alnylam, Amgen, AnaCardio, AstraZeneca, Bayer, Berlin Cures, Bristol Myers Squibb, Cardurion, Cytokinetics, Ionis, Novartis, Regeneron, and River 2 Renal; personal lecture fees from Abbott, Alkem Metabolics, AstraZeneca, Blue Ocean Scientific Solutions, Boehringer Ingelheim, Canadian Medical and Surgical Knowledge, Emcure Pharmaceuticals, Eris Lifesciences, European Academy of CME, Hikma Pharmaceuticals, Imagica Health, Intas Pharmaceuticals, JB Chemicals & Pharmaceuticals, Lupin Pharmaceuticals, Medscape, ProAdWise Communications, Radcliffe Cardiology, Sun Pharmaceuticals, The Corpus, Translation Research Group, and the Translational Medicine Academy; participation on a data safety monitoring board for WIRB-Copernicus Group; and directorship of Global Clinical Trial Partners. ADH declares no competing interests.

Data sharing

Data will be made available to qualified scientific and medical researchers through vivli.org. All requests will be reviewed by an independent scientific review panel and data provided according to the conditions laid out at https://vivli.org/ourmember/bayer/.

References

1 Pop-Busui R, Januzzi JL, Bruemmer D, et al. Heart failure: an underappreciated complication of diabetes. A consensus report of the American Diabetes Association. *Diabetes Care* 2022; **45:** 1670–90.

2 Dunlay SM, Givertz MM, Aguilar D, et al. Type 2 diabetes mellitus and heart failure: a scientific statement from the American Heart Association and the Heart Failure Society of America: this statement does not represent an update of the 2017 ACC/AHA/HFSA heart failure guideline update. *Circulation* 2019; published online June 6. https://doi.org/10.1161/CIR.0000000000000691.

3 Inzucchi SE, Claggett BL, Vaduganathan M, et al. Efficacy and safety of dapagliflozin in patients with heart failure with mildly reduced or preserved ejection fraction by baseline glycaemic status (DELIVER): a subgroup analysis from an international, multicentre, double-blind, randomised, placebo-controlled trial. *Lancet Diabetes Endocrinol* 2022; **10:** 869–81.

4 Jackson AM, Rørth R, Liu J, et al. Diabetes and pre-diabetes in patients with heart failure and preserved ejection fraction. *Eur J Heart Fail* 2022; **24:** 497–509.

5 Huynh T, Harty BJ, Claggett B, et al. Comparison of outcomes in patients with diabetes mellitus treated with versus without insulin + heart failure with preserved left ventricular ejection fraction (from the TOPCAT study). *Am J Cardiol* 2019; **123:** 611–17.

6 Ferreira JP, Lamiral Z, McMurray JJV, et al. Impact of insulin treatment on the effect of eplerenone: insights from the EMPHASIS-HF trial. *Circ Heart Fail* 2021; published online June 15. https://doi.org/10.1161/CIRCHEARTFAILURE.120.008075.

7 Petrie MC, Verma S, Docherty KF, et al. Effect of dapagliflozin on worsening heart failure and cardiovascular death in patients with heart failure with and without diabetes. *JAMA* 2020; **323:** 1353–68.

8 Dauriz M, Mantovani A, Bonapace S, et al. Prognostic impact of diabetes on long-term survival outcomes in patients with heart failure: a meta-analysis. *Diabetes Care* 2017; **40:** 1597–605.

9 MacDonald MR, Petrie MC, Varyani F, et al. Impact of diabetes on outcomes in patients with low and preserved ejection fraction heart failure: an analysis of the candesartan in heart failure: assessment of reduction in mortality and morbidity (CHARM) programme. *Eur Heart J* 2008; **29:** 1377–85.

10 Ashrafian H, Frenneaux MP, Opie LH. Metabolic mechanisms in heart failure. *Circulation* 2007; **116:** 434–48.

11 Riehle C, Abel ED. Insulin signaling and heart failure. *Circ Res* 2016; **118:** 1151–69.

12 Yusuf S, Ostergren JB, Gerstein HC, et al. Effects of candesartan on the development of a new diagnosis of diabetes mellitus in patients with heart failure. *Circulation* 2005; **112:** 48–53.

13 Effect of valsartan on the incidence of diabetes and cardiovascular events. *N Engl J Med* 2010; **362:** 1477–90.

14 Elliott WJ, Meyer PM. Incident diabetes in clinical trials of antihypertensive drugs: a network meta-analysis. *Lancet* 2007; **369:** 201–07.

15 Solomon SD, Ostrominski JW, Vaduganathan M, et al. Baseline characteristics of patients with heart failure with mildly reduced or preserved ejection fraction: the FINEARTS-HF trial. *Eur J Heart Fail* 2024; **26:** 1334–46.

16 Vaduganathan M, Claggett BL, Lam CSP, et al. Finerenone in patients with heart failure with mildly reduced or preserved ejection fraction: rationale and design of the FINEARTS-HF trial. *Eur J Heart Fail* 2024; **26:** 1324–33.

17 Kolkhof P, Lawatscheck R, Filippatos G, Bakris GL. Nonsteroidal mineralocorticoid receptor antagonism by finerenone—translational aspects and clinical perspectives across multiple organ systems. *Int J Mol Sci* 2022; **23:** 9243.

18 Agarwal R, Kolkhof P, Bakris G, et al. Steroidal and non-steroidal mineralocorticoid receptor antagonists in cardiorenal medicine. *Eur Heart J* 2021; **42:** 152–61.

