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RESEARCH ARTICLE

Finerenone, chronic obstructive pulmonary disease, and heart failure with mildly reduced or preserved ejection fraction: A prespecified analysis of the FINEARTS-HF trial

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Aims Chronic obstructive pulmonary disease (COPD) is associated with worse outcomes in heart failure (HF) with mildly reduced or preserved ejection fraction (HFmrEF/HFpEF). A post hoc analysis of TOPCAT suggested that the effectiveness of the steroidal mineralocorticoid receptor antagonist (MRA), spironolactone, may be modified by pulmonary disease, with a greater benefit in patients with COPD/asthma. We examined the effects of the non-steroidal MRA, finerenone, compared to placebo, according to COPD status in a prespecified analysis of FINEARTS-HF.

Methods and results A history of COPD was investigator-reported. The primary outcome was the composite of cardiovascular death and total worsening HF events. Of the 6001 patients randomized in FINEARTS-HF, 773 patients (12.9%) had COPD. Compared to patients without COPD, those with COPD had more adverse clinical features, including worse New York Heart Association class and Kansas City Cardiomyopathy Questionnaire (KCCQ) scores, more prior HF hospitalization, atrial fibrillation/flutter, obesity, peripheral artery disease, and hypertension, as well as elevated high-sensitivity troponin T levels. Patients with COPD had a higher risk of the primary endpoint (adjusted rate ratio [RR] 1.44, 95% confidence interval [CI] 1.21–1.71). The benefit of finerenone on the primary outcome was consistent irrespective of COPD status (no COPD: RR 0.84 [95% CI 0.73–0.97]; COPD: 0.84 [95% CI 0.61–1.16]; $p_{\text{interaction}} = 0.93$). Consistent effects were also observed for all secondary outcomes. Finerenone improved KCCQ total symptom score from baseline to 12 months to a similar extent in patients with and without COPD ($p_{\text{interaction}} = 0.46$).

Conclusion In patients with HFmrEF/HFpEF, the beneficial effects of finerenone on clinical events and symptoms were consistent, regardless of COPD status.
Clinical Trial Registration: ClinicalTrials.gov ID NCT04435626.

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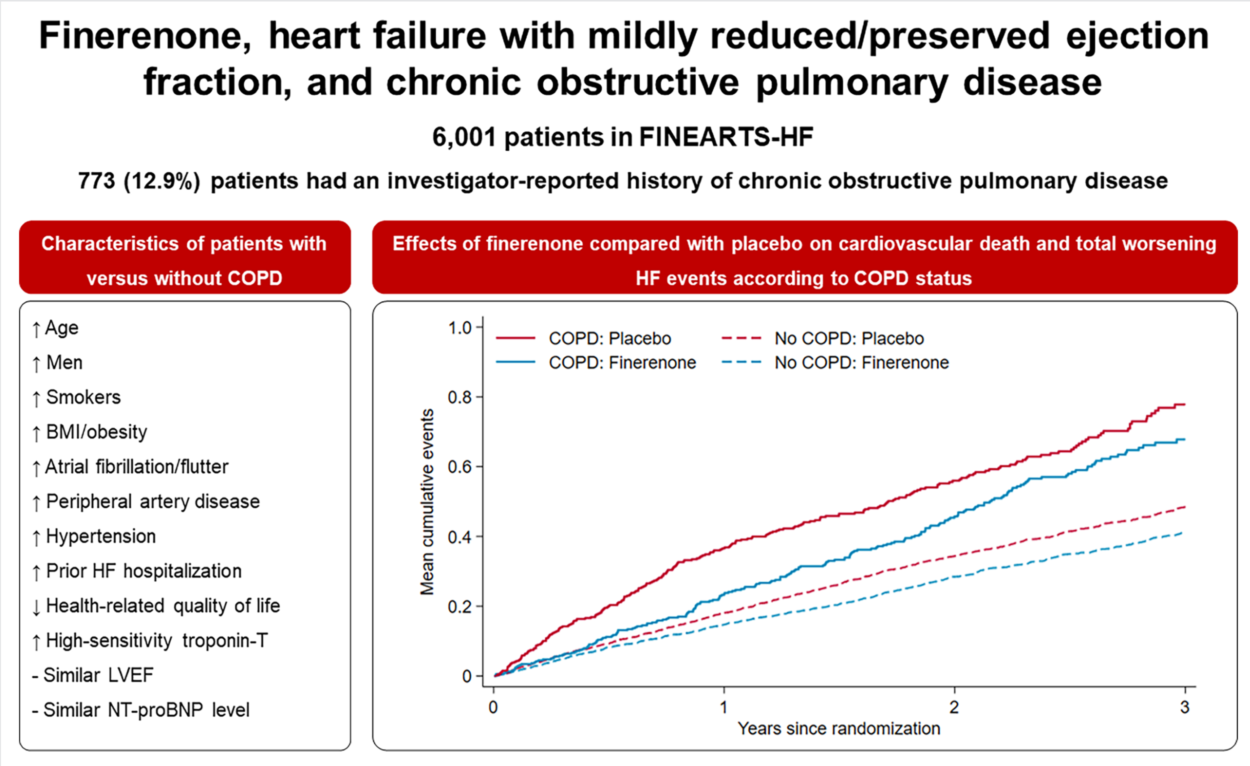
Graphical Abstract



The beneficial effects of finerenone in patients with heart failure (HF) and mildly reduced or preserved ejection fraction were consistent, regardless of a history of chronic obstructive pulmonary disease (COPD) status. BMI, body mass index; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

Keywords Heart failure with preserved ejection fraction • Mineralocorticoid receptor antagonist • Chronic obstructive pulmonary disease

Introduction

Chronic obstructive pulmonary disease (COPD) is common in patients with heart failure (HF) and mildly reduced or preserved ejection fraction (HFmrEF/HFpEF), and individuals with both conditions have a substantially worse prognosis than those with either condition alone.[1–7] Consequently, there is a need for effective therapies in these high-risk individuals with concomitant HFmrEF/HFpEF and COPD.

