Title: Effects of mineralocorticoid receptor antagonists in HFrEF patients with COPD in EMPHASIS-HF and RALES.

Short title: Effects of MRAs in HFrEF patients with COPD

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is more common in patients with heart failure and reduced ejection fraction (HFrEF) than in the general population because each condition can arise as a complication of smoking.[1-5] Concomitant COPD is associated with even worse symptoms, functional limitation and clinical outcomes than in HFrEF alone.[6-8] Coexisting COPD also creates therapeutic difficulties. Beta-blockers are a key, life-saving treatment for HFrEF, but may not be tolerated in people with COPD, antagonise the effects of beta-2 adrenoceptor-agonists, a core therapy for COPD, and can cause exacerbations of COPD.[9] However, many if not most patients with COPD can tolerate a beta-1 selective beta-blocker and this treatment should not be withheld in patients with COPD. Conversely, beta-2 adrenoceptor-agonists can cause tachycardia and hypokalaemia, neither of which is desirable in HFrEF. Both hypokalaemia and methylxanthines, another therapy for COPD, can predispose to arrhythmias. Corticosteroids, especially if given orally, cause fluid retention which is undesirable in HFrEF and in COPD, which is itself a sodium- and water-retaining state (although both methylxanthines and systemic corticosteroids are used in a small minority of patients in most countries).

Clearly, it would be ideal to be able to use all other effective therapies for HFrEF in patients with concomitant COPD in view of their heightened risk of adverse outcomes and potential intolerance of beta blockers. In many ways mineralocorticoid receptor antagonists (MRAs) seem an ideal treatment for patients with both HFrEF and COPD. Each condition is associated with an increase in plasma aldosterone concentration and MRAs should help counter fluid-retention, block any adverse effects of exogenous corticosteroids at the mineralocorticoid receptor and mitigate the risk of hypokalaemia with beta-2 agonists.[4,10-12] In addition, MRAs seem to attenuate pathogenic vascular remodelling in the lungs, and right ventricular failure, in experimental models of pulmonary hypertension.[13-17] These problems also occur as secondary complications in some patients with COPD. Surprisingly, however, in a large Danish nationwide cohort, use of spironolactone in such patients was associated with a higher mortality than no use of spironolactone, the opposite of what was found for beta-blockers and renin-angiotensin system antagonists.[18] While this unexpected finding may reflect the specific characteristics of the Danish patients (all of whom had right heart failure) or unmeasured or uncorrected confounding in an observational cohort, it does suggest the subject merits further investigation. MRAs can cause worsening of kidney function and renal dysfunction is common in both HFrEF and COPD. MRAs can also lead to hyperkalaemia which may lead to ventricular arrhythmias and patients with the combination of HFrEF and COPD may be particularly vulnerable to these.[19-21] Despite the Danish observational data and potential for hyperkalaemia to increase the risk of arrhythmias, our hypothesis was that MRAs would be as beneficial in HFrEF patients with COPD, as in those without. Fortunately, there are prospective randomised controlled trial data which allow us to examine both the efficacy and safety of MRAs in HFrEF patients with concomitant COPD. Therefore, in a post hoc analysis, we examined the effect of MRAs in relation to COPD status in patients with HFrEF enrolled in the RALES (Randomized Aldactone Evaluation Study) and EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure) trials.[22-23]

METHODS

RALES and EMPHASIS-HF were each prospective, double-blind, placebo-controlled, event-driven mortality/morbidity trials. Each trial received ethics committee approval and all participants provided written informed consent. Their design, baseline findings, and primary results are published in full.[22-25] The mean follow-up in RALES was 24 months and median follow-up in EMPHASIS-HF was 21 months.

Trial patients

In RALES, patients with New York Heart Association (NYHA) functional class III or IV heart failure, a left ventricular ejection fraction (LVEF) of ≤35% and receiving current treatment with an angiotensin-converting enzyme (ACE) inhibitor (if tolerated) and a loop diuretic, were randomly assigned to receive either spironolactone or placebo. In EMPHASIS-HF, patients with NYHA functional class II heart failure, LVEF of ≤30% (or ≤35% if QRS duration >130 milliseconds) and receiving optimal ACE inhibitor/angiotensin receptor blocker (ARB) and beta-blocker therapy (unless contraindicated), were randomly assigned to either eplerenone or placebo. Exclusion criteria are detailed in the design and results papers.[22,25]

There was no exclusion related to COPD in either trial, although investigators were asked to exclude patients with another clinically important condition (e.g. cancer) likely to greatly shorten life-expectancy.

