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Original research

Relationship between heart failure and the risk of acute exacerbation of COPD

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ABSTRACT

Rationale Heart failure (HF) management in chronic obstructive pulmonary disease (COPD) is often delayed or suboptimal.

Objectives To examine the effect of HF and HF medication use on moderate-to-severe COPD exacerbations.

Methods and measurements Retrospective cohort studies from 2006 to 2016 using nationally representative English primary care electronic healthcare records linked to national hospital and mortality data. Patients with COPD with diagnosed and possible HF were identified. Possible HF was defined as continuous loop diuretic use in the absence of a non-cardiac indication. Incident exposure to HF medications was defined as ≥ 2 prescriptions within 90 days with no gaps > 90 days during ≤ 6 months of continuous use; prevalent exposure as 6+ months of continuous use. HF medications investigated were angiotensin receptor blockers, ACE inhibitors, beta-blockers, loop diuretics and mineralocorticoid receptor antagonists. Cox regression, stratified by sex and age, further adjusted for patient characteristics, was used to determine the association of HF with exacerbation risk.

Main results 86 795 patients with COPD were categorised as no evidence of HF ($n=60\,047$), possible HF ($n=8476$) and newly diagnosed HF ($n=2066$). Newly diagnosed HF (adjusted HR (aHR): 1.45, 95% CI: 1.30 to 1.62) and possible HF (aHR: 1.65, 95% CI: 1.58 to 1.72) similarly increased exacerbation risk. Incident and prevalent use of all HF medications were associated with increased exacerbation risk. Prevalent use was associated with reduced exacerbation risk compared with incident use.

Conclusions Earlier opportunities to improve the diagnosis and management of HF in the COPD population are missed. Managing HF may reduce exacerbation risk in the long term.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is characterised by persistent, irreversible airflow limitation resulting from exposure to harmful particulates and is often accompanied by progressive inflammatory disease of the airways. Patients with COPD experience periods of acute symptom worsening or exacerbations.¹ Heart failure (HF) is a common comorbidity in people with COPD, with an estimated global prevalence of HF comorbidity in patients with COPD at over 14.8 million²; however, HF remains under-recognised in the COPD population.³

Key messages

What is the key question?

- What is the relationship of heart failure (HF) and HF medication use with risk of moderate-to-severe chronic obstructive pulmonary disease (COPD) exacerbations?

What is the bottom line?

- Earlier opportunities to improve the diagnosis and management of heart failure in UK primary care patients with COPD could reduce exacerbation risk.

Why read on?

- We find evidence that managing HF may reduce risk of acute exacerbations of COPD in the long term.

The diagnosis of HF in the presence of COPD is difficult due to shared risk factors and symptomatology.^{4–5} HF diagnosis and management are significantly delayed in patients with COPD compared with patients without COPD.⁶

There is underuse of cardiovascular medications, particularly beta-blockers (BB), in patients with COPD with cardiovascular indications.^{7–9} Studies have also investigated the effect of cardiovascular medications on patients with COPD with respect to survival, with mixed results^{10–13}; however, studies examining the effect on risk of COPD exacerbations are rarer. One observational study found that angiotensin receptor blocker (ARB) use was associated with fewer severe exacerbations than ACE inhibitor (ACEi) use.¹⁴ A systematic review of BB use on exacerbation risk concluded that most evidence supported no change or reduced exacerbation risk in BB users compared with non-users in patients with COPD with, or at risk of, cardiovascular disease.¹⁵ Long-term effects of HF medications on exacerbation risk in patients with COPD with HF have not been assessed.

We investigated the relationship between having HF diagnosed and exacerbation risk and the effect of possible HF diagnosis on exacerbation risk. In addition, we investigated the effect of incident and prevalent use of HF medications on exacerbation risk in patients with COPD with diagnosed HF.

METHODS

Data source

Pseudonymised primary care electronic records from the Clinical Practice Research Datalink



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(CPRD) Global Initiative for Chronic Obstructive Lung Disease (GOLD) database were obtained. CPRD represents 6.9% of the UK population and is representative in terms of sex, age, body mass index (BMI) and ethnicity.¹⁶ Linked mortality data from the Office for National Statistics, socioeconomic data from the Index of Multiple Deprivation (IMD) and secondary care data from Hospital Episode Statistics (HES) were provided for this study by CPRD for patients in England.

General inclusion and exclusion criteria

Patients with COPD were identified using a validated algorithm¹⁷ between 1 January 2006 and 31 December 2016. Briefly, patients with COPD diagnosed at age ≥ 35 years with validated primary care codes and a history of smoking were eligible for inclusion.^{17–18} HF was identified in CPRD using a previously published Read code list (see online supplemental material).¹⁹

Outcome

Moderate acute exacerbations of COPD (AECOPD) (those managed in primary care) were identified from CPRD using a validated algorithm identifying AECOPD Read codes, lower respiratory tract infection, antibiotic prescription and oral corticosteroid prescription.²⁰ Severe AECOPD (those requiring hospitalisation) were identified from HES using validated International Classification of Diseases, 10th Revision codes.²¹ The outcome was time-to-first moderate-or-severe AECOPD.

Covariates

Age groups were 35–64 years, 65–74 years, 75–84 years and 85+ years. Patients were categorised as current or former smokers. BMI (kg/m^2) was categorised as 'underweight' (<18.5), 'healthy weight' (18.5 – 24.9), 'overweight' (25 – 29.9) and 'obese' (≥ 30). Socioeconomic status was evaluated using IMD 2010 divided into quintiles. The severity of airflow limitation was assessed using the GOLD guidelines and grouped as GOLD1 (forced expiratory volume in 1 s (FEV1) % predicted $>80\%$, mild), GOLD2 (FEV1 % predicted 50% – 79% , moderate),

GOLD3 (FEV1 % predicted 30% – 49% , severe) and GOLD4 (FEV1 % predicted less than 30% , very severe).¹ The number of moderate-to-severe exacerbations in the year prior to the start of follow-up was considered as baseline exacerbation history. History of cardiovascular disease included prior diagnosis of ischaemic heart disease, peripheral artery disease, atrial fibrillation, hypertension and/or stroke. Baseline use of short-acting beta agonists, short-acting muscarinic antagonists, long-acting beta agonists (LABA), long-acting muscarinic antagonist (LAMA), inhaled corticosteroids (ICS) or combination was defined as at least two prescriptions for a given drug class in the year prior to the start of follow-up. Baseline cardiovascular medication use, including ACEi, ARB, BB, calcium channel blockers, loop diuretics, mineralocorticoid receptor antagonists (MRA), statins and vasodilators, was defined as at least two prescriptions for a given drug class in the year prior to the start of follow-up.

HF hospitalisation and investigation

History of HF hospitalisation was identified as those with an HF diagnostic code (I11.0, I13.0, I13.2, I50.0, I50.1 or I50.9) as the primary or secondary condition related to a hospitalisation.²²

History of echocardiography was identified in CPRD using the echocardiography Read codes from the Quality and Outcomes Framework.²³ Tests for B-type natriuretic peptide (BNP) levels²⁴ were identified using the following Read codes: 44AN.00, 44AR.00, 44AP.00, 44AF.00 or 44AF.00. Cardiology outpatient visits were identified in HES Outpatient data using the main or treatment specialty code '320—Cardiology'.