Although a history of COPD does not appear to modify the beneficial effects of guideline-recommended therapies in patients with HF with reduced ejection fraction (HFrEF) nor sodium–glucose cotransporter 2 (SGLT2) inhibitors in HFmrEF/HFpEF,[1,3,8–10] there is some evidence that the effectiveness of mineralocorticoid receptor antagonists (MRAs) may be modified by COPD status in HFmrEF/HFpEF. In a post hoc analysis of the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist trial (TOPCAT) (Americas only), the effect of the steroidal MRA, spironolactone, compared with placebo, on cardiovascular and all-cause death was modified by a history of pulmonary disease (COPD or asthma), such that the risk reduction with spironolactone was greater among those with pulmonary disease compared to those without.[2] The authors of this analysis speculated that aldosterone may play a role in the reduction in alveolar surface area in COPD, proliferation of alveolar type II cells, thickening of the alveolar-capillary interstitium, and lung fibrosis. Spironolactone has also been shown to improve lung diffusion capacity in patients with HF.[11]

However, TOPCAT did not show a significant benefit of spironolactone overall,[12] and, therefore, before the Finerenone Trial to Investigate Efficacy and Safety Superior to Placebo in Patients with Heart Failure trial (FINEARTS-HF), the benefits of MRAs in HFmrEF/HFpEF were unproven and their effects according to COPD status in these patients remained uncertain.[13]

Consequently, we examined the efficacy and safety of the non-steroidal MRA, finerenone, compared with placebo, according to a history of COPD in a prespecified analysis of FINEARTS-HF, which demonstrated that finerenone reduced the risk of total (first and recurrent) worsening HF events and cardiovascular death and improved health-related quality of life in 6001 patients with HFmrEF/HFpEF.[13–15]

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.[13–15] 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 (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 brain 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). 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. In addition, patients with a history of primary pulmonary arterial hypertension or severe pulmonary disease requiring home oxygen or chronic oral steroid therapy were excluded. A complete list of exclusion criteria is provided in the design paper.[15]

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.[15]

History of chronic obstructive pulmonary disease

Data on medical conditions at baseline, including a history of COPD and asthma, were investigator-reported and retrieved from the trial case report forms. In a sensitivity analysis, the definition of COPD was expanded to include asthma.

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), non-cardiovascular death, total (first and recurrent) hospitalizations for any reason, and causes of death. All deaths and potential primary non-fatal events were adjudicated by an independent clinical events committee.

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-normally and normally distributed continuous variables, respectively.

The incidence rate of clinical outcomes was estimated as the number of events per 100 person-years, and 95% confidence intervals (CIs) were estimated with Poisson regression with robust standard errors. Rate differences were estimated from these models using counterfactual predictions. The association between COPD 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,[16] and hazard ratios (HRs) and rate ratios (RRs), 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, smoking status, log of NT-proBNP, eGFR, LVEF, NYHA functional class, prior HF hospitalization, type 2 diabetes, myocardial infarction or coronary revascularization, and atrial fibrillation/flutter were reported. We also examined the association between seven other common comorbidities and clinical outcomes using Cox proportional-hazards models and semiparametric proportional-rates models, and HRs and RRs, respectively, were stratified by geographic region and LVEF stratification and adjusted for treatment assignment, age, sex, NYHA functional class, and log of NT-proBNP.

To compare the effects of finerenone versus placebo on clinical outcomes according to COPD 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 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.

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

Results

Patient characteristics according to a history of chronic obstructive pulmonary disease

Of the 6001 patients analysed in FINEARTS-HF, 773 patients (12.9%) had an investigator-reported history of COPD. The baseline characteristics of patients according to a history of COPD are shown in *Table 1*. Compared to patients without a history of COPD, those with COPD were older, more often male and White (and less often Asian), more likely to be current/former smokers, and had a higher body mass index. Although there were no significant differences in LVEF and NT-proBNP levels between patients with and without a history of COPD, those with COPD had a higher median high-sensitivity troponin-T (hs-TnT) level, and they were more likely to have a prior HF hospitalization, atrial fibrillation/flutter, peripheral artery disease, obesity, and hypertension. Compared to patients without COPD, those with COPD had more advanced NYHA functional class and lower (worse) KCCQ scores. KCCQ scores in patients with COPD were lower than in participants with each of the seven other most common comorbidities (*Figure 1*).

Regarding pharmacological therapy, patients with COPD were more frequently treated with a loop diuretic than those without COPD, but a similar proportion of patients were treated with a beta-blocker.

Among patients with COPD, 38.8% were treated with a long-acting beta-2-adrenoreceptor agonist (5.3% with a short-acting agent in this class), 30.3% with a muscarinic antagonist, 21.0% with an inhaled corticosteroid, 4.9% with a xanthine derivative, and 3.4% with a leukotriene receptor antagonist.

Clinical outcomes according to a history of chronic obstructive pulmonary disease

Patients with a history of COPD had a significantly higher risk of all clinical outcomes, except for the composite renal outcome, compared with those without. After adjustment for other recognized prognostic variables, these associations persisted (*Table 2*). The adjusted risk of the primary endpoint and all-cause death was higher than for the seven other most common comorbidities in these patients (*Figure 2*).

The most commonly adjudicated cause of death was attributed to cardiovascular causes, mainly sudden death and death due to worsening HF. Among those who died, the proportion of deaths attributed to sudden death was lower in the COPD group compared to the no COPD group, whereas the proportion of deaths attributed to worsening HF was higher in the COPD group (*Figure 3*). Infection was the second most common cause of death, and the proportion of deaths attributed to infection was higher in patients with COPD compared to patients without COPD. The cause of death was undetermined in less than 15% of cases, and this proportion was similar in both groups (*Figure 3*).

Effects of finerenone on clinical outcomes according to a history of chronic obstructive pulmonary disease

Compared with placebo, finerenone reduced the risk of total (first and recurrent) worsening HF events and cardiovascular death in patients with (RR 0.84 [95% CI 0.61−1.16]) and without a history of COPD (RR 0.84 [95% CI 0.73−0.97]), with no interaction between COPD and effect of treatment ($p_{interaction} = 0.93$) (*Table 3*, *Figure 4*). The effects of finerenone on secondary clinical outcomes were consistent regardless of a history of COPD (*Table 3*).

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 COPD ($p_{interaction} = 0.46$) (*Table 3*). There was a nominally significant interaction between COPD status and the effect of finerenone on improvement in NYHA class from baseline to 12 months, such that finerenone appeared to improve NYHA class in patients with COPD, but not in those without COPD ($p_{interaction} = 0.048$) (*Table 3*).

Compared to participants in the placebo arm, those in the finerenone treatment arm were more likely to experience increases in potassium and creatinine levels and a decrease in systolic blood pressure (to <100 mmHg), and this pattern was similar in patients with and without a history of COPD (*Table 4*). Finerenone reduced the risk of hypokalaemia compared to placebo, but the magnitude of this effect was greater in patients without COPD ($p_{interaction} = 0.03$) (*Table 4*).

Patient characteristics, clinical outcomes, and effects of finerenone according to a history of chronic obstructive pulmonary disease and/or asthma

In a sensitivity analysis, the patients with asthma were added to those with COPD. A total of 1035 patients (17.2%) had a history of COPD and/or asthma at baseline (i.e. 712 patients had a history of COPD, but not asthma; 262 patients had a history of asthma, but not COPD; 61 patients had a history of both COPD and asthma). Data on baseline characteristics and clinical outcomes according to a history of COPD and/or asthma are shown in online supplementary *Tables S1* and *S2*, respectively, and data on the effects of finerenone, compared with placebo, on clinical outcomes and adverse events, are presented in online supplementary *Tables S3* and *S4*, respectively. These analyses yielded similar findings to those observed for COPD alone. Similar findings were also yielded when the 61 patients with both a history of COPD and asthma were excluded (online supplementary *Table S5*).