Trial treatments

In RALES, patients were assigned to a starting dosage of 25mg of spironolactone once daily or a matching placebo. After 8 weeks, the dose could be increased to 50 mg once daily “if the patient showed signs or symptoms of progression of heart failure without evidence of hyperkalaemia”. In EMPHASIS-HF, eplerenone was started at a dose of 25 mg once daily and was increased after 4 weeks to 50 mg once daily (or started at 25 mg on alternate days, and increased to 25 mg daily, if the estimated GFR was 30 to 49 ml per minute per 1.73 m^2), provided the serum potassium level was no more than 5.0 mmol/L.

Identification of COPD

Diagnosis of COPD was reported by investigators in the medical history section of the case report forms in each of RALES and EMPHASIS-HF. There was a specific “yes or no” question about COPD, but no specific criteria were provided for a diagnosis of COPD.

Study outcomes

The primary outcome in RALES was death from any cause and in EMPHASIS-HF it was time to first occurrence of heart failure hospitalisation or death from a cardiovascular cause. The latter was used as the primary endpoint in the present analysis. We also examined the components of this composite, non-cardiovascular and all-cause death, as well as pump failure and sudden cardiac death.

Statistical analysis

In order to maximise the number of COPD patients and events, as well as cover the full spectrum of heart failure symptom severity (NYHA class II to IV), we merged the RALES and EMPHASIS-HF databases. Certain baseline data were collected in EMPHASIS-HF, but not RALES. Hence, the baseline analysis is presented in two tables: Table 1 (baseline characteristics collected in both RALES and EMPHASIS-HF) and Supplemental Table 1 (additional baseline data collected in EMPHASIS-HF only).

Baseline characteristics are reported as means and standard deviations (SD) for continuous variables and frequencies with percentages for categorical variables. Time-to-event endpoints were evaluated using Kaplan–Meier estimates and Cox proportional hazard models, stratified according to trial and adjusted for randomised treatment group to estimate hazard ratios (HRs) with 95% confidence intervals (CIs). Along with crude HRs, we also report HRs adjusted for age, sex, race, heart rate, systolic blood pressure (SBP), NYHA classification, LVEF, estimated glomerular filtration rate (eGFR), history of myocardial infarction (MI), diabetes and atrial fibrillation (AF). In a sensitivity analysis, we also adjusted for beta-blocker use at baseline, given the anticipated imbalance in the use of these drugs between patients with and without COPD and their powerful effect of clinical outcomes in HFrEF.

The treatment effect for each time-to-event endpoint was estimated using Cox models with an interaction term between baseline COPD status and treatment group. The interaction between COPD status and effect of randomised treatment on adverse events and study drug discontinuation was analysed using a logistic regression model with an interaction term between baseline COPD status and treatment.

A P-value of <0.05 was considered significant. Statistical analyses were conducted using STATA version 16.0 (Stata Corp. College Station, Texas, USA).

RESULTS

Overall, 4397 patients were included in the analysis, of whom 2,212 were randomised to placebo and 2,185 to an MRA. Of the included patients, 625 (14.2%) had COPD: 321 (14.7%) in the MRA group and 304 (13.7%) in the placebo group.

Baseline characteristics according to COPD status

The baseline characteristics of patients in the combined RALES and EMPHASIS-HF dataset are shown in Table 1 according to COPD status. Patients with COPD were older and more often men. They were also more likely than patients without COPD to have a history of hypertension, atrial fibrillation and stroke but not of coronary heart disease. NYHA functional class distribution, LVEF and kidney function were similar in each COPD subgroup.

Patients with COPD were significantly less likely to be treated with a beta-blocker. Data on beta-blocker selectivity were not available.

Supplemental Table I contains additional data collected in EMPHASIS-HF only. In EMPHASIS-HF, patients with COPD were more often current smokers (21.7%) than those without COPD (8.9%).

Clinical outcomes according to COPD status

The incidence rate (per 100 person-years) and unadjusted risk of most outcomes examined were higher in patients with COPD compared to those without (the exception was pump failure death, although numbers of this event in the COPD groups were small). The elevated risks were attenuated by multivariable adjustment (Table 2).

Primary outcome (composite of heart failure hospitalisation or cardiovascular death): The event rates were 25.2 (95% CI 22.1 – 28.7) in patients with COPD, versus 19.9 (18.8 – 21.1) in those without COPD with unadjusted HR 1.25 (1.08 – 1.44), using patients without COPD as the reference group. The elevated risk was attenuated to HR 1.16 (1.00 – 1.35) after adjustment for standard prognostic variables. A similar picture was seen for the components of the composite outcome.

Mortality: The higher rate of cardiovascular mortality in patients with COPD was driven by an elevated risk of sudden death compared with pump failure death, compared to patients without COPD: unadjusted HR 1.44 (1.09-1.91) for sudden death versus 1.14 (0.88-1.49) for pump failure death.