Analyses of the effect of possible and diagnosed HF on AECOPD risk

Identification of the patient populations for analyses of the effect of possible and diagnosed HF on exacerbation risk is outlined in figure 1, following the left pathway. To be included, a patient's COPD diagnosis must have preceded his or her HF diagnosis, and his or her HF diagnosis had to occur in primary care when a patient met the other eligibility criteria for follow-up and

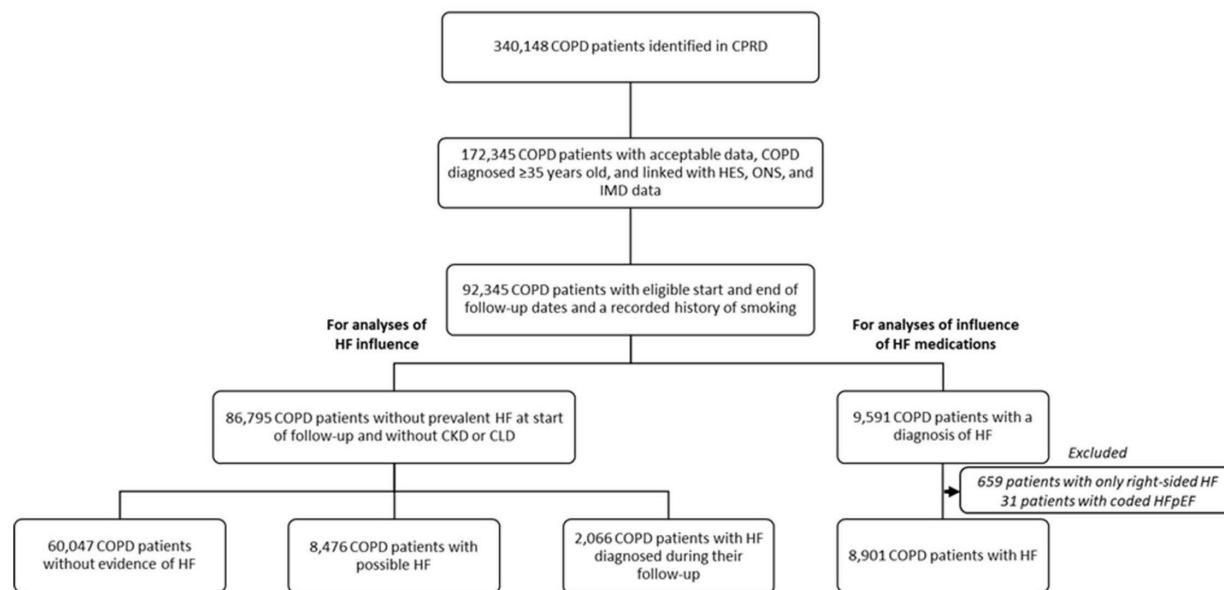


Figure 1 Derivation of the study populations. For analyses of the influences of HF and HF medications on exacerbation risk from the CPRD. CKD, chronic kidney disease; CLD, chronic liver disease; COPD, chronic obstructive pulmonary disease; CPRD, Clinical Practice Research Datalink; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HES, Hospital Episode Statistics; IMD, Index of Multiple Deprivation; ONS, Office for National Statistics.

between 1 January 2006 and 31 December 2016. Patients with non-cardiac indications for loop diuretic use (chronic kidney disease (CKD) stages 3–5, nephrotic syndrome and chronic liver disease (CLD)) were excluded. 'Possible HF' was defined as continuous loop diuretic use, in the absence of other indications and in the absence of an HF diagnosis in primary care.²⁵ Continuous use was defined as three consecutive prescriptions within 100 days.

Patients with COPD with possible HF or diagnosed HF were matched 1:2 on sex and age (± 1.0 year) to patients with COPD without evidence of HF with replacement. Matching and analyses were performed separately for each exposure group. Start of follow-up was defined as the latest of (1) date data were deemed to be acceptable for research as determined by CPRD (ie, had passed a number of quality checks), (2) date from which the patient has continuous data available, (3) start of the study (1 January 2006) or (4) date of COPD diagnosis, date of HF diagnosis or date of first loop diuretic prescription for possible HF. Patients were censored on (1) transferring from the practice, (2) last date of data collection from the practice, (3) last date of linked data collection, (4) death or (5) end of study (31 December 2016).

Stratified Cox regression was used to assess the hazard for moderate-to-severe exacerbation. Each regression was stratified by matched set, to account for matching on sex and age.²⁶ Robust variance estimates were used to account for clustering on general practice. Regression was adjusted for smoking status, BMI, IMD, exacerbation history, inhaler use, severity of airflow limitation, a history of cardiovascular disease and use of cardiovascular medications. Adjusted HRs (aHRs) were used to assess exacerbation risk comparing patients with COPD with possible or diagnosed HF with patients with COPD without evidence of HF.

Analyses of the effect of HF medications on AECOPD risk

Identification of the patient population for analyses of the effect of HF medications on exacerbation is outlined in figure 1, following the right pathway. To be included, a patient must have diagnoses for COPD and HF in primary care, regardless of which condition came first. Patients with incident and prevalent comorbidity were eligible for inclusion, as were patients with CKD or CLD because loop diuretic use was not used to define HF status in these analyses. Patients with right-sided HF codes only ($n=659$) and patients with explicitly coded HF with preserved ejection fraction (HFpEF; $n=31$) were excluded from these analyses as we were interested in left-sided HF specifically, and HFpEF does not have the same treatment recommendations and outcomes as HFrEF.²⁷

Cardiovascular medications of interest were those commonly used in the management of HF,²⁷ including ACEi, ARB, BB, loop diuretics and MRA, and were assessed in separate analyses. A patient was considered to be exposed to a given medication providing they had at least two prescriptions within 90 days. Continuous use was defined as having regular prescriptions for a given medication with gaps between prescriptions being no more than 90 days. Incident use was defined as <6 months of continuous exposure. Prevalent use was defined as ≥ 6 months of continuous exposure. A period of 6 months was chosen to represent prevalent use to minimise effects of drugs being trialled and then discontinued. Start and end of follow-up were defined as above, except that start of follow-up could begin only on comorbidity diagnosis. Exposed patients were additionally censored 90 days after their last prescription for a given medication as longer gaps between prescriptions make determining continuous

exposure less accurate. Exposure was defined using person-time, meaning that patients could have multiple exposure statuses throughout follow-up, whereby patients whose exposure status changed during the study period were censored from their original exposure cohort and would begin contributing person-time to their new exposure cohort. (online supplemental figure E1).

The hazard for moderate-to-severe exacerbation in incident and prevalent users of a given medication was compared with non-users using Cox proportional hazards regression with robust variance estimates, adjusted for smoking status, BMI, IMD, exacerbation history, inhaler use, severity of airflow limitation, a history of cardiovascular disease and use of other cardiovascular medications.

Sensitivity analyses

First, to assess whether removing patients with CKD or CLD noticeably changed the exacerbation risk of our study populations, we assessed exacerbation risk comparing patients with COPD with a diagnosis of HF (combined patients with newly diagnosed HF with and without CKD or CLD) with patients with COPD without a diagnosis of HF (combined patients with no evidence of HF, possible HF and patients with COPD with CKD or CLD without a diagnosis of HF in primary care).

Second, we identified possible patients with HF with evidence of being investigated for HF, defined as a cardiology outpatient visit or echocardiography or BNP test. We compared exacerbation risk in patients with COPD with possible HF who had evidence of being investigated for HF with those without evidence of HF investigations.

Third, we included patients with a history of HF hospitalisation without a primary care diagnosis as having newly diagnosed HF, as opposed to possible HF.