Table 1 **Baseline characteristics according to a history of chronic obstructive pulmonary disease**

	No COPD ($n = 5228$)	COPD ($n = 773$)	*p*-value
Age (years), mean (SD)	71.8 ± 9.8	73.4 ± 8.7	<0.001
Sex, *n* (%)			<0.001
Men	2784 (53.3)	485 (62.7)	
Women	2444 (46.7)	288 (37.3)	
Race, *n* (%)			<0.001
White	4078 (78.0)	657 (85.0)	
Black	72 (1.4)	16 (2.1)	
Asian	921 (17.6)	75 (9.7)	
Other	157 (3.0)	25 (3.2)	
Geographic region, *n* (%)			<0.001
Western Europe, Oceania and Others	1072 (20.5)	184 (23.8)	
Eastern Europe	2305 (44.1)	345 (44.6)	
Asia	907 (17.3)	76 (9.8)	
North America	364 (7.0)	107 (13.8)	
Latin America	580 (11.1)	61 (7.9)	
Physiological measures			
Systolic blood pressure (mmHg), mean (SD)	129.6 ± 15.4	128.2 ± 14.7	0.018
Diastolic blood pressure (mmHg), mean (SD)	75.7 ± 10.4	74.1 ± 10.0	<0.001
Heart rate (bpm), mean (SD)	71.3 ± 11.8	72.2 ± 11.7	0.053
Body mass index (kg/m^2), median (IQR)	29.1 (25.5–33.5)	29.6 (25.8–34.8)	0.004
Body mass index (kg/m^2), *n* (%)			<0.001
<18.5	50 (1.0)	15 (1.9)	
18.5–24.9	1103 (21.1)	138 (17.9)	
25.0–29.9	1743 (33.4)	247 (32.1)	
30–34.9	1359 (26.0)	187 (24.3)	
>35.0	963 (18.5)	183 (23.8)	
Biomarkers			
NT-proBNP (pg/ml), median (IQR)	1037 (443–1930)	1067 (483–2047)	0.095
Atrial fibrillation/flutter on ECG	1697 (1141–2812)	1824 (1228–2763)	0.33
No atrial fibrillation/flutter on ECG	583 (304–1244)	580 (336–1226)	0.54
High-sensitivity troponin T (ng/L), median (IQR)	17.4 (6.5–27.4)	19.8 (6.5–31.5)	<0.001
High-sensitivity troponin T (ng/L), *n* (%)			<0.001
<14	1886 (37.3)	217 (28.9)	
≥14	3176 (62.7)	533 (71.1)	
Haemoglobin A1c (%), mean (SD)	6.4 ± 1.2	6.4 ± 1.2	0.71
Creatinine (µmol/L), mean (SD)	99.4 ± 32.8	102.1 ± 29.9	0.026
eGFR (ml/min/1.73 m^2), mean (SD)	62.3 ± 19.9	61.1 ± 18.8	0.11
eGFR (ml/min/1.73 m^2), *n* (%)			0.11
≥60	2733 (52.3)	380 (49.2)	
<60	2495 (47.7)	393 (50.8)	
Urine albumin-to-creatinine ratio (mg/g), median (IQR)	18.0 (7.0–66.0)	19.0 (8.0–70.0)	0.10
Urine albumin-to-creatinine ratio (mg/g), *n* (%)			0.19
<30	3073 (60.9)	438 (58.5)	
30–299	1470 (29.1)	242 (32.3)	
≥300	505 (10.0)	69 (9.2)	
Potassium (mmol/L), mean (SD)	4.4 ± 0.5	4.4 ± 0.5	0.98
Sodium (mmol/L), mean (SD)	140.7 ± 3.0	140.6 ± 3.2	0.44
Haemoglobin (g/L), mean (SD)	133.8 ± 16.5	133.8 ± 17.0	0.98
Bilirubin (total) (mg/dl), mean (SD)	0.65 ± 0.39	0.60 ± 0.33	0.003
Alkaline phosphatase (U/L), mean (SD)	85.6 ± 33.1	89.1 ± 39.0	0.007
Alanine aminotransferase (U/L), mean (SD)	20.8 ± 14.0	19.4 ± 11.3	0.009
Blood urea nitrogen (mg/dl), mean (SD)	22.6 ± 9.5	23.4 ± 10.2	0.029
White blood cell count (10^9/L), mean (SD)	6.8 ± 4.4	7.2 ± 2.2	0.042

Table 1 (Continued)

	No COPD ($n = 5228$)	COPD ($n = 773$)	p-value
Echocardiographic measures, mean (SD)			
LVEF (%)	52.5 ± 7.8	52.7 ± 7.7	0.51
LVEF (%), n (%)			0.44
<50	1906 (36.5)	266 (34.5)	
50–59	2326 (44.6)	348 (45.1)	
≥60	989 (18.9)	158 (20.5)	
Left atrial area (cm^2), mean (SD)	26.6 ± 7.3	26.6 ± 8.4	0.93
Left atrium dimension (cm), mean (SD)	4.6 ± 0.8	4.6 ± 0.8	0.96
Left atrial volume index (ml/m^2), mean (SD)	48.2 ± 20.0	48.0 ± 19.6	0.84
Left ventricular mass index (g/m^2), mean (SD)	122.4 ± 42.8	123.2 ± 49.3	0.81
Left ventricular end-diastolic interventricular septum thickness (cm), mean (SD)	1.2 ± 0.4	1.2 ± 0.4	0.18
Left ventricular end-diastolic posterior wall thickness (cm), mean (SD)	1.1 ± 0.3	1.1 ± 0.3	0.15
Atrial fibrillation/flutter on ECG, n (%)	1997 (38.3)	317 (41.1)	0.15
Smoking status, n (%)			<0.001
Never	3390 (64.8)	307 (39.7)	
Former	1441 (27.6)	352 (45.5)	
Current	397 (7.6)	114 (14.7)	
NYHA class, n (%)			<0.001
II	3692 (70.6)	454 (58.7)	
III	1498 (28.7)	315 (40.8)	
IV	37 (0.7)	4 (0.5)	
KCCQ-TSS, mean (SD)	67.9 ± 23.8	61.2 ± 23.9	<0.001
KCCQ-OSS, mean (SD)	63.6 ± 22.1	57.2 ± 22.3	<0.001
Medical history, n (%)			
Hospitalization for HF	3111 (59.5)	508 (65.7)	<0.001
Time from last HF hospitalization			0.006
No prior HF hospitalization	2117 (40.5)	265 (34.3)	
0–7 days	852 (16.3)	153 (19.8)	
8 days–3 months	1411 (27.0)	209 (27.0)	
3–12 months	343 (6.6)	59 (7.6)	
>1 year	505 (9.7)	87 (11.3)	
Atrial fibrillation/flutter	2864 (54.8)	455 (58.9)	0.033
Stroke	730 (14.0)	101 (13.1)	0.50
Myocardial infarction	1356 (25.9)	185 (23.9)	0.23
Peripheral arterial occlusive disease	438 (8.4)	99 (12.8)	<0.001
Hypertension	4614 (88.3)	711 (92.0)	0.002
Type 2 diabetes	2104 (40.3)	335 (43.5)	0.10
Treatment, n (%)			
ACEi/ARB	3721 (71.2)	525 (67.9)	0.063
ARNI	448 (8.6)	65 (8.4)	0.88
Beta-blocker	4452 (85.2)	643 (83.2)	0.15
Beta-1 selective beta-blocker	3712 (71.0)	539 (69.7)	0.47
Atenolol	74 (1.4)	13 (1.7)	0.56
Bisoprolol	2154 (41.2)	302 (39.1)	0.26
Metoprolol	1187 (22.7)	168 (21.7)	0.55
Nebivolol	256 (4.9)	51 (6.6)	0.045
Non-selective beta-blocker and alpha-blocker	678 (13.0)	97 (12.5)	0.75
Carvedilol	665 (12.7)	96 (12.4)	0.81
Other non-selective beta-blocker	134 (2.6)	15 (1.9)	0.30
SGLT2 inhibitor	718 (13.7)	99 (12.8)	0.48
Loop diuretic	4536 (86.8)	703 (90.9)	0.001
Any diuretic	5163 (98.8)	767 (99.2)	0.26
Digoxin	404 (7.7)	67 (8.7)	0.36