19 Solomon SD, McMurray JJV, Vaduganathan M, et al. Finerenone in heart failure with mildly reduced or preserved ejection fraction. *N Engl J Med* 2024; **391:** 1475–85.

20 ElSayed NA, Aleppo G, Bannuru RR, et al. 2. Diagnosis and classification of diabetes: standards of care in diabetes 2024. *Diabetes Care* 2024; **47:** S20–42.

21 Harrison XA, Donaldson L, Correa-Cano ME, et al. A brief introduction to mixed effects modelling and multi-model inference in ecology. *PeerJ* 2018; **6:** e4794.

22 Cox DR. Regression models and life-tables. *J R Stat Soc Series B Stat Methodol* 1972; **34:** 187–202.

23 Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc* 1999; **94:** 496.

24 Lin DY, Wei LJ, Yang I, Ying Z. Semiparametric regression for the mean and rate functions of recurrent events. *J R Stat Soc Series B Stat Methodol* 2000; **62:** 711–30.

25 Zhang Z, Reinikainen J, Adeleke KA, Pieterse ME, Groothuis-Oudshoorn CGM. Time-varying covariates and coefficients in Cox regression models. *Ann Transl Med* 2018; **6:** 121.

26 Preiss D, van Veldhuisen DJ, Sattar N, et al. Eplerenone and new-onset diabetes in patients with mild heart failure: results from the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF). *Eur J Heart Fail* 2012; **14:** 909–15.

27 Torp-Pedersen C, Metra M, Charlesworth A, et al. Effects of metoprolol and carvedilol on pre-existing and new onset diabetes in patients with chronic heart failure: data from the Carvedilol Or Metoprolol European Trial (COMET). *Heart* 2007; **93:** 968–73.

28 Zareini B, Rørth R, Holt A, et al. Heart failure and the prognostic impact and incidence of new-onset of diabetes mellitus: a nationwide cohort study. *Cardiovasc Diabetol* 2019; **18:** 79.

29 Rossing P, Inzucchi SE, Vart P, et al. Dapagliflozin and new-onset type 2 diabetes in patients with chronic kidney disease or heart failure: pooled analysis of the DAPA-CKD and DAPA-HF trials. *Lancet Diabetes Endocrinol* 2022; **10:** 24–34.

30 Kjekshus J, Apetrei E, Barrios V, et al. Rosuvastatin in older patients with systolic heart failure. *N Engl J Med* 2007; **357:** 2248–61.

31 Kristensen SL, Mogensen UM, Tarnesby G, et al. Aliskiren alone or in combination with enalapril vs. enalapril among patients with chronic heart failure with and without diabetes: a subgroup analysis from the ATMOSPHERE trial. *Eur J Heart Fail* 2018; **20:** 136–47.

32 Inzucchi SE, Docherty KF, Køber L, et al. Dapagliflozin and the incidence of type 2 diabetes in patients with heart failure and reduced ejection fraction: an exploratory analysis from DAPA-HF. *Diabetes Care* 2021; **44:** 586–94.

33 Saelee R, Hora IA, Pavkov ME, et al. Diabetes prevalence and incidence inequality trends among U.S. adults, 2008–2021. *Am J Prev Med* 2023; **65:** 973–82.

34 Yamaji M, Tsutamoto T, Kawahara C, et al. Effect of eplerenone versus spironolactone on cortisol and hemoglobin A1c levels in patients with chronic heart failure. *Am Heart J* 2010; **160:** 915–21.

35 Swaminathan K, Davies J, George J, Rajendra NS, Morris AD, Struthers AD. Spironolactone for poorly controlled hypertension in type 2 diabetes: conflicting effects on blood pressure, endothelial function, glycaemic control and hormonal profiles. *Diabetologia* 2008; **51:** 762–68.

36 Matsumoto S, Takebayashi K, Aso Y. The effect of spironolactone on circulating adipocytokines in patients with type 2 diabetes mellitus complicated by diabetic nephropathy. *Metabolism* 2006; **55:** 1645–52.

37 Davies JI, Band M, Morris A, Struthers AD. Spironolactone impairs endothelial function and heart rate variability in patients with type 2 diabetes. *Diabetologia* 2004; **47:** 1687–94.

38 McGill JB, Agarwal R, Anker SD, et al. Effects of finerenone in people with chronic kidney disease and type 2 diabetes are independent of HbA_{1c} at baseline, HbA_{1c} variability, diabetes duration and insulin use at baseline. *Diabetes Obes Metab* 2023; **25:** 1512–22.

39 Garg R, Hurwitz S, Williams GH, Hopkins PN, Adler GK. Aldosterone production and insulin resistance in healthy adults. *J Clin Endocrinol Metab* 2010; **95:** 1986–90.

40 Chatterjee R, Yeh H-C, Edelman D, Brancati F. Potassium and risk of type 2 diabetes. *Expert Rev Endocrinol Metab* 2011; **6:** 665–72.

41 Pitt B, Filippatos G, Agarwal R, et al. Cardiovascular events with finerenone in kidney disease and type 2 diabetes. *N Engl J Med* 2021; **385:** 2252–63.

42 Bakris GL, Agarwal R, Anker SD, et al. Effect of finerenone on chronic kidney disease outcomes in type 2 diabetes. *N Engl J Med* 2020; **383:** 2219–29.

43 Marzolla V, Feraco A, Limana F, Kolkhof P, Armani A, Caprio M. Class-specific responses of brown adipose tissue to steroidal and nonsteroidal mineralocorticoid receptor antagonists. *J Endocrinol Invest* 2022; **45:** 215–20.