RESULTS

Description of patients with COPD without evidence of HF, with possible HF and with newly diagnosed HF

We identified 86 795 patients with COPD without prevalent HF at the start of follow-up, of whom 60 047 patients had no evidence of HF, 8476 patients had possible HF and 2066 patients had HF diagnosed during follow-up (figure 1). Compared with patients with COPD without evidence of HF, patients with COPD with possible or diagnosed HF were older, former smokers, obese, with severe-to-very-severe airflow limitation (GOLD3–4), greater history of exacerbations, more use of triple (LABA+LAMA+ICS) inhaler therapy and with a greater history of cardiovascular disease (table 1). The proportion of newly diagnosed and possible patients with HF with a history of HF investigations and the median time since the most recent investigation are summarised in online supplemental table E1.

Relationship between newly diagnosed HF and AECOPD risk

We matched 2066 patients (100%) with newly diagnosed HF to 4132 patients without evidence of HF (online supplemental table E2). Patients with COPD with newly diagnosed HF experienced greater risk of moderate-to-severe exacerbation than patients with COPD without evidence of HF (figure 2A; aHR: 1.45; 95% CI: 1.30 to 1.62).

Relationship between possible HF and AECOPD risk

We matched 8423 patients (99.4%) with possible HF to 16 792 patients without evidence of HF (online supplemental table E3). Patients with COPD with possible HF experienced greater risk of moderate-to-severe exacerbation than patients with COPD

Table 1 Descriptive statistics for patients with COPD without evidence of HF, possible HF and newly diagnosed HF

	COPD patients without evidence of HF	COPD patients with possible HF	COPD patients with diagnosed HF		COPD patients without evidence of HF	COPD patients with possible HF	COPD patients with diagnosed HF
Number of patients (N)	60 047	8476	2066	Exacerbation history*	1.52 (0–15)	2.17 (0–13)	2.70 (0–14)
Female	27 155 (45.2)	4247 (50.1)	743 (36.0)	COPD medications*			
				SABA/SAMA	37 990 (63.3)	6222 (73.4)	1489 (72.1)
Age, years (IQR)	66 (59, 74)	73 (66, 80)	74 (67, 81)	LABA alone	1453 (2.4)	250 (3.0)	31 (1.5)
				LAMA alone	4744 (7.9)	537 (6.3)	163 (7.9)
Smoking status				ICS alone	5969 (9.9)	947 (11.2)	92 (4.5)
Current Smoker	26 291 (43.8)	2566 (30.3)	497 (24.1)	LABA+LAMA	631 (1.1)	81 (1.0)	29 (1.4)
Former Smoker	33 756 (56.2)	5910 (69.7)	1569 (75.9)	LABA+ICS	14 685 (24.5)	2435 (28.7)	476 (23.0)
				LAMA+ICS	1121 (1.9)	206 (2.4)	27 (1.3)
Body mass index				Triple	10 239 (17.1)	1925 (22.7)	823 (39.8)
Underweight (<18.5)	3295 (5.49)	356 (4.20)	113 (5.47)	No long-acting inhaler	21 205 (35.3)	2095 (24.7)	425 (20.6)
Healthy weight (18.5–24.9)	21 463 (35.7)	2253 (26.6)	640 (31.0)				
Overweight (25.0–29.9)	18 982 (31.6)	2339 (27.6)	595 (28.8)	History of cardiovascular disease†	29 504 (49.1)	6527 (77.0)	1687 (81.7)
Obese (≥30)	14 581 (24.3)	3183 (37.6)	667 (32.3)	Atrial fibrillation	2120 (3.5)	999 (11.8)	671 (32.5)
Missing data	1726 (2.9)	345 (4.1)	51 (2.5)	Hypertension	24 759 (41.2)	5474 (64.6)	1033 (50.0)
				Ischaemic heart disease	7343 (12.2)	2231 (26.3)	838 (40.6)
Index of Multiple Deprivation				Peripheral artery disease	3023 (5.0)	654 (7.7)	222 (10.8)
1: Most deprived	8581 (14.3)	1144 (13.5)	268 (13.0)	Stroke	3195 (5.3)	788 (9.3)	231 (11.2)
2	11 540 (19.2)	1718 (20.3)	403 (19.5)				
3	11 698 (19.5)	1613 (19.0)	406 (19.7)	Diabetes mellitus	5794 (9.7)	1358 (16.0)	459 (22.2)
4	13 978 (23.3)	1972 (23.3)	473 (22.9)				
5: Least deprived	14 250 (23.7)	2029 (23.9)	516 (25.0)	CVD medications*			
				ACEi	9789 (16.3)	2446 (28.7)	1230 (59.5)
GOLD Stage				ARB	3538 (5.9)	900 (10.6)	332 (16.1)
1: Mild	23 860 (39.7)	2998 (35.4)	703 (34.0)	Beta-blockers	4491 (7.5)	1007 (11.9)	737 (35.7)
2: Moderate	15 336 (25.5)	1762 (20.8)	486 (23.5)	Calcium channel blockers	5054 (8.4)	1464 (17.3)	329 (15.9)
3: Severe	7767 (12.9)	1449 (17.1)	426 (20.6)	MRA	248 (0.4)	276 (3.3)	479 (23.2)
4: Very Severe	1776 (3.0)	401 (4.7)	166 (8.0)	Statins	17 000 (28.3)	3499 (41.3)	1152 (55.8)
Missing	11 308 (18.8)	1866 (22.0)	285 (13.8)	Vasodilators	3504 (5.8)	1257 (14.8)	320 (15.5)

Severity of airflow limitation using the GOLD guidelines.¹

*At least two prescriptions >15 days apart in the year prior to the start of follow-up.

†Prior diagnosis of ischaemic heart disease, peripheral artery disease, atrial fibrillation, hypertension and/or stroke.

‡Average number of exacerbations per patient (range) in the year prior to the start of follow-up.

ACEi, ACE inhibitor; ARB, angiotensin receptor blockers; BB, beta-blockers; CCB, calcium channel blockers; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HF, heart failure; ICS, inhaled corticosteroids; LABA, long-acting beta agonists; LAMA, long-acting muscarinic antagonists; MRA, mineralocorticoid receptor antagonists; SABA, short-acting beta agonists; SAMA, short-acting muscarinic antagonists.

without evidence of HF (figure 2A; aHR: 1.65; 95% CI: 1.58 to 1.72).

Description of patients with COPD with diagnosed HF for analysis of HF medications

For analysis of the effect of HF medications on exacerbation risk, we identified 8901 patients with COPD with diagnosed HF (figure 1). Patient characteristics are summarised in online supplemental table E4). Patient characteristics stratified for non-users, incident users and prevalent users of ACEi, ARB, BB, loop diuretic and MRA are detailed in online supplemental tables E5–E9. Most patients were non-users or prevalent users of HF

medications at the start of follow-up and did not change status (online supplemental figure E2).