Table 1 (Continued)

	No COPD ($n = 5228$)	COPD ($n = 773$)	p-value
Inhaled corticosteroid	–	162 (21.0)	–
Beclometasone	–	33 (4.3)	–
Budesonide	–	41 (5.3)	–
Fluticasone	–	89 (11.5)	–
Muscarinic antagonist	–	234 (30.3)	–
Ipratropium	–	36 (4.7)	–
Tiotropium	–	120 (15.5)	–
Aclidinium	–	17 (2.2)	–
Umeclidinium	–	54 (7.0)	–
Short-acting beta-2-adrenoreceptor agonist	–	41 (5.3)	–
Salbutamol	–	22 (2.8)	–
Fenoterol	–	18 (2.3)	–
Long-acting beta-2-adrenoreceptor agonist	–	300 (38.8)	–
Formoterol	–	121 (15.7)	–
Salmeterol	–	66 (8.5)	–
Vilanterol	–	66 (8.5)	–
Olodaterol	–	41 (5.3)	–
Xanthine derivative	–	38 (4.9)	–
Leukotriene receptor antagonist	–	26 (3.4)	–

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; COPD, chronic obstructive pulmonary disease; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; HF, heart failure; IQR, interquartile range; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; OSS, overall summary score; SD, standard deviation; SGLT2, sodium–glucose cotransporter 2; TSS, total symptom score.

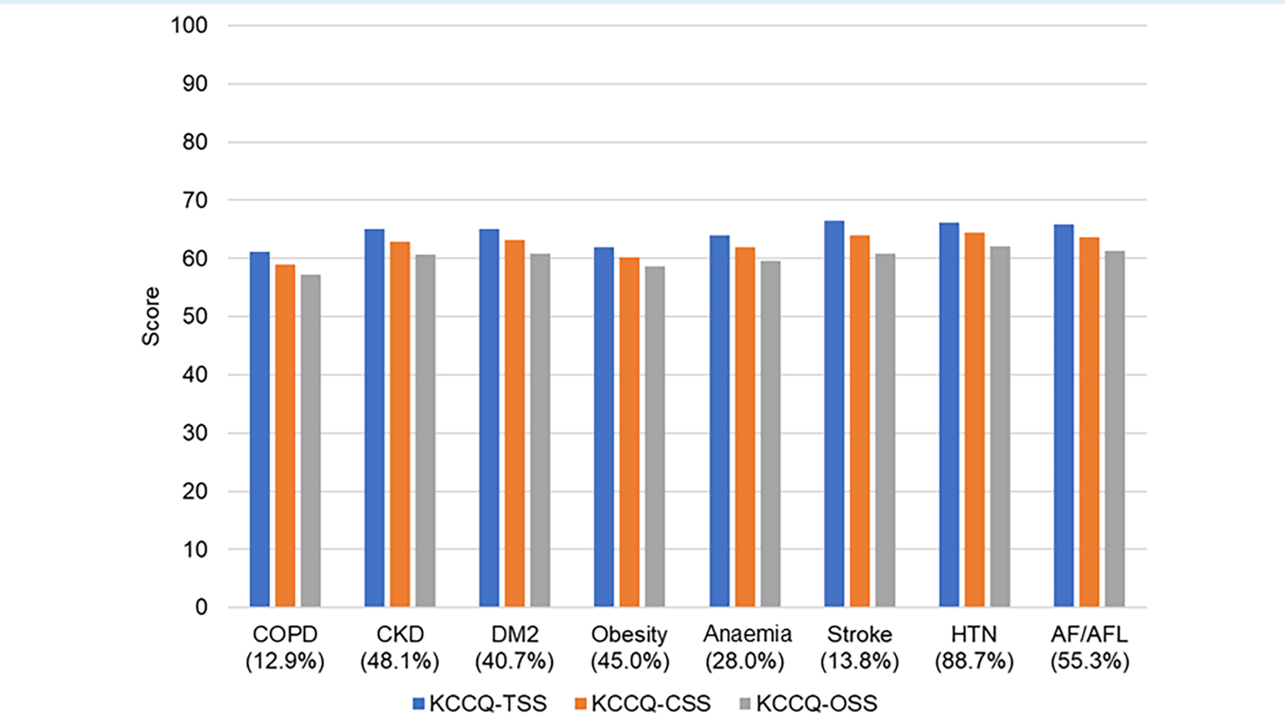


Figure 1 Mean baseline Kansas City Cardiomyopathy Questionnaire (KCCQ) scores associated with major comorbidities. Anaemia is defined as a haemoglobin level <130 g/L for men and <120 g/L for women; CKD is defined as an estimated glomerular filtration rate <60 ml/min/1.73 m^2; obesity is defined as a body mass index >30 kg/m^2. AF/AFL, atrial fibrillation/flutter; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CSS, clinical summary score; DM2, type 2 diabetes; HTN, hypertension; OSS, overall summary score; TSS, total symptom score.