The rate of non-cardiovascular mortality, and therefore all-cause mortality, was also higher in patients with COPD, with a greater elevation in risk of non-cardiovascular death versus cardiovascular death, compared to participants without COPD: unadjusted HR 1.82 (1.28-2.58) for non-cardiovascular death versus 1.25 (1.04-1.49) for cardiovascular death. Examination of causes of non-cardiovascular deaths showed an excess of deaths due to infection/sepsis in patients with COPD compared to those without COPD (Supplemental Figure I).

Hospitalisations: Patients with COPD had higher all-cause, heart failure and non-cardiovascular hospitalisations: unadjusted HR 1.33 (1.17 – 1.51), 1.25 (1.05 – 1.49) and 1.79 (1.44 – 2.22), respectively. In contrast to heart failure hospitalisations, the elevated risk of all-cause and non-cardiovascular hospitalisations persisted with multivariable adjustment.

In the sensitivity analyses, further adjusting for beta-blocker slightly attenuated the excess risk related to COPD, more so for heart failure hospitalisation than the other outcomes.

These findings were consistent when RALES and EMPHASIS-HF were analysed separately (Supplemental Tables II and III).

Efficacy of mineralocorticoid receptor antagonists according to COPD status

The benefits of MRAs, compared with placebo, were consistent in patients with and without COPD for all mortality and hospitalisation outcomes (Table 3). The hazard ratio (HR) for the for the primary outcome, was 0.66 (95% CI 0.50 – 0.85) in patients with COPD and 0.65 (0.58 – 0.73) in patients without COPD, P-value for interaction=0.93. The HR for all-cause mortality was 0.77 (0.58 – 1.03) in patients with COPD and 0.72 (0.63 – 0.82) in patients without COPD, P-value for interaction=0.65.

These findings were consistent when RALES and EMPHASIS-HF were analysed separately (Supplemental Tables IV and V).

Safety of mineralocorticoid receptor antagonists according to COPD status

Mild hyperkalaemia (potassium >5.5 mmol/L) was more common on an MRA than on placebo in patients with or without COPD although moderate-to-severe hyperkalaemia (potassium >6.0 mmol/L) appeared to be increased by MRA therapy only in patients without COPD (Table 4).

DISCUSSION

The prevalence of COPD in this combined RALES and EMPHASIS-HF cohort (14.2%), was similar to that reported in other large-scale HFrEF trials including the Prospective Comparison of ARNI with an ACE-Inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure trial (PARADIGM-HF; prevalence 12.9%), the Dapagliflozin And Prevention of Adverse-outcomes in Heart Failure trial (DAPA-HF; prevalence 12.3%) and in a "real-world" study (the European Society of Cardiology long-term registry; prevalence 14.1%).[26-28]

As expected, patients with COPD in RALES and EMPHASIS-HF were older and more often male than those without COPD, smoked more (in EMPHASIS-HF) and had more hypertension and atrial fibrillation, although not diabetes, coronary artery disease or chronic kidney disease.[7,8, 29,30] There was also no difference in LVEF or NYHA class between the two groups. Therefore, it was notable that despite these rather modest differences in recognised prognostic factors, participants with COPD were at considerably higher risk of hospitalisation and death, as has been documented in other studies. As anticipated, some of the excess mortality in patients with COPD was due to non-cardiovascular causes, primarily due to infection/sepsis. Interestingly, however, we found a higher risk of sudden death in patients with COPD, compared with those without. We are not aware of a prior report of this finding. It suggests the possibility of a proarrhythmic milieu in patients with COPD related, for example, to beta-2 agonist induced hypokalaemia, methylxanthine and digoxin use, and hypoxaemia, as well as loss of the antiarrhythmic protection of beta-blockers. Interestingly, the excess risk of sudden death (and heart failure hospitalisation) was slightly attenuated by adjustment for baseline beta-blocker use. Concomitant right ventricular dysfunction which is common in patients with COPD may further elevate the risk of arrhythmias and sudden death.[3, 4, 19-21]

Indeed, because some patients with COPD cannot tolerate beta-blockers, it is even more important that other treatments are available and shown to be effective in HFrEF patients with concomitant COPD. In fact, MRAs may be particularly suited to HFrEF patients with COPD. The importance in avoiding hyperkalaemia has already been highlighted. COPD is itself a fluid-retaining state associated with hyperaldosteronism.[4,10-12] The harmful effects of hyperaldosteronism in HFrEF are well recognised and aldosterone may also have detrimental effects in the pulmonary vasculature which is especially relevant given the propensity of patients with COPD to develop pulmonary hypertension.[13-17]