Relationship between incident and prevalent HF medication use and AECOPD risk

Incident use of ACEi, ARB, BB, loop diuretics and MRA was associated with higher risk of moderate-to-severe exacerbation compared with non-use (figure 3A; online supplemental table E10). Prevalent use of ACEi, ARB, BB, loop diuretics and MRA was also associated with higher risk of moderate-to-severe exacerbation compared with non-use (figure 3B; online supplemental table E11). Prevalent use of ACEi, ARB, BB, loop diuretics and

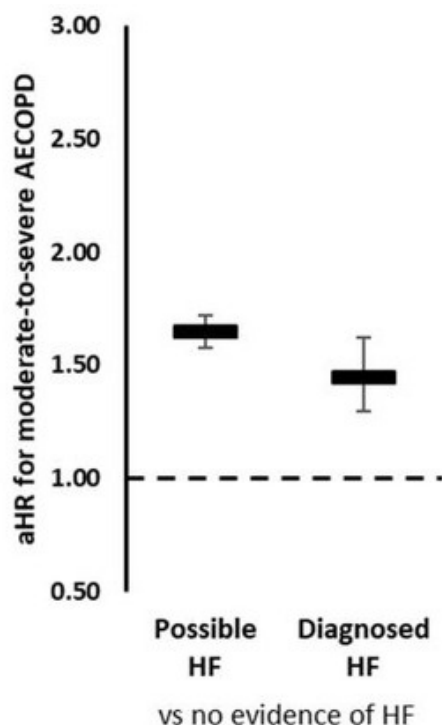


Figure 2 Effect of newly diagnosed and possible HF on AECOPD risk. aHR comparing risk of moderate-to-severe AECOPD in patients with COPD with possible HF and newly diagnosed HF compared with patients with COPD without evidence of HF. Estimates from stratified Cox regression stratified by matched set (sex and age) and adjusted for smoking status, body mass index, index of multiple deprivation, exacerbation history, severity of airflow limitation, inhaler use, a history of cardiovascular disease and cardiovascular medication use. AECOPD, acute exacerbations of chronic obstructive pulmonary disease; aHR, adjusted HR; COPD, chronic obstructive pulmonary disease; HF, heart failure.

MRA was associated with lower risk of moderate-to-severe exacerbation compared with incident use (figure 3C; online supplemental table E12).

Sensitivity analyses

We conducted three sensitivity analyses; results were similar to those in the main analysis (see online supplemental material).

DISCUSSION

Patients with COPD with newly diagnosed HF experienced a significantly higher risk of moderate and severe exacerbations compared with patients with COPD without evidence of HF diagnosis. Patients with COPD with possible HF also experienced a similarly increased risk. Patients with COPD with possible HF who had evidence of investigation but no HF diagnosed still experienced a higher risk of exacerbation than patients with COPD without evidence of HF.

Both incident (<6 months) and prevalent (≥ 6 months) use of HF medications were associated with a higher risk of exacerbation compared with non-use, for each of the medication investigated; however, exacerbation risk was lower with prevalent use compared with incident use. The similarity in effects suggests that it is not the effect of individual medications on exacerbation risk that is being seen, but rather the effect of symptomatic HF indicative for medication use on exacerbation risk that is being

seen—confounding by indication.²⁸ Patients with COPD with diagnosed HF who were prescribed medication may be more likely to be symptomatic than those not prescribed medication. With prevalent use, BB and MRA were associated with slightly greater exacerbation risk compared with non-use than seen in the other drug types. BB and MRA use in patients with COPD may indicate more severe HF, with a greater symptom burden and therefore higher risk of exacerbation compared with non-users of these medications.

Prevalent use (≥ 6 months) of all HF medications was associated with lower exacerbation risk compared with incident use. The effect was similar for all drug types, suggesting again that it is not the individual medication affecting exacerbation risk but appropriate HF management. Previously, Matamis *et al* hypothesised that identification and subsequent management of HF in patients admitted to intensive care for exacerbation were responsible for better outcomes following exacerbations, even in the short term.²⁹ Our study also suggests that HF contributes to exacerbation risk and that early diagnosis and management of HF in the COPD population may reduce that risk.

These results suggest there may be opportunity for earlier diagnosis of HF in primary care in the COPD population and that early diagnosis and optimal management of HF may reduce COPD exacerbation risk in these patients. There are a number of possible reasons by which patients with COPD with newly diagnosed and possible HF experience greater exacerbation risk than patients with COPD without HF. Failure to optimally manage HF may hasten the progression of HF or general patient decline, both of which may increase exacerbation risk. Patients with COPD with HF are more likely to have additional comorbidities than patients with only COPD.^{30 31} Higher comorbidity burden is associated with increased risk of death in patients with COPD³² and increased systemic inflammation.^{31 33} Previous cohort studies have found that up to 26% of exacerbations may be triggered by HF or other cardiovascular conditions, such as arrhythmia.^{34–36} Underlying cardiac problems have been seen in around a quarter of exacerbation episodes when echocardiography has been performed.^{37 38} In addition, there is the potential for misclassification whereby events are labelled as COPD exacerbation but may be acute HF.^{39 40} Pathophysiologically, there are a number of mechanisms by which underlying HF, particularly uncontrolled HF, may increase exacerbation risk. Chronic congestion may lead to reduced airflow in some patients, and airflow obstruction can be reversed with proper management of congestion.^{41 42} Pulmonary oedema, and impaired oxygen transport due to HF, may intensify dyspnoea and reduced exercise capacity already present due to lung hyperinflation in COPD.⁴³ Cardiomegaly may contribute to worsening alveolar gas diffusion, resulting in a restrictive lung pattern and reduced alveolar volume.⁴⁴ Obesity and diabetes, risk factors for HF and more common in our patients with COPD with HF, are associated with reduced pulmonary function and airway hyperactivity.⁴⁵

These results suggest that HF may be an underlying factor triggering exacerbation of COPD. There are a number of challenges facing clinicians in the management of patients with COPD and HF. COPD exacerbation is a diagnosis of exclusion, with no biomarkers for exacerbation; the overlapping symptoms with HF make misdiagnosis possible.⁴⁰ Similarly, the signs and symptoms of HF are non-specific and many patients with HF are initially treated for exacerbation of other conditions.⁴⁶ COPD and HF share common risk factors (eg, smoking) and symptoms (eg, dyspnoea, fatigue, exercise intolerance) that can make diagnosing one in the presence of the other difficult.^{4 5} Air trapping due to pulmonary disease can affect echocardiogram acoustic