Table 2 Outcomes according to a history of chronic obstructive pulmonary disease

	No COPD (*n* = 5228)	COPD (*n* = 773)
Cardiovascular death and total worsening HF events		
No. of events	1917	449
Event rate per 100 person-years (95% CI)	15.0 (14.0–16.1)	25.2 (21.5–29.5)
Rate difference (95% CI)	Reference	10.2 (6.0–14.3)
RR (95% CI)[a]	Reference	1.61 (1.36–1.92)
RR (95% CI)[b]	Reference	1.44 (1.21–1.71)
Total worsening HF events		
No. of events	1498	368
Event rate per 100 person-years (95% CI)	11.8 (10.8–12.7)	20.6 (17.3–24.6)
Rate difference (95% CI)	Reference	8.9 (5.1–12.7)
RR (95% CI)[a]	Reference	1.67 (1.37–2.03)
RR (95% CI)[b]	Reference	1.48 (1.22–1.79)
Total hospitalizations for any reason		
No. of events	5252	1197
Event rate per 100 person-years (95% CI)	41.0 (39.3–42.9)	67.0 (60.7–73.9)
Rate difference (95% CI)	Reference	25.9 (19.1–32.8)
RR (95% CI)[a]	Reference	1.55 (1.40–1.73)
RR (95% CI)[b]	Reference	1.41 (1.27–1.57)
Cardiovascular death or first worsening HF event		
No. of events (%)	1111 (21.3)	232 (30.0)
Event rate per 100 person-years (95% CI)	9.5 (9.0–10.1)	15.1 (13.2–17.2)
Rate difference (95% CI)	Reference	5.6 (3.5–7.6)
HR (95% CI)[a]	Reference	1.53 (1.32–1.76)
HR (95% CI)[b]	Reference	1.38 (1.19–1.60)
First worsening HF event		
No. of events (%)	864 (16.5)	188 (24.3)
Event rate per 100 person-years (95% CI)	7.4 (6.9–7.9)	12.2 (10.5–14.1)
Rate difference (95% CI)	Reference	4.8 (2.9–6.7)
HR (95% CI)[a]	Reference	1.56 (1.33–1.83)
HR (95% CI)[b]	Reference	1.38 (1.17–1.64)
Cardiovascular death		
No. of events (%)	420 (8.0)	82 (10.6)
Event rate per 100 person-years (95% CI)	3.3 (3.0–3.6)	4.6 (3.7–5.7)
Rate difference (95% CI)	Reference	1.3 (0.3–2.4)
HR (95% CI)[a]	Reference	1.42 (1.12–1.81)
HR (95% CI)[b]	Reference	1.30 (1.01–1.66)
Non-cardiovascular death		
No. of events (%)	391 (7.5)	120 (15.5)
Event rate per 100 person-years (95% CI)	3.1 (2.8–3.4)	6.7 (5.6–8.0)
Rate difference (95% CI)	Reference	3.7 (2.4–4.9)
HR (95% CI)[a]	Reference	2.15 (1.74–2.65)
HR (95% CI)[b]	Reference	1.87 (1.50–2.33)
All-cause death		
No. of events (%)	811 (15.5)	202 (26.1)
Event rate per 100 person-years (95% CI)	6.3 (5.9–6.8)	11.3 (9.9–12.9)
Rate difference (95% CI)	Reference	5.0 (3.4–6.6)
HR (95% CI)[a]	Reference	1.78 (1.52–2.08)
HR (95% CI)[b]	Reference	1.58 (1.34–1.86)
Renal composite endpoint		
No. of events (%)	112 (2.1)	18 (2.3)
Event rate per 100 person-years (95% CI)	1.0 (0.8–1.2)	1.2 (0.7–1.8)
Rate difference (95% CI)	Reference	0.2 (−0.4 to 0.8)
HR (95% CI)[a]	Reference	1.20 (0.72–1.98)
HR (95% CI)[b]	Reference	1.29 (0.77–2.18)
Stroke, myocardial infarction, or cardiovascular death		
No. of events (%)	638 (12.2)	123 (15.9)
Event rate per 100 person-years (95% CI)	5.1 (4.7–5.5)	7.1 (6.0–8.5)
Rate difference (95% CI)	Reference	2.0 (0.7–3.3)
HR (95% CI)[a]	Reference	1.39 (1.14–1.68)
HR (95% CI)[b]	Reference	1.30 (1.06–1.59)

CI, confidence interval; COPD, chronic obstructive pulmonary disease; 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, smoking status, 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, type 2 diabetes, myocardial infarction or coronary revascularization, and atrial fibrillation/flutter.