We showed that MRAs have substantial benefits in HFrEF patients with COPD. The proportional risk reductions in all key outcomes were similar to those obtained in HFrEF patients without COPD, with around a 35% relative risk reduction in the primary composite endpoint and a 30% reduction in cardiovascular death. The absolute risk reductions were also large. In both patient subgroups, the number needed treat (NNT) to prevent one patient experiencing the primary endpoint was only 10-12 over a median follow-up of approximately 2 years. Our findings appear to refute those of the Danish observational study which reported higher mortality in patients with COPD and right heart failure using spironolactone. While this is likely due to unmeasured or uncorrected confounding in the Danish cohort, the patients in the two studies were different. All patients in RALES and EMPHASIS-HF had HFrEF whereas the patients in the Danish observational study were selected because of a diagnosis of COPD and pulmonary hypertension and treatment with diuretics; approximately 60% had a concomitant diagnosis of heart failure (ejection phenotype not defined).[18]

Finally, MRA therapy was as well tolerated in patients with COPD, as in those without. While severe hyperkalaemia was more common in placebo treated patients with COPD, compared to those without COPD , severe hyperkalaemia was significantly less common in MRA treated patients with COPD, compared to without COPD, potentially due to the “protective” effect of chronic respiratory acidosis, metabolic alkalosis, and corticosteroid therapy or beta-agonist treatment, or both.

MRA use in patients with HFrEF has been increasing with rates in patients with COPD, compared with no COPD, of 65.6 versus 71.8% in DAPA-HF (2019), 54.2 versus 55.8% in PARADIGM-HF (2014) and 57.0 versus 52.3% in the ESC Long Term registry (data collected 2011–13).

Translational outlook: Although the exact reasons why patients with HFrEF and concomitant COPD are at such high risk is unknown, these data show the risk of sudden death is particularly elevated, compared to patients without COPD. This may be an area of additional research into other preventive strategies.

Limitations: This study has several limitations. The analyses conducted were not pre-specified. COPD was investigator-reported, COPD severity was not recorded, and we did not know in whom spirometry had been performed. The patients studied were selected for a clinical trial and will differ from those in ordinary every-day practice. Biomarkers and quality of life data were not collected, and smoking status was only documented in EMPHASIS-HF (and not in RALES).

Conclusion

This analysis highlights the importance of MRA therapy in HFrEF patients with COPD. In the RALES and EMPHASIS-HF trials, one-in-seven patients with HFrEF had coexisting COPD. Patients with HFrEF and concomitant COPD had much worse outcomes but the benefit of MRA therapy was consistent across all morbidity and mortality outcomes examined, regardless of COPD status.

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Table Legends

Table 1: Baseline characteristics according to COPD status

Table 2: Event rate (per 100 patient-years) and risk of study endpoints according to COPD status

Table 3: Clinical outcomes and treatment effect according to COPD status (MRA vs placebo event rates and hazard ratios with 95% confidence interval)

Table 4: Adverse effects of interest and permanent study drug discontinuation according to randomised treatment and COPD status at baseline

Figure Legends

Figure 1:

Title: Kaplan-Meier curves for key outcomes, according to baseline COPD status and randomised treatment

Caption: The panels in this figure show cumulative event curves for: Primary composite outcome (HF hospitalisation or death from cardiovascular causes) and death from any cause

APPENDIX

Supplemental Table I: Additional baseline characteristics according to COPD status (EMPHASIS-HF only)

Table 1: Baseline characteristics according to COPD status

	All Patients (N=4397)*	Without COPD (N=3772)	With COPD (N=625)	*P*-value
Age (years)	67.4 ± 9.6	67.1 ± 9.8	69.1 ± 7.9	<0.001
Women	1056 (24.0)	946 (25.1)	110 (17.6)	<0.001
Race				<0.001
White	3706 (84.3)	3140 (83.2)	566 (90.6)	
Black	187 (4.3)	178 (4.7)	9 (1.4)	
Asian	347 (7.9)	308 (8.2)	39 (6.2)	
Other	157 (3.6)	146 (3.9)	11 (1.8)	
Heart rate (bpm)	75.2 ± 13.9	74.9 ± 13.8	76.8 ± 13.9	0.001
SBP (mmHg)	123.4 ± 18.2	123.4 ± 18.3	123.2 ± 17.4	0.80
DBP (mmHg)	74.6 ± 10.8	74.7 ± 10.7	74.1 ± 11.0	0.16
Hypertension	2208 (50.2)	1857 (49.2)	351 (56.2)	0.001
Diabetes	1228 (27.9)	1054 (27.9)	174 (27.8)	0.96
Myocardial infarction	1852 (42.1)	1571 (41.6)	281 (45.0)	0.12
Atrial Fibrillation/Flutter	1026 (23.3)	861 (22.8)	165 (26.4)	0.051
Ischaemic CVA	248 (5.7)	199 (5.3)	49 (7.9)	0.010
HF aetiology				0.22
• **Ischaemic**	2792 (63.6)	2383 (63.2)	409 (65.8)	
• **Non-Ischaemic**	1600 (36.4)	1387 (36.8)	213 (34.2)	
NYHA				0.19
• **II**	2740 (62.3)	2349 (62.3)	391 (62.6)	
• **III**	1173 (26.7)	1021 (27.1)	152 (24.3)	
• **IV**	483 (11.0)	401 (10.6)	82 (13.1)	
LVEF (%)	25.8 ± 5.6	25.9 ± 5.5	25.6 ± 5.8	0.30
eGFR (ml/min/1.73m^2)	68.6 ± 22.4	68.6 ± 22.4	68.3 ± 22.4	0.74
eGFR<60	1702 (38.8)	1460 (38.8)	242 (38.8)	0.97
Creatinine (mg/dL)	1.2 ± 0.3	1.2 ± 0.3	1.2 ± 0.3	0.24