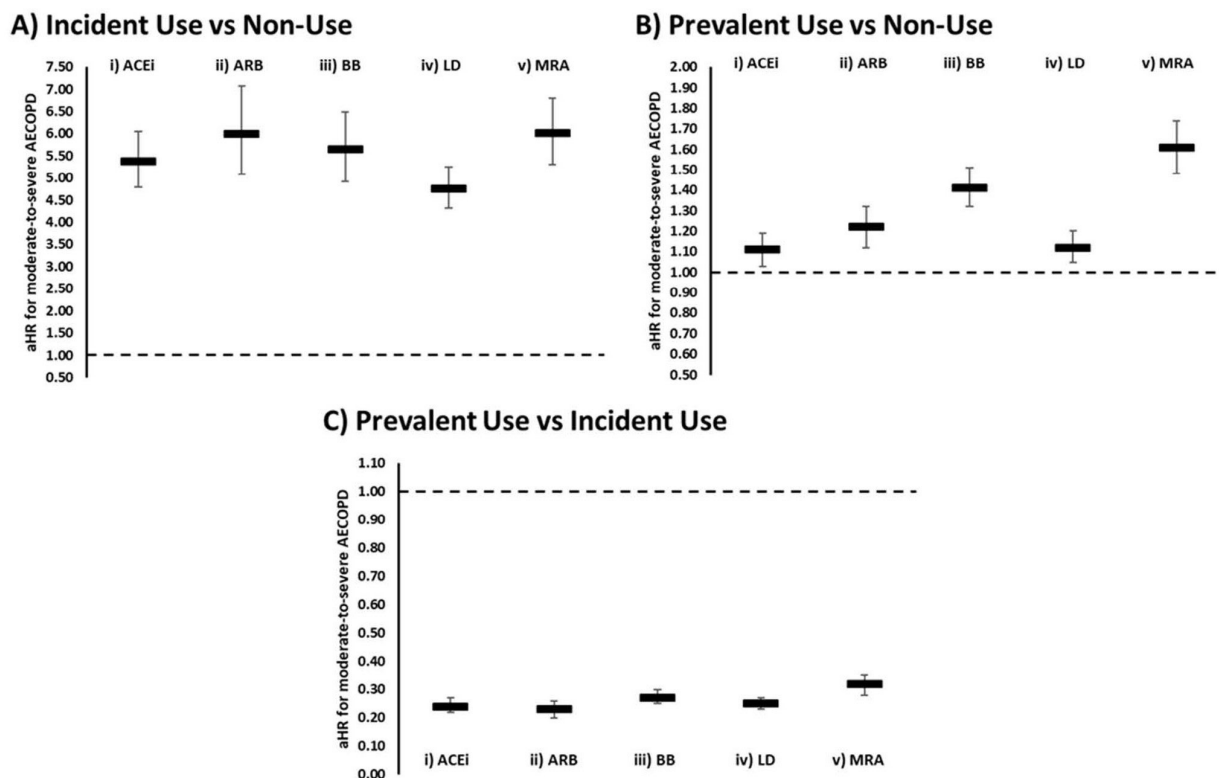


Figure 3 Effect of HF medication use on AECOPD risk. aHR for the risk of moderate-to-severe AECOPD in patients with diagnosed HF comparing incident medication use (<6 months) with non-use, (B) prevalent medication use (≥6 months) with non-use and (C) prevalent medication use with incident medication use for (I) ACEi, (II) ARB, (III) BB, (IV) LD and (v) MRA. Estimates with 95% CIs from Cox regression adjusted for age, sex, smoking status, body mass index, Index of Multiple Deprivation, exacerbation history, severity of airflow limitation, inhaler use, a history of cardiovascular disease and cardiovascular medication use. ACEi, ACE inhibitor; AECOPD, acute exacerbations of chronic obstructive pulmonary disease; aHR, adjusted HR; ARB, angiotensin receptor blockers; BB, beta-blockers; COPD, chronic obstructive pulmonary disease; HF, heart failure; LD, loop diuretics; MRA, mineralocorticoid receptor antagonists.

windows, leading to unsatisfactory imaging quality and making diagnosis more difficult.⁴⁷ The severity of COPD may be overestimated in patients with comorbid HF as part of the reduction in lung function may be caused by HF.⁴⁸ In patients with COPD, the median time between symptom presentation and HF diagnosis in UK primary care has been shown to be over 3 years, compared with only 2.4 years in patients without COPD.⁶ HF treatment is also delayed, with patients with COPD waiting 2.9 years compared with only 1.9 years in patients without COPD.⁶ There are currently no bespoke guidelines available for the management of patients with COPD and HF, despite the ongoing debate around the use of beta-agonists^{49 50} and the lingering hesitancy around BB use, which appears to be largely unfounded.^{51 52}

There is increasing recognition of the multimorbid patient,^{53 54} but the translation of this into clinical practice has been slow. These results highlight the need for more collaborative management of patients with chronic heart and lung conditions, increased awareness and screening for conditions beyond the first one to be recognised, and the development of bespoke guidelines for diagnosis and management of patients with coexisting COPD and HF. Increasing patient-centred care over specialty-focused care could reduce symptom burden in patients with COPD and HF.

Strengths and limitations

A strength of this study is the use of one of the largest longitudinal, nationally representative databases in the world, CPRD.¹⁶

A validated definition for COPD was used,¹⁷ and exacerbations were identified using validated algorithms.^{20 21} There is no validated case definition for the identification of HF in CPRD. HF was identified using a previously published code list¹⁹ that was created by clinicians, and unfortunately, explicit coding of HF type and severity is not common in CPRD. Duration of prescription is not always recorded in CPRD, and the issuing of a prescription does not mean the patient used the prescription, which limits the accuracy of determining continuous medication exposure; however, stratification of medication use into incident and prevalent use allowed for a more nuanced evaluation of the effect of HF medication use on exacerbation risk.

Possible patients with HF had characteristics similar to newly diagnosed patients with HF and a similarly increased risk of exacerbation, suggesting internal validity. Similar techniques have been used in previous research to identify possible HF.²⁵ However, at best, the definition requiring long-term loop diuretic use for a probable cardiac indication would only identify possible patients with HF with fluid congestion, which is not experienced in all cases. The exclusion of patients with CKD or CLD was designed to restrict cases to those patients taking loop diuretics for a cardiac indication; however, these conditions were more common in patients with diagnosed HF than in those without an HF diagnosis. We conducted a sensitivity analysis by looking at a less selected population that included patients with CKD or CLD. Comparing patients with COPD with an HF diagnosis with those without an HF diagnosis demonstrated similarly increased risk of exacerbation as did our more selected

comparison of patients with COPD with newly diagnosed HF and patients with COPD without evidence of HF that excluded patients with CKD or CLD. Nevertheless, the patients with COPD in our population with long-term loop diuretic use in the absence of non-cardiac indications experienced greater risk of exacerbation than patients without this characteristic, suggesting that, whether or not they have HF or develop HF in the future, they are a high-risk patient group that should be recognised and for whom special consideration regarding treatment and management should be taken. Finally, we did consider time-varying covariates in the model; however, from previous COPD studies, and given the relatively short follow-up period and similarity in characteristics between exposure groups, we do not think this would have significantly changed our findings.

CONCLUSIONS

Newly diagnosed HF and possible HF were associated with similar, higher exacerbation risk compared with patients without evidence of HF. All HF medications examined were associated with higher exacerbation risk with both incident and prevalent use compared with non-use. Importantly, prevalent use of all HF medications examined was associated with lower exacerbation risk compared with incident use. There appears to be opportunity for earlier recognition and management of HF in the COPD population in primary care, which may reduce COPD exacerbation risk.

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Patient consent for publication Not required.

Ethics approval This work is based in part on data from the Clinical Practice Research Datalink (CPRD) obtained under license from the UK Medicines and Healthcare products Regulatory Agency (MHRA). The data are provided by patients and collected by the National Health Service (NHS) as part of their care and support. The interpretation and conclusions contained in this study are those of the authors alone. A protocol for this research was approved by the Independent Scientific Advisory Committee (ISAC) for MHRA Database Research (protocol number 18_074RARA2), and the approved protocol was made available to the journal in which this research is published and to the reviewers during peer review. Generic ethical approval for observational research using the CPRD with approval from ISAC has been granted by a Health Research Authority (HRA) Research Ethics Committee (East Midlands—Derby, REC reference number 05/MRE04/87).

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Data availability statement Data may be obtained from a third party and are not publicly available. Linked pseudonymised mortality data from the Office for National Statistics (ONS), socioeconomic data from the Index of Multiple Deprivation (IMD) and secondary care data from Hospital Episode Statistics (HES) were provided for this study by CPRD for patients in England. Data are linked by NHS Digital, the statutory trusted third party for linking data, using identifiable

data held only by NHS Digital. Select general practices consent to this process at a practice level, with individual patients having the right to opt-out. Use of HES and ONS data is Copyright © (2018), reused with the permission of The Health & Social Care Information Centre, all rights reserved. Data are available on request from the CPRD. Their provision requires the purchase of a license, and this license does not permit the authors to make them publicly available to all. This work used data from the version collected in January 2018 and have clearly specified the data selected in each Methods section. To allow identical data to be obtained by others, via the purchase of a license, the code lists will be provided upon request. Licenses are available from the CPRD (<http://www.cprd.com>): The Clinical Practice Research Datalink Group, The Medicines and Healthcare products Regulatory Agency, 10 South Colonnade, Canary Wharf, London E14 4PU.