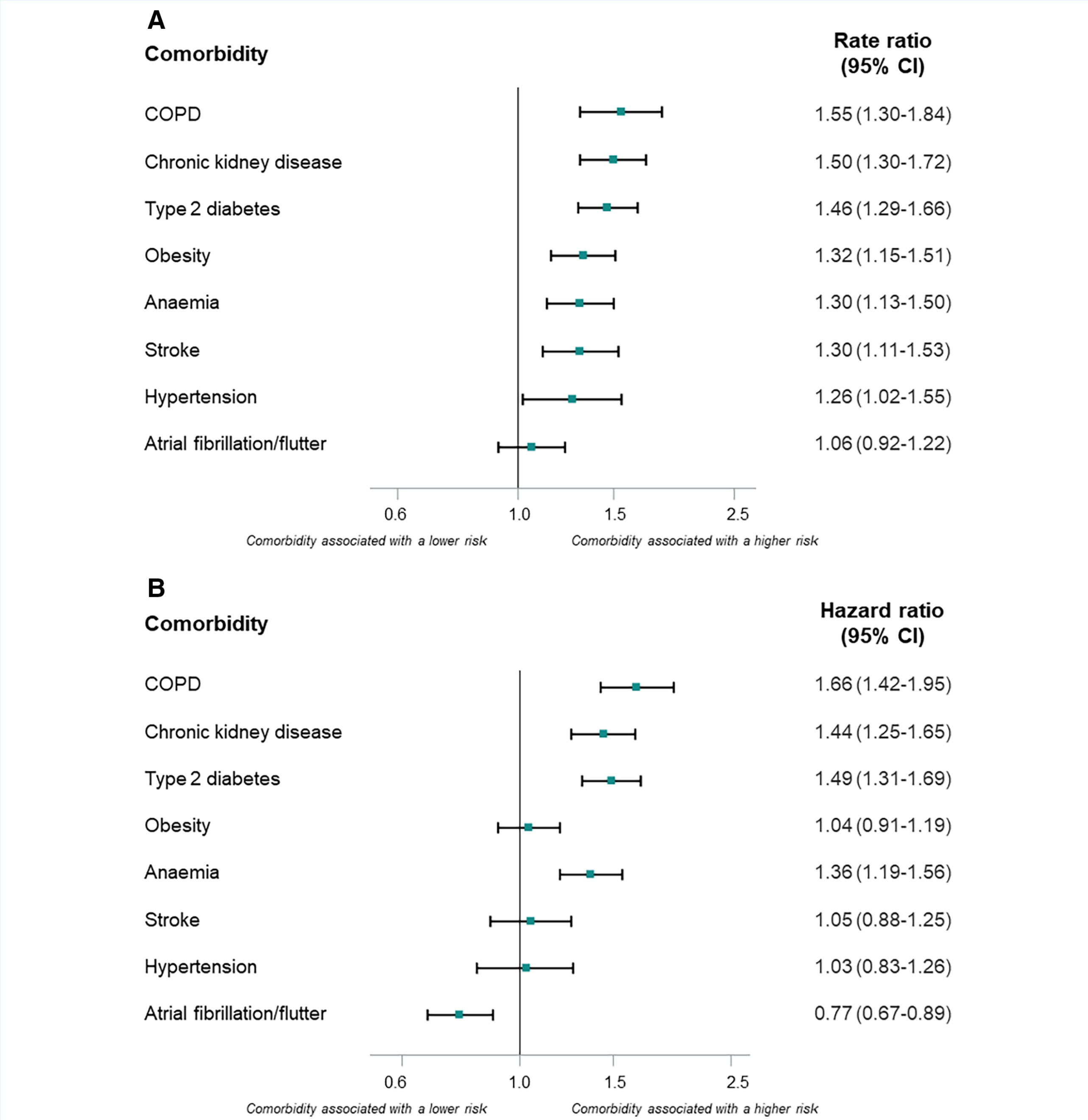


Figure 2 Outcomes associated with major comorbidities. (*A*) Cardiovascular death and total worsening heart failure events. (*B*) All-cause death. Anaemia is defined as a haemoglobin level <130 g/L for men and <120 g/L for women; chronic kidney disease is defined as an estimated glomerular filtration rate <60 ml/min/1.73 m^2; obesity is defined as a body mass index >30 kg/m^2. Rate/hazard ratio >1: a history of the comorbidity of interest is associated with a higher risk compared with no history. Rate/hazard ratio <1: a history of the comorbidity of interest is associated with a lower risk compared with no history. One model was created for each comorbidity, and models were stratified by geographic region and left ventricular ejection fraction stratification and adjusted for treatment assignment, age, sex, New York Heart Associational functional class, and log of N-terminal pro-B-type natriuretic peptide. CI, confidence interval; COPD, chronic obstructive pulmonary disease.

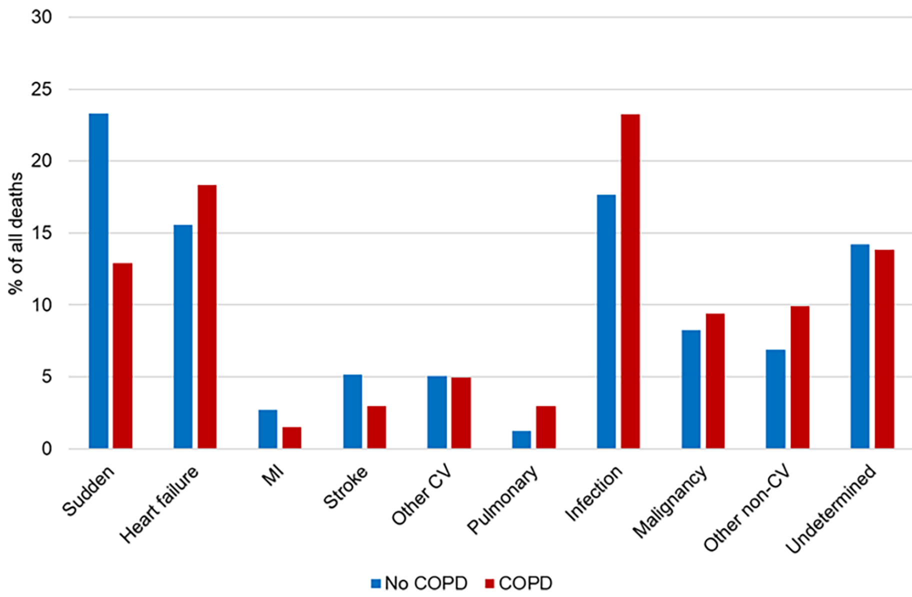


Figure 3 Adjudicated causes of death according to a history of chronic obstructive pulmonary disease (COPD). CV, cardiovascular; MI, myocardial infarction.

Discussion

In this prespecified analysis of FINEARTS-HF, we confirmed that a history of COPD was common in HFmrEF/HFpEF and associated with worse health status and clinical outcomes. Treatment with the non-steroidal MRA, finerenone, compared with placebo, reduced the risk of clinical events, improved health status, and was well-tolerated, regardless of COPD history (*Graphical Abstract*).

Patient characteristics and clinical outcomes according to a history of chronic obstructive pulmonary disease

In FINEARTS-HF, approximately 13% of study participants had an investigator-reported history of COPD, confirming findings from other contemporary HFmrEF/HFpEF trials.[1,3,17–19] This is also consistent with the findings of a recent pooled analysis of more than 8000 patients enrolled in 14 cohort studies, where 15% of patients had a history of COPD.[20] However, the proportion with COPD was less than in other registry-based studies.[5–7] Possible explanations for this difference are the exclusion of patients with severe COPD in FINEARTS-HF and other recent HFmrEF/HFpEF trials (this criterion was applied to avoid including participants with COPD misdiagnosed as HFpEF) and the lack of systematic pulmonary function testing in participants before enrolment in clinical trials. However, even if performed, the interpretation of the results of spirometry and other pulmonary function tests can be difficult in patients with HF.[21]

In keeping with reports from other HFmrEF/HFpEF trials,[1–3] patients with COPD were older, more often male, more comorbid, and more likely to be current or former smokers. Although there were no significant differences in measures of HF severity, including LVEF and NT-proBNP levels, between patients with and without a history of COPD, patients with COPD had a higher level of hs-TnT, which may reflect the effects of inflammation and hypoxia and may be a surrogate marker of the impact of these processes on clinical outcomes.[22,23] In addition, those with COPD had substantially worse NYHA class and KCCQ scores, compared to patients without COPD. Indeed, patients with COPD had lower KCCQ scores compared to those with each of the seven other most common comorbidities. Presumably, this reflects the effect of concomitant HF and COPD on symptom burden, physical function, and health-related quality of life. A further aggravating factor in these patients is the higher rate of obesity, compared to patients without COPD, as obesity also causes dyspnoea and is associated with markedly reduced health-related quality of life.

Other clinical characteristics of patients with COPD in FINEARTS-HF raise concern. First, current smoking remained common in patients with COPD, emphasizing the need to intensify efforts to aid smoking cessation in these patients. Second, the use of beta-blockers in patients with COPD remained high, even though the value of these drugs in HFpEF is unproven (and they may worsen chronotropic incompetence), and they also increase the risk of exacerbations of COPD.[24–27] Third, the use of long-acting beta-2-adrenoreceptor agonists and muscarinic antagonists was relatively low in patients with COPD, and both drug classes individually, and in combination synergistically, improve lung function and reduce dyspnoea and exacerbations.[28]

The present analysis confirmed the strong relationship between a history of COPD and a wide range of adverse clinical outcomes, including worsening HF events, hospitalizations, and death,[1–4] and these associations persisted even after comprehensive adjustment

Table 3 Effects of finerenone compared with placebo on outcomes according to a history of chronic obstructive pulmonary disease