Potassium (mmol/L)	4.3 ± 0.4	4.3 ± 0.4	4.3 ± 0.4	0.054
Diuretic	3826 (87.3)	3283 (87.3)	543 (87.6)	0.83
ACEi/ARB	4145 (94.6)	3552 (94.4)	593 (95.6)	0.21
Beta-blocker	2543 (58.0)	2234 (59.4)	309 (49.8)	<0.001
Digoxin	1955 (44.6)	1680 (44.7)	275 (44.4)	0.89

Data are presented as mean ± SD for continuous measures and n (%) for categorical measures.

Chronic obstructive pulmonary disease (COPD); systolic blood pressure (SBP); diastolic blood pressure (DBP); cerebrovascular accident (CVA); heart failure (HF); New York Heart Association classification (NYHA); left ventricular ejection fraction (LVEF); estimated glomerular filtration rate (eGFR); angiotensin converting enzyme inhibitor (ACEI); angiotensin receptor blocker (ARB).

Units: millimetres of mercury (mmHg), beats per minute (bpm), milligrams per decilitre (mg/dL), millimoles per litre (mmol/L).

*For 4,397 patients of the 4,400 randomised because COPD status was not recorded in 3 patients.

Table 2: Event rate (per 100 patient-years) and risk of study endpoints according to COPD status

	Without COPD (N=3772)	With COPD (N=625)	*P*-value
HF hospitalisation or cardiovascular death			
Events – no. (%)	1195 (31.7)	227 (36.3)	
Event rate per 100 pt. years	19.9 (18.8 – 21.1)	25.2 (22.1 – 28.7)	
Unadjusted HR	1.00 (ref.)	1.25 (1.08 – 1.44)	0.002
Adjusted HR*	1.00 (ref.)	1.16 (1.00 – 1.35)	0.045
Adjusted HR†	1.00 (ref.)	1.12 (0.96 – 1.30)	0.139
HF hospitalisation			
Events – no. (%)	783 (20.8)	150 (24.0)	
Event rate per 100 pt. years	13.1 (12.2 – 14.0)	16.6 (14.2 – 19.5)	
Unadjusted HR	1.00 (ref.)	1.25 (1.05 – 1.49)	0.011
Adjusted HR*	1.00 (ref.)	1.17 (0.98 – 1.40)	0.091
Adjusted HR†	1.00 (ref.)	1.12 (0.93 – 1.34)	0.225
All-cause hospitalisation			
Events – no. (%)	1510 (40.0)	294 (47.0)	
Event rate per 100 pt. years	29.2 (27.8 – 30.7)	39.9 (35.6 – 44.7)	
Unadjusted HR	1.00 (ref.)	1.33 (1.17 – 1.51)	<0.001
Adjusted HR*	1.00 (ref.)	1.25 (1.10 – 1.42)	0.001
Adjusted HR†	1.00 (ref.)	1.23 (1.08 – 1.40)	0.002

Non-Cardiovascular hospitalisation			
Events – no. (%)	394 (10.4)	105 (16.8)	
Event rate per 100 pt. years	6.8 (6.1 – 7.5)	12.2 (10.0 – 14.8)	
Unadjusted HR	1.00 (ref.)	1.79 (1.44 – 2.22)	<0.001
Adjusted HR*	1.00 (ref.)	1.68 (1.34 – 2.10)	<0.001
Adjusted HR[†]	1.00 (ref.)	1.69 (1.35 – 2.12)	<0.001
Cardiovascular death			
Events – no. (%)	729 (19.3)	142 (22.7)	
Event rate per 100 pt. years	10.8 (10.0 – 11.6)	13.4 (11.4 – 15.8)	
Unadjusted HR	1.00 (ref.)	1.25 (1.04 – 1.49)	0.016
Adjusted HR*	1.00 (ref.)	1.13 (0.93 – 1.36)	0.211
Adjusted HR[†]	1.00 (ref.)	1.10 (0.91 – 1.32)	0.329
Non-Cardiovascular death			
Events – no. (%)	142 (3.8)	40 (6.4)	
Event rate per 100 pt. years	2.1 (1.8 – 2.5)	3.8 (2.8 – 5.2)	
Unadjusted HR	1.00 (ref.)	1.82 (1.28 – 2.58)	0.001
Adjusted HR*	1.00 (ref.)	1.85 (1.29 – 2.65)	0.001
Adjusted HR[†]	1.00 (ref.)	1.81 (1.26 – 2.60)	0.001
All-cause death			
Events – no. (%)	871 (23.1)	182 (29.1)	
Event rate per 100 pt. years	12.8 (12.0 – 13.7)	17.2 (14.9 – 19.9)	