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Online Data Supplement

Axson EL, Bottle A, Cowie MC, and Quint JK. The relationship between heart failure and the risk of acute exacerbation of COPD.

Read codes used to identify HF in CPRD GOLD

G580.00	G5yyA00	G583.12
G581.00	G581000	G583.11
G58..00	662p.00	G580400
G580.11	G580100	8CMW800
9N0k.00	8CL3.00	G21z100
G5yy900	585g.00	G232.00
G58z.00	8B29.00	G211100
8HBE.00	G580200	G234.00
662T.00	G5yyD00	8CeC.00
662W.00	8CMK.00	G210100
G58..11	G58z.12	SP11111
101..00	G580000	G1yz100
662g.00	G582.00	G580.14
585f.00	Zrad.00	G580.12
G581.13	662i.00	G580.13
33BA.00	G583.00	G584.00
662f.00	8H2S.00	G41z.11
662h.00	G580300	G400.00

Results of Sensitivity Analyses

Keeping patients with chronic kidney and liver disease, COPD patients with a diagnosis of HF experienced greater risk for moderate-to-severe AECOPD (aHR = 1.47, 95%CI: 1.32, 1.63) compared to COPD patients without a diagnosis of HF.

COPD patients with possible HF who had no evidence of ever being investigated for HF experienced greater risk for moderate-to-severe AECOPD (aHR = 1.27, 95%CI: 1.18, 1.38) compared to COPD patients with possible HF with evidence of ever being investigated for HF. COPD patients with possible HF with evidence of ever being investigated for HF still experienced greater risk for moderate-to-severe AECOPD (aHR = 1.54, 95%CI: 1.43, 1.65) than COPD patients with no evidence of HF.

Classifying COPD patients with a HF hospitalisation during follow-up, but no HF diagnosis recorded in primary, as having a HF diagnosis made 449 possible HF patients become prevalent HF patients prior to the start of follow-up and made 532 possible HF patients become newly diagnosed HF patients during follow-up. Patients were then matched according to their new status and regression performed per the methods.

Compared to COPD patients without evidence of HF, COPD patients with newly diagnosed HF (including patients with HF hospitalisation during follow-up, but no primary care HF diagnosis) experienced greater risk for moderate-to-severe AECOPD (aHR = 1.63, 95%CI: 1.49, 1.79). This estimate is larger than that seen in the main analysis. The new definition by its nature shifted more symptomatic and sicker individuals into the newly diagnosed HF category and that would increase AECOPD risk.

Compared to COPD patients without evidence of HF, COPD patients with possible HF (excluding patients with history of HF hospitalisation or HF hospitalisation during follow-up, but no primary care diagnosis) experienced a greater risk for moderate-to-severe AECOPD (aHR = 1.69, 95%CI: 1.61, 1.76). The risk for moderate-to-severe AECOPD was not affected by the new categories compared to the main analysis.

	Possible HF N = 8,476	Newly Diagnosed HF N = 2,066
Median length of time on LDs before end of follow-up or HF diagnosis	1.85 years (IQR: 0.90, 3.81)	0.50 years (IQR: 0.11, 2.12)
History of HF hospitalisation (n, %) HF as primary or secondary diagnostic code	981 (11.6)	692 (33.5)
Median time between most recent HF hospitalisation and end of follow-up or HF diagnosis	1.68 years (IQR: 0.42, 4.13)	1.00 year (IQR: 0.72, 1.04)
History of echocardiography (n, %)	3,569 (42.1)	1,854 (89.7)
Median time between most recent echocardiography and end of follow-up or HF diagnosis	2.76 years (IQR: 1.18, 5.28)	1.00 year (IQR: 0.83, 1.15)
History of BNP test (n, %)	1,480 (17.5)	425 (20.6)
Median time between most recent BNP test and end of follow-up or HF diagnosis	1.78 (IQR: 0.81, 3.18)	1.08 years (IQR: 1.00, 1.31)
History of an outpatient cardiology visit (n, %)	1,249 (14.7)	435 (21.1)
Median time between most recent outpatient cardiology visit and end of follow-up or HF diagnosis	1.93 years (IQR: 0.67, 4.63)	2.98 years (IQR: 1.54, 4.99)
History of HF investigation: echocardiography, BNP test, and/or outpatient cardiology visit	4,545 (53.6)	1,898 (91.9)

Table E1. Proportion of chronic obstructive pulmonary disease (COPD) patients with possible heart failure (HF) and newly diagnosed HF with a history of hospitalisation due to HF, a history of echocardiography, a history of brain natriuretic peptide (BNP) measures, and/or a history of an outpatient cardiology visit and the median (interquartile range, IQR) time between the most recent of these and the end of follow-up or HF diagnosis.

	COPD patients without evidence of HF	COPD patients with diagnosed HF		COPD patients without evidence of HF	COPD patients with diagnosed HF
Number of Patients (N)	4,132	2,066	Exacerbation History*	1 (0, 2)	2 (1, 4)
Female	1,486 (36.0)	743 (36.0)	COPD medications†		
Age, years (IQR)	71 (64, 78)	74 (67, 81)	SABA/SAMA	2,600 (62.9)	1,489 (72.1)
Smoking Status			LABA alone	106 (2.57)	31 (1.50)
Current Smoker	1,411 (34.2)	497 (24.1)	LAMA alone	256 (6.20)	163 (7.89)
Former Smoker	2,721 (65.9)	1,569 (75.9)	ICS alone	532 (12.9)	92 (4.45)
Body Mass Index			LABA+LAMA	35 (0.85)	29 (1.40)
Underweight (< 18.5)	200 (4.84)	113 (5.47)	LABA+ICS	1,077 (26.1)	476 (23.0)
Healthy Weight (18.5-24.9)	1,521 (36.8)	640 (31.0)	LAMA+ICS	78 (1.89)	27 (1.31)
Overweight (25.0-29.9)	1,415 (34.2)	595 (28.8)	Triple	578 (14.0)	823 (39.8)
Obese (>= 30)	910 (22.0)	667 (32.3)	No long-acting inhaler	1,470 (35.6)	425 (20.6)
Missing Data	86 (2.08)	51 (2.47)	History of Cardiovascular Disease‡	2,288 (55.4)	1,687 (81.7)
Index of Multiple Deprivation			Atrial fibrillation	172 (4.16)	671 (32.5)
1 – Most deprived	695 (16.8)	268 (13.0)	Hypertension	1,935 (46.8)	1,033 (50.0)
2	856 (20.7)	403 (19.5)	Ischaemic heart disease	610 (14.8)	838 (40.6)
3	826 (20.0)	406 (19.7)	Peripheral artery disease	210 (5.08)	222 (10.8)
4	909 (22.0)	473 (22.9)	Stroke	229 (5.54)	231 (11.2)
5 – Least deprived	846 (20.5)	516 (25.0)	Diabetes mellitus	341 (8.25)	459 (22.2)
GOLD Stage			CVD medications†		
1: Mild	1,577 (38.2)	703 (34.0)	ACEi	697 (16.9)	1,230 (59.5)
2: Moderate	1,122 (27.2)	486 (23.5)	ARB	262 (6.34)	332 (16.1)
3: Severe	605 (14.6)	426 (20.6)	Beta-blockers	293 (7.09)	737 (35.7)
4: Very Severe	112 (2.71)	166 (8.03)	Calcium channel blockers	397 (9.61)	329 (15.9)
Missing	716 (17.3)	285 (13.8)	MRA	10 (0.24)	479 (23.2)
			Statins	1,215 (29.4)	1,152 (55.8)
			Vasodilators	254 (6.15)	320 (15.5)