	No COPD ($n = 5228$)		COPD ($n = 773$)		*p*-value for interaction
	Finerenone ($n = 2623$)	Placebo ($n = 2605$)	Finerenone ($n = 380$)	Placebo ($n = 393$)	
Cardiovascular death and total worsening HF events					0.93
No. of events	877	1040	206	243	
Event rate per 100 person-years (95% CI)	13.7 (12.4–15.2)	16.3 (14.8–18.0)	23.0 (17.9–29.5)	27.4 (22.3–33.7)	
Rate difference (95% CI)	−2.6 (−4.7 to −0.5)		−4.4 (−12.5 to 3.7)		
Rate ratio (95% CI)[a]	0.84 (0.73–0.97)		0.84 (0.61–1.16)		
Total worsening HF events					0.84
No. of events	671	827	171	197	
Event rate per 100 person-years (95% CI)	10.5 (9.3–11.8)	13.0 (11.6–14.5)	19.1 (14.5–25.1)	22.2 (17.7–27.9)	
Rate difference (95% CI)	−2.5 (−4.4 to −0.6)		−3.1 (−10.5 to 4.2)		
Rate ratio (95% CI)[a]	0.81 (0.69–0.95)		0.86 (0.60–1.22)		
Cardiovascular death or worsening HF event					0.81
No. of events (%)	517 (19.7)	594 (22.8)	107 (28.2)	125 (31.8)	
Event rate per 100 person-years (95% CI)	8.7 (8.0–9.5)	10.3 (9.5–11.2)	13.6 (11.2–16.5)	16.6 (13.8–19.9)	
Rate difference (95% CI)	−1.5 (−2.7 to −0.4)		−3.0 (−7.0 to 1.1)		
Hazard ratio (95% CI)[a]	0.85 (0.75–0.95)		0.81 (0.63–1.06)		
First worsening HF event					0.95
No. of events (%)	392 (14.9)	472 (18.1)	87 (22.9)	101 (25.7)	
Event rate per 100 person-years (95% CI)	6.6 (6.0–7.3)	8.2 (7.4–9.0)	11.1 (8.9–13.7)	13.4 (10.9–16.4)	
Rate difference (95% CI)	−1.5 (−2.5 to −0.5)		−2.3 (−6.0 to 1.3)		
Hazard ratio (95% CI)[a]	0.81 (0.71–0.92)		0.81 (0.60–1.08)		
Cardiovascular death					0.41
No. of events (%)	206 (7.9)	214 (8.2)	36 (9.5)	46 (11.7)	
Event rate per 100 person-years (95% CI)	3.2 (2.8–3.7)	3.4 (2.9–3.8)	4.0 (2.9–5.6)	5.2 (3.9–6.9)	
Rate difference (95% CI)	−0.1 (−0.8 to 0.5)		−1.2 (−3.2 to 0.8)		
Hazard ratio (95% CI)[a]	0.96 (0.79–1.16)		0.77 (0.49–1.20)		
All-cause death					0.59
No. of events (%)	396 (15.1)	415 (15.9)	95 (25.0)	107 (27.2)	
Event rate per 100 person-years (95% CI)	6.2 (5.6–6.8)	6.5 (5.9–7.1)	10.6 (8.7–12.9)	12.1 (10.0–14.5)	
Rate difference (95% CI)	−0.3 (−1.2 to 0.5)		−1.5 (−4.6 to 1.6)		
Hazard ratio (95% CI)[a]	0.95 (0.83–1.09)		0.85 (0.64–1.13)		
Renal composite endpoint					0.50
No. of events (%)	66 (2.5)	46 (1.8)	9 (2.4)	9 (2.3)	
Event rate per 100 person-years (95% CI)	1.2 (0.9–1.5)	0.8 (0.6–1.1)	1.2 (0.6–2.2)	1.2 (0.6–2.2)	
Rate difference (95% CI)	0.3 (0.0–0.7)		0.0 (−1.2 to 1.1)		
HR (95% CI)[a]	1.39 (0.95–2.03)		0.88 (0.34–2.26)		
Stroke, myocardial infarction, or cardiovascular death					0.31
No. of events (%)	330 (12.6)	308 (11.8)	58 (15.3)	65 (16.5)	
Event rate per 100 person-years (95% CI)	5.3 (4.8–5.9)	4.9 (4.4–5.5)	6.7 (5.2–8.6)	7.5 (5.9–9.6)	
Rate difference (95% CI)	0.4 (−0.4 to 1.2)		−0.9 (−3.4 to 1.6)		
Hazard ratio (95% CI)[a]	1.08 (0.93–1.26)		0.86 (0.60–1.24)		
Improvement in NYHA class from baseline to 12 months					0.048
No. (%)	479 (18.3)	492 (18.9)	78 (20.5)	61 (15.5)	
Odds ratio (95% CI)[b]	0.96 (0.83–1.10)		1.48 (1.02–2.15)		
Change in KCCQ-TSS from baseline to 12 months					0.46
Mean change (SD)	9.11 (20.99)	7.79 (21.23)	7.06 (23.27)	8.00 (21.51)	
Difference in mean (95% CI)[c]	1.81 (0.81–2.81)		0.63 (−2.40 to 3.66)		

CI, confidence interval; COPD, chronic obstructive pulmonary disease; 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.

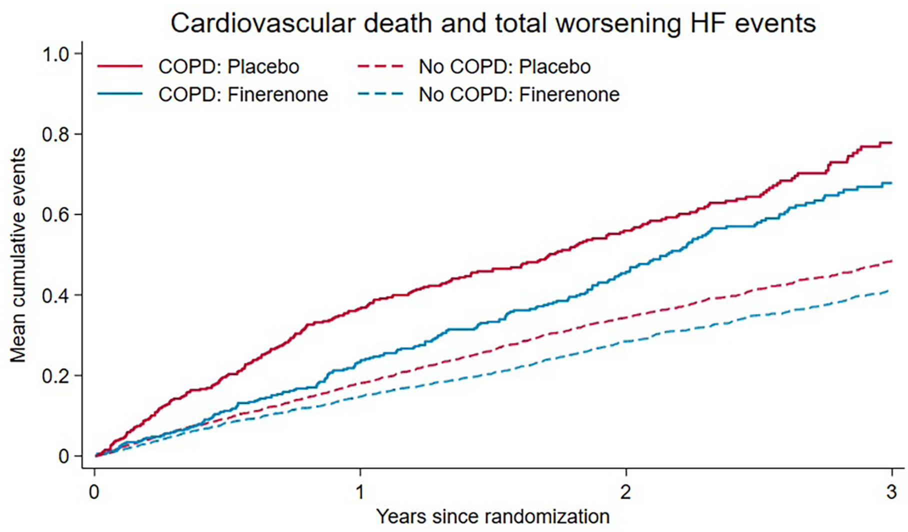


Figure 4 Cardiovascular death and total worsening heart failure (HF) events in patients randomized to finerenone or placebo according to a history of chronic obstructive pulmonary disease (COPD).