Unadjusted HR	1.00 (ref.)	1.34 (1.14 – 1.57)	<0.001
Adjusted HR*	1.00 (ref.)	1.24 (1.05 – 1.46)	0.010
Adjusted HR†	1.00 (ref.)	1.21 (1.03 – 1.43)	0.024
Pump failure death			
Events – no. (%)	358 (9.5)	64 (10.2)	
Event rate per 100 pt. years	5.3 (4.7 – 5.8)	6.1 (4.7 – 7.7)	
Unadjusted HR	1.00 (ref.)	1.14 (0.88 – 1.49)	0.327
Adjusted HR*	1.00 (ref.)	0.96 (0.73 – 1.27)	0.778
Adjusted HR†	1.00 (ref.)	0.94 (0.71 – 1.24)	0.656
Sudden cardiac death			
Events – no. (%)	267 (7.1)	60 (9.6)	
Event rate per 100 pt. years	3.9 (3.5 – 4.4)	5.7 (4.4 – 7.3)	
Unadjusted HR	1.00 (ref.)	1.44 (1.09 – 1.91)	0.011
Adjusted HR*	1.00 (ref.)	1.35 (1.01 – 1.80)	0.042
Adjusted HR†	1.00 (ref.)	1.31 (0.98 – 1.76)	0.064

* Model adjusted for age, sex, race, heart rate, systolic blood pressure, New York Heart Association classification, left ventricular ejection fraction, estimated glomerular filtration rate, history of myocardial infarction, diabetes and atrial fibrillation.
† Adjusted as for * with additional adjustment for beta blocker prescription at baseline.
Chronic obstructive pulmonary disease (COPD); heart failure (HF); hazard ratio (HR).

Table 3: Clinical outcomes and treatment effect according to COPD status (MRA vs placebo event rates and hazard ratios with 95% confidence interval)

	Without COPD		With COPD		
	Placebo (N=1908)	MRA (N=1864)	Placebo (N=304)	MRA (N=321)	*P*-value for interaction
HF hospitalisation or cardiovascular death					
Events – no. (%)	700 (36.7)	495 (26.6)	128 (42.1)	99 (30.8)	
Event rate per 100 pt. yrs.	24.4 (22.6 – 26.2)	15.8 (14.5 – 17.3)	31.5 (26.5 – 37.5)	20.0 (16.4 – 24.3)	
Unadjusted HR	0.65 (0.58 – 0.73)		0.66 (0.50 – 0.85)		0.93
HF hospitalisation					
Events – no. (%)	465 (24.4)	318 (17.1)	88 (28.9)	62 (19.3)	
Event rate per 100 pt. yrs.	16.2 (14.8 – 17.7)	10.2 (9.1 – 11.4)	21.7 (17.6 – 26.7)	12.5 (9.8 – 16.1)	
Unadjusted HR	0.64 (0.55 – 0.73)		0.59 (0.43 – 0.82)		0.79
All-cause hospitalisation					
Events – no. (%)	814 (42.7)	696 (37.3)	158 (52.0)	136 (42.4)	
Event rate per 100 pt. yrs.	32.8 (30.6 – 35.1)	25.9 (24.1 – 27.9)	48.6 (41.6 – 56.8)	33.0 (27.9 – 39.1)	
Unadjusted HR	0.80 (0.72 – 0.89)		0.71 (0.57 – 0.90)		0.28
Non-Cardiovascular hospitalisation					
Events – no. (%)	185 (9.7)	209 (11.2)	53 (17.4)	52 (16.2)	
Event rate per 100 pt. yrs.	6.5 (5.6 – 7.5)	7.0 (6.1 – 8.1)	13.9 (10.6 – 18.2)	10.8 (8.2 – 14.2)	
Unadjusted HR	1.06 (0.87 – 1.30)		0.78 (0.53 – 1.14)		0.16
Cardiovascular death					
Events – no. (%)	420 (22.0)	309 (16.6)	79 (26.0)	63 (19.6)	
Event rate per 100 pt. yrs.	12.5 (11.4 – 13.8)	9.0 (8.1 – 10.1)	16.1 (12.9 – 20.1)	11.1 (8.7 – 14.3)	
Unadjusted HR	0.72 (0.62 – 0.83)		0.72 (0.52 – 1.00)		1.00
All-cause death					
Events – no. (%)	501 (26.3)	370 (19.8)	98 (32.2)	84 (26.2)	
Event rate per 100 pt. yrs.	15.0 (13.7 – 16.3)	10.8 (9.7 – 11.9)	20.0 (16.4 – 24.3)	14.8 (12.0 – 18.4)	
Unadjusted HR	0.72 (0.63 – 0.82)		0.77 (0.58 – 1.03)		0.65
Pump failure death					
Events – no. (%)	212 (11.1)	146 (7.8)	38 (12.5)	26 (8.1)	
Event rate per 100 pt. yrs.	6.3 (5.5 – 7.2)	4.3 (3.6 – 5.0)	7.7 (5.6 – 10.6)	4.6 (3.1 – 6.7)	