Table E2. Descriptive statistics for the matched cohort of chronic obstructive pulmonary disease (COPD) patients without evidence of heart failure (HF) and COPD patients with diagnosed HF. Proportions may not sum to 100% due to rounding. Severity of airflow limitation using the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines [1]. Angiotensin converting enzyme inhibitors (ACEi). Angiotensin receptor blockers (ARB). Beta-blockers (BB). Calcium channel blockers (CCB). Interquartile range (IQR). Long-acting beta agonists (LABA). Inhaled corticosteroids (ICS). Long-acting muscarinic antagonist (LAMA). Mineralocorticoid receptor antagonists (MRA). Short-acting beta agonists (SABA). Short-acting muscarinic antagonist (SAMA). *Average number of exacerbations per patient (range) in the year prior to the start of follow-up. †At least two prescriptions >15 days apart in the year prior to the start of follow-up. ‡Prior diagnosis of ischaemic heart disease, peripheral artery disease, atrial fibrillation, hypertension, and/or stroke.

	COPD patients without evidence of HF	COPD patients with possible HF		COPD patients without evidence of HF	COPD patients with possible HF
Number of Patients (N)	16,792	8,423	Exacerbation History*	1 (0, 2)	2 (0, 3)
Female	8,365 (49.8)	4,206 (49.9)	COPD medications†		
Age, years (IQR)	73 (65, 80)	73 (66, 80)	SABA/SAMA	10,834 (64.5)	6,194 (73.5)
Smoking Status			LABA alone	454 (2.70)	250 (2.97)
Current Smoker	5,872 (35.0)	2,561 (30.4)	LAMA alone	1,068 (6.36)	535 (6.35)
Former Smoker	10,920 (65.0)	5,862 (69.6)	ICS alone	2,115 (12.6)	939 (11.2)
Body Mass Index			LABA+LAMA	129 (0.77)	80 (0.95)
Underweight (< 18.5)	1,005 (5.98)	351 (4.17)	LABA+ICS	4,421 (26.3)	2,423 (28.8)
Healthy Weight (18.5-24.9)	6,448 (38.4)	2,231 (26.5)	LAMA+ICS	373 (2.22)	205 (2.43)
Overweight (25.0-29.9)	5,458 (32.5)	2,323 (27.6)	Triple	2,414 (14.4)	1,915 (22.7)
Obese (>= 30)	3,353 (20.0)	3,180 (37.8)	No long-acting inhaler	5,818 (34.7)	2,076 (24.7)
Missing Data	528 (3.14)	338 (4.01)	History of Cardiovascular Disease‡	9,353 (55.7)	6,485 (77.0)
Index of Multiple Deprivation			Atrial fibrillation	716 (4.26)	987 (11.7)
1 – Most deprived	2,699 (16.1)	1,123 (13.4)	Hypertension	7,818 (46.6)	5,444 (64.6)
2	3,491 (20.8)	1,707 (20.3)	Ischaemic heart disease	2,381 (14.2)	2,218 (26.3)
3	3,310 (19.7)	1,602 (19.0)	Peripheral artery disease	1,004 (5.98)	652 (7.74)
4	3,759 (22.4)	1,964 (23.3)	Stroke	1,018 (6.06)	786 (9.33)
5 – Least deprived	3,533 (21.0)	2,021 (24.0)	Diabetes mellitus	1,388 (8.27)	1,354 (16.1)
GOLD Stage			CVD medications†		
1: Mild	6,208 (37.0)	2,985 (35.4)	ACEi	2,721 (16.2)	2,436 (28.9)
2: Moderate	4,347 (25.9)	1,753 (20.8)	ARB	1,053 (6.27)	896 (10.6)
3: Severe	2,383 (14.2)	1,447 (17.2)	Beta-blockers	1,062 (6.32)	1,002 (11.9)
4: Very Severe	503 (3.00)	401 (4.76)	Calcium channel blockers	1,770 (10.5)	1,462 (17.4)
Missing	3,351 (20.0)	1,837 (21.8)	MRA	62 (0.37)	276 (3.28)
			Statins	4,611 (27.5)	3,490 (41.4)
			Vasodilators	1,142 (6.80)	1,250 (14.8)

Table E3. Descriptive statistics for the matched cohort of chronic obstructive pulmonary disease (COPD) patients without evidence of heart failure (HF) and COPD patients with possible HF. Proportions may not sum to 100% due to rounding. Severity of airflow limitation using the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines [1]. Angiotensin converting enzyme inhibitors (ACEi). Angiotensin receptor blockers (ARB). Beta-blockers (BB). Calcium channel blockers (CCB). Interquartile range (IQR). Long-acting beta agonists (LABA). Inhaled corticosteroids (ICS). Long-acting muscarinic antagonist (LAMA). Mineralocorticoid receptor antagonists (MRA). Short-acting beta agonists (SABA). Short-acting muscarinic antagonist (SAMA). *Average number of exacerbations per patient (range) in the year prior to the start of follow-up. †At least two prescriptions >15 days apart in the year prior to the start of follow-up. ‡Prior diagnosis of ischaemic heart disease, peripheral artery disease, atrial fibrillation, hypertension, and/or stroke.

COPD-HF Patients		COPD-HF Patients	
Number of Patients (N)	8,901	Exacerbation History (IQR)	2 (0, 3)
Female	3,278 (36.8)	COPD medications[†]	
Age, years (IQR)	77.5 (70.5, 83.3)	SABA/SAMA	8,901 (100)
Smoking Status		LABA alone	194 (2.18)
Current Smoker	1,848 (20.8)	LAMA alone	703 (7.90)
Former Smoker	7,053 (79.2)	ICS alone	775 (8.71)
Body Mass Index		LABA+LAMA	109 (1.22)
Underweight (< 18.5)	303 (3.40)	LABA+ICS	2,203 (24.8)
Healthy Weight (18.5-24.9)	2,470 (27.8)	LAMA+ICS	150 (1.69)
Overweight (25.0-29.9)	2,769 (31.1)	Triple	2,174 (24.4)
Obese (>= 30)	3,014 (33.9)	No long-acting inhaler	0
Missing Data	345 (3.88)	History of Cardiovascular Disease[‡]	7,926 (89.1)
Index of Multiple Deprivation		Atrial fibrillation	3,142 (35.3)
1 – Most deprived	1,236 (13.9)	Hypertension	5,037 (56.6)
2	1,770 (19.9)	Ischaemic heart disease	4,878 (54.8)
3	1,760 (19.8)	Peripheral artery disease	1,202 (13.5)
4	2,041 (22.9)	Stroke	1,271 (14.3)
5 – Least deprived	2,094 (23.5)	Diabetes mellitus	2,366 (26.6)
GOLD Stage			
1: Mild	3,220 (36.2)		
2: Moderate	1,923 (21.6)		
3: Severe	1,345 (15.1)		
4: Very Severe	353 (3.97)		
Missing	2,060 (23.1)		

Table E4. Descriptive statistics of chronic obstructive pulmonary disease (COPD) patients with heart failure (HF) comorbidity at baseline. Interquartile range (IQR). Global Initiative for Chronic Obstructive Lung Diseases (GOLD) staging of COPD severity [1]. [†]Recorded at baseline; patients could have multiple risk factors.