Table 4 Effects of finerenone compared with placebo on laboratory measures and systolic blood pressure according to a history of chronic obstructive pulmonary disease

	No COPD ($n = 5215$)		COPD ($n = 771$)		p-value for interaction
	Finerenone ($n = 2614$)	Placebo ($n = 2601$)	Finerenone ($n = 379$)	Placebo ($n = 392$)	
Creatinine ≥2.5 mg/dl					0.82
No. of events (%)	117/2531 (4.62)	72/2512 (2.87)	24/366 (6.56)	17/376 (4.52)	
Odds ratio (95% CI)[a]	1.64 (1.22–2.22)		1.59 (0.83–3.05)		
Creatinine ≥3 mg/dl					0.22
No. of events (%)	50/2531 (1.98)	26/2512 (1.04)	7/366 (1.91)	8/376 (2.13)	
Odds ratio (95% CI)[a]	1.92 (1.19–3.09)		1.00 (0.36–2.83)		
Potassium >5.5 mmol/L					0.90
No. of events (%)	362/2532 (14.30)	173/2513 (6.88)	51/366 (13.93)	26/376 (6.91)	
Odds ratio (95% CI)[a]	2.28 (1.89–2.77)		2.16 (1.31–3.57)		
Potassium >6 mmol/L					0.70
No. of events (%)	74/2532 (2.92)	34/2513 (1.35)	12/366 (3.28)	7/376 (1.86)	
Odds ratio (95% CI)[a]	2.21 (1.47–3.34)		1.77 (0.68–4.59)		
Potassium <3.5 mmol/L					0.03
No. of events (%)	104/2532 (4.11)	252/2513 (10.03)	23/366 (6.28)	29/376 (7.71)	
Odds ratio (95% CI)[a]	0.38 (0.30–0.48)		0.70 (0.39–1.26)		
Systolic blood pressure <100 mmHg					0.52
No. of events (%)	470/2542 (18.49)	311/2525 (12.32)	68/369 (18.43)	50/379 (13.19)	
Odds ratio (95% CI)[a]	1.71 (1.45–2.02)		1.52 (1.00–2.32)		

CI, confidence interval; COPD, chronic obstructive pulmonary disease.
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.

for NT-proBNP and other prognostic variables. Importantly, the associations between COPD and adverse clinical outcomes were at least as strong as those observed with chronic kidney disease or type 2 diabetes, highlighting the significant burden of comorbid COPD in patients with HF. Interestingly, the relationship between COPD and broader outcomes, such as hospitalizations for any reason and all-cause death, was at least as pronounced as that observed for HF-specific outcomes, emphasizing the more general impact of COPD on health.

Sudden death was the single most common mode of death in patients without COPD, with infection and death from worsening HF the next most common causes. In those with concomitant COPD, the order of these causes was reversed with infection the most common, followed by worsening HF and then sudden death.

Effect of finerenone according to a history of chronic obstructive pulmonary disease

In a post hoc analysis of participants with HFmrEF/HFpEF enrolled in TOPCAT in the Americas suggested that a history of pulmonary disease (COPD and/or asthma) modified the effect of spironolactone on all-cause and cardiovascular death, with a greater benefit of spironolactone on these outcomes among individuals with pulmonary disease compared to those without.[2] However, a history of pulmonary disease did not modify the effects of spironolactone on the primary composite endpoint (i.e. cardiovascular death, aborted cardiac arrest, or HF hospitalization) or HF hospitalization,[2] and TOPCAT did not show a significant benefit of spironolactone overall.[12] Therefore, before FINEARTS-HF, the benefits of MRAs in HFmrEF/HFpEF were unproven, and their effects according to COPD status in these patients were uncertain. In the present prespecified analysis of FINEARTS-HF, we demonstrated that a history of COPD did not modify the beneficial effects of finerenone on a range of clinical outcomes. Specifically, finerenone, compared with placebo, reduced the risk of the primary composite outcome of total worsening HF events and cardiovascular death, as well as first and total worsening HF events, in both patients with and without COPD. Importantly, given that patients with COPD were at higher absolute risk, their absolute benefit was greater. For example, finerenone, compared with placebo, reduced the incidence rate of the primary outcome with 4.4 fewer events per 100 person-years in the COPD group versus 2.6 fewer events per 100 person-years in the non-COPD group.

These observations, coupled with the findings from prior trials of MRAs in HFrEF and other therapies in both HFrEF and HFmrEF/HFpEF, strongly suggest that the effect modification by pulmonary disease status observed in TOPCAT may have resulted from the play of chance. Our findings are consistent with data from two separate trials in HFrEF (RALES and EMPHASIS-HF) with two different steroidal MRAs (spironolactone and eplerenone) which showed that the beneficial effects of steroidal MRA treatment were consistent in patients with and without COPD.[10]

In addition to preventing hospitalizations and reducing mortality, improving patients' health status is a key goal of HF management,[26,27] and this is all the more important in patients with COPD, who have a considerably greater symptom burden and worse physical function and quality of life than those without. Therefore, it was important to show that finerenone was as effective in increasing (improving) the mean KCCQ-TSS after 12 months of treatment in patients with COPD as it was in individuals without COPD. Although finerenone, compared with placebo, did not improve NYHA functional class at 12 months in FINEARTS-HF overall, there was a borderline statistically significant interaction between COPD status and the effect of finerenone on this outcome, suggesting that finerenone improved NYHA functional class in patients with COPD, but not in those without. Given that the interaction tests were not sufficiently powered and were not adjusted for multiple comparisons, this borderline interaction could constitute a chance finding.

Increases in potassium and creatinine levels and a decrease in systolic blood pressure (to <100 mmHg) were more common in the finerenone group than in the placebo group, whereas hypokalaemia was less common with finerenone. These effects were generally consistent regardless of COPD status. However, the magnitude of the effect of finerenone in reducing the risk of hypokalaemia appeared to be greater in patients without COPD, possibly due to a lower use of loop diuretics and beta-2-adrenoreceptor agonists (both of which induce hypokalaemia) in these patients.

Taken together, these data underscore the clinically meaningful benefits and tolerability of finerenone in individuals with HFmrEF/HFpEF, regardless of COPD status and provide further evidence for finerenone as a new treatment option for patients with HF and COPD.

Limitations

This study has several limitations. First, patients enrolled in clinical trials are selected according to specific inclusion and exclusion criteria, and the results from the present analysis may not be generalizable to all individuals with HFmrEF/HFpEF in the general population, including those with severe COPD. A clinical trial examining the efficacy and safety of finerenone in patients with right-sided HF secondary to severe COPD would be of particular interest. Second, COPD was investigator-reported, and no specific instructions as to how to diagnose COPD were provided in the protocol. The possibility of some degree of misclassification of COPD status, therefore, cannot be excluded. Third, data on COPD staging, previous exacerbation history, or use frequency of rescue inhalers were not available. Finally, data on right ventricular function (e.g. right ventricular ejection fraction, pulmonary artery systolic pressure) were not available at baseline or during follow-up.

Conclusions

In patients with HFmrEF/HFpEF enrolled in FINEARTS-HF, COPD was common and associated with worse health status and clinical outcomes. The beneficial effects of the non-steroidal MRA, finerenone, on clinical events and symptoms were observed in both patients with and without COPD.

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. Director GCTP Ltd. A.D.H. has nothing to disclose. 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. 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