Unadjusted HR	0.67 (0.54 – 0.83)		0.61 (0.37 – 1.01)		0.80
Sudden cardiac death					
Events – no. (%)	154 (8.1)	113 (6.1)	32 (10.5)	28 (8.7)	
Event rate per 100 pt. yrs.	4.6 (3.9 – 5.4)	3.3 (2.7 – 4.0)	6.5 (4.6 – 9.2)	4.9 (3.4 – 7.2)	
Unadjusted HR	0.71 (0.56 – 0.91)		0.80 (0.48 – 1.33)		0.73

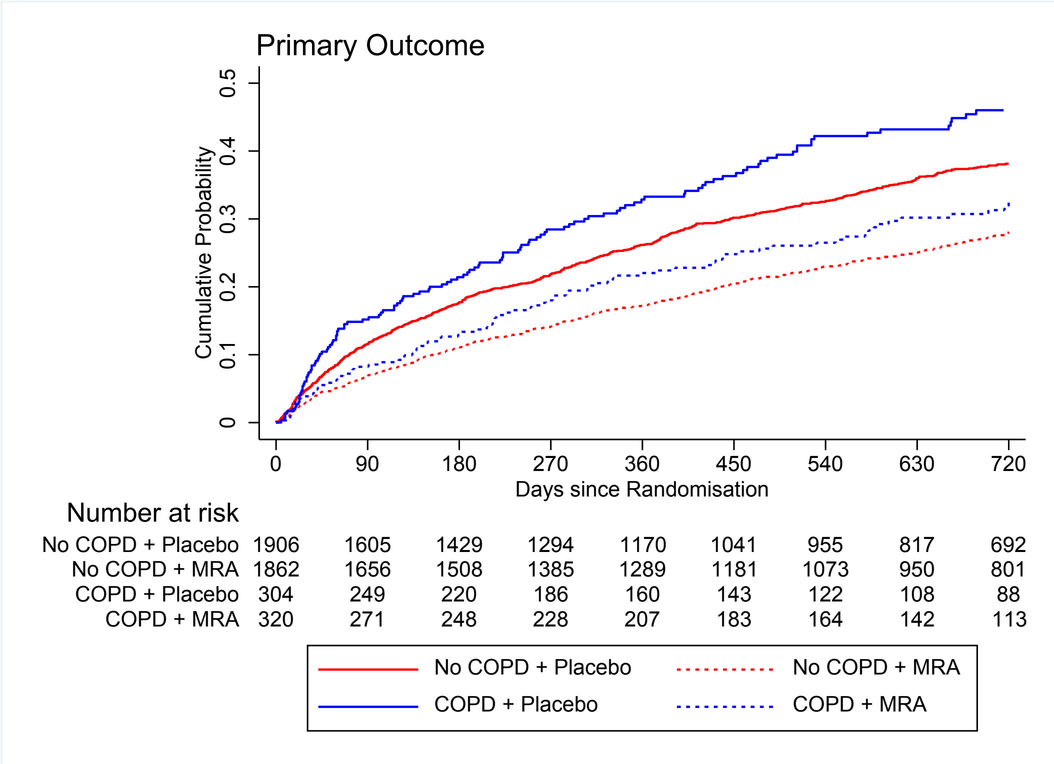
Chronic obstructive pulmonary disease (COPD); mineralocorticoid receptor antagonist (MRA); heart failure (HF); hazard ratio (HR).

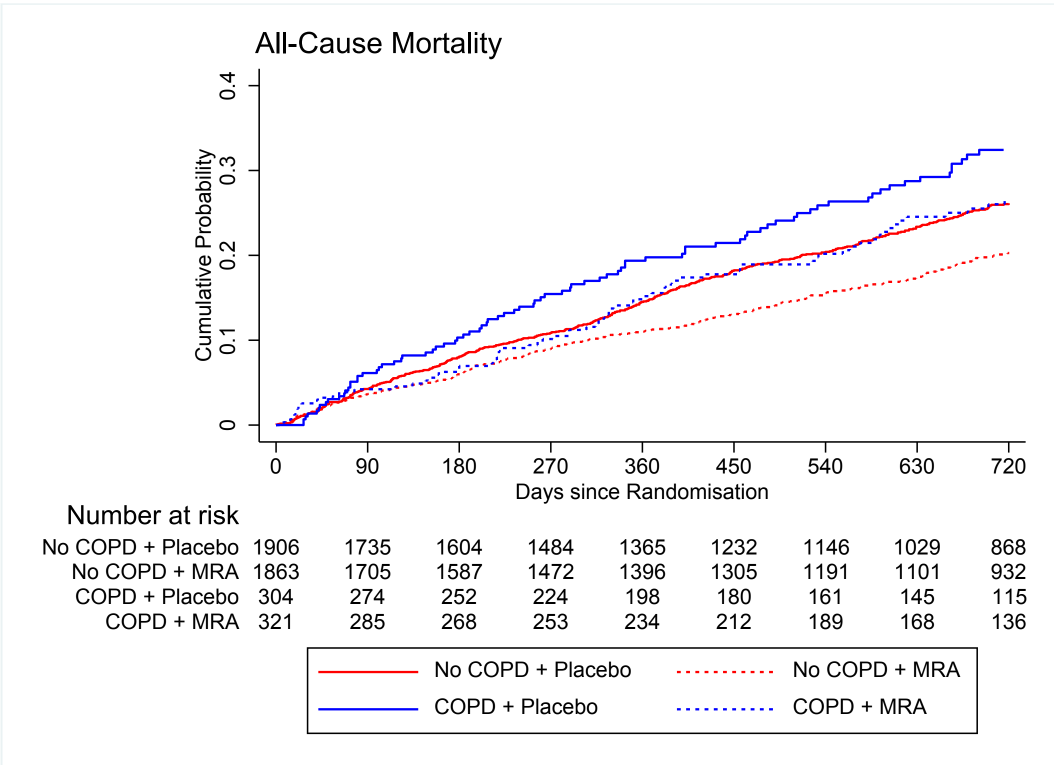
Table 4: Adverse effects of interest and permanent study drug discontinuation according to randomised treatment and COPD status at baseline

Event	Without COPD		With COPD		*P*-value for interaction
	Placebo (N=1908)	MRA (N=1864)	Placebo (N=304)	MRA (N=321)	
Hypotension					
Events (%)	76 (4.0)	86 (4.6)	10 (3.3)	14 (4.4)	
Unadjusted OR	1.17 (0.85 – 1.60)		1.36 (0.59 – 3.12)		0.76
Creatinine ≥2.5mg/dL					
Events (%)	59 (3.1)	83 (4.5)	6 (2.0)	14 (4.4)	
Unadjusted OR	1.47 (1.05 – 2.08)		2.38 (0.89 – 6.33)		0.39
Creatinine ≥3.0mg/dL					
Events (%)	25 (1.3)	32 (1.7)	3 (1.0)	7 (2.2)	
Unadjusted OR	1.32 (0.78 – 2.24)		2.32 (0.59 – 9.12)		0.47
Potassium >5.5mmol/L					
Events (%)	111 (5.8)	244 (13.1)	22 (7.2)	42 (13.1)	
Unadjusted OR	2.44 (1.93 – 3.08)		1.95 (1.13 – 3.36)		0.44
Potassium >6.0mmol/L					
Events (%)	23 (1.2)	60 (3.2)	9 (3.0)	6 (1.9)	
Unadjusted OR	2.73 (1.68 – 4.43)		0.63 (0.22 – 1.79)		**0.01**
Potassium <3.5mmol/L					
Events (%)	263 (13.8)	130 (7.0)	36 (11.8)	24 (7.5)	
Unadjusted OR	0.47 (0.38 – 0.58)		0.60 (0.35 – 1.04)		0.41
Study Drug Discontinuation (all-cause)					
Events (%)	377 (19.8)	365 (19.6)	64 (21.1)	71 (22.1)	
Unadjusted OR	0.99 (0.84 – 1.16)		1.08 (0.73 – 1.58)		0.73

OR-odds ratio with 95% confidence interval.
The *P*-value for interaction in bold indicates statistical significance.
Chronic obstructive pulmonary disease (COPD); mineralocorticoid receptor antagonist (MRA).

Figure 1: Kaplan-Meier curves for key outcomes, according to baseline COPD status and randomised treatment. The primary outcome was the composite of heart failure hospitalisation and death from cardiovascular causes.





Title: Effects of mineralocorticoid receptor antagonists in HFrEF patients with COPD in EMPHASIS-HF and RALES.

Permissions note: N/A