	Non-Users of ACEi	Incident Users of ACEi (<6 months)	Prevalent Users of ACEi (≥6 months)		Non-Users of ACEi	Incident Users of ACEi (<6 months)	Prevalent Users of ACEi (≥6 months)
Number of Patients (N)	4,136	1,237	5,055	Exacerbation History (IQR)	2 (1, 4)	3 (1, 4)	2 (1, 4)
Female	1,707 (41.3)	455 (36.8)	1,698 (33.6)	COPD medications [‡]			
Age, years (IQR)	78.5 (72.0, 84.2)	77.2 (70.4, 83.0)	76.5 (69.5, 82.5)	SABA/SAMA	4,136 (100)	1,237 (100)	5,055 (100)
Smoking Status				LABA alone	81 (1.96)	30 (2.43)	111 (2.20)
Current Smoker	776 (18.8)	281 (22.7)	1,131 (22.4)	LAMA alone	331 (8.00)	92 (7.44)	395 (7.81)
Former Smoker	3,360 (81.2)	956 (77.3)	3,924 (77.6)	ICS alone	356 (8.61)	97 (7.84)	422 (8.35)
Body Mass Index				LABA+LAMA	45 (1.09)	16 (1.29)	73 (1.44)
Underweight (< 18.5)	158 (3.82)	41 (3.31)	156 (3.09)	LABA+ICS	1,055 (25.5)	321 (26.0)	1,221 (24.2)
Healthy Weight (18.5-24.9)	1,167 (28.2)	386 (31.2)	1,403 (27.8)	LAMA+ICS	58 (1.40)	19 (2.34)	94 (1.86)
Overweight (25.0-29.9)	1,260 (30.5)	367 (29.7)	1,592 (31.5)	Triple	1,016 (24.6)	313 (25.3)	1,253 (24.8)
Obese (≥ 30)	1,340 (32.4)	414 (33.5)	1,766 (34.9)	No long-acting inhaler	0	0	0
Missing Data	211 (5.10)	29 (2.34)	138 (2.73)	History of Cardiovascular Disease [‡]	3,604 (87.1)	1,119 (90.5)	4,583 (90.7)
Index of Multiple Deprivation				Atrial fibrillation	1,461 (35.3)	450 (36.4)	1,803 (35.7)
1 – Most deprived	572 (13.8)	155 (12.5)	696 (13.8)	Hypertension	2,265 (54.8)	707 (57.2)	2,940 (58.2)
2	823 (19.9)	242 (19.6)	1,006 (19.9)	Ischaemic heart disease	2,105 (50.9)	699 (56.5)	2,916 (57.7)
3	840 (20.3)	233 (18.8)	978 (19.4)	Peripheral artery disease	548 (13.3)	140 (11.3)	693 (13.7)
4	961 (23.2)	306 (24.7)	1,156 (22.9)	Stroke	603 (14.6)	181 (14.6)	719 (14.2)
5 – Least deprived	940 (22.7)	301 (24.3)	1,219 (24.1)	Diabetes mellitus	1,038 (25.1)	353 (28.5)	1,420 (28.1)
GOLD Stage				CVD medications [‡]			
1: Mild	1,511 (36.5)	429 (34.7)	1,826 (36.1)	ARB	1,648 (39.9)	106 (8.57)	147 (2.91)
2: Moderate	850 (20.6)	279 (22.6)	1,156 (22.9)	Beta-blockers	1,140 (27.6)	331 (26.8)	1,780 (35.2)
3: Severe	569 (13.8)	213 (17.2)	819 (16.2)	Calcium channel blockers	687 (16.6)	221 (17.9)	775 (15.3)
4: Very Severe	149 (3.60)	72 (5.82)	223 (4.41)	Loop diuretics	2,760 (66.7)	801 (64.8)	3,523 (69.7)
Missing	1,057 (25.6)	244 (19.7)	1,031 (20.4)	MRA	858 (20.7)	226 (18.3)	1,130 (22.4)
				Statins	2,180 (52.7)	713 (57.6)	3,294 (65.2)
				Vasodilators	907 (21.9)	287 (23.2)	1,162 (23.0)

Table E5. Descriptive statistics for non-users, incident users, and prevalent users of angiotensin converting enzyme inhibitors (ACEi) at start of follow-up. Proportions may not sum to 100% due to rounding. Severity of airflow limitation using the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines [1]. Angiotensin receptor blockers (ARB). Beta-blockers (BB). Calcium channel blockers (CCB). Interquartile range (IQR). Long-acting beta agonists (LABA). Inhaled corticosteroids (ICS). Long-acting muscarinic antagonist (LAMA). Mineralocorticoid receptor antagonists (MRA). Short-acting beta agonists (SABA). Short-acting muscarinic antagonist (SAMA). [‡]At least two prescriptions >15 days apart in the year prior to the start of follow-up. [‡]Prior diagnosis of ischaemic heart disease, peripheral artery disease, atrial fibrillation, hypertension, and/or stroke.

	Non-Users of ARB	Incident Users of ARB (<6 months)	Prevalent Users of ARB (≥6 months)		Non-Users of ARB	Incident Users of ARB (<6 months)	Prevalent Users of ARB (≥6 months)
Number of Patients (N)	7,253	668	1,914	Exacerbation History (IQR)	2 (0, 3)	2 (1, 4)	2 (1, 4)
Female	2,645 (36.5)	257 (38.5)	723 (37.8)	COPD medications [‡]			
Age, years (IQR)	77.5 (70.5, 83.5)	76.9 (69.6, 82.4)	76.6 (70.1, 82.2)	SABA/SAMA	7,253 (100)	668 (100)	1,914 (100)
Smoking Status				LABA alone	156 (2.15)	10 (1.50)	45 (2.35)
Current Smoker	1,606 (22.1)	110 (16.5)	277 (14.5)	LAMA alone	554 (7.64)	60 (8.98)	166 (8.67)
Former Smoker	5,647 (77.9)	558 (83.5)	1,637 (85.5)	ICS alone	648 (8.93)	54 (8.08)	143 (7.47)
Body Mass Index				LABA+LAMA	90 (8.93)	6 (0.90)	21 (1.10)
Underweight (< 18.5)	280 (3.86)	14 (2.10)	29 (1.52)	LABA+ICS	1,776 (24.5)	162 (24.3)	494 (25.8)
Healthy Weight (18.5-24.9)	2,092 (28.8)	177 (26.5)	445 (23.3)	LAMA+ICS	121 (1.67)	15 (2.25)	33 (1.72)
Overweight (25.0-29.9)	2,242 (30.9)	205 (30.7)	611 (31.9)	Triple	1,759 (24.3)	206 (30.8)	519 (27.1)
Obese (≥ 30)	2,328 (32.1)	263 (39.4)	796 (41.6)	No long-acting inhaler	0	0	0
Missing Data	311 (4.29)	9 (1.35)	33 (1.72)	History of Cardiovascular Disease [‡]	6,369 (87.8)	616 (92.2)	1,803 (94.2)
Index of Multiple Deprivation				Atrial fibrillation	2,548 (35.1)	242 (36.2)	697 (36.4)
1 – Most deprived	988 (13.6)	108 (16.2)	287 (15.0)	Hypertension	3,927 (54.1)	435 (65.1)	1,269 (66.3)
2	1,428 (19.7)	136 (20.4)	403 (21.1)	Ischaemic heart disease	3,886 (53.6)	394 (59.0)	1,149 (60.0)
3	1,383 (19.1)	144 (21.6)	430 (22.5)	Peripheral artery disease	968 (13.4)	102 (15.3)	283 (14.8)
4	1,690 (23.3)	143 (21.4)	408 (21.3)	Stroke	1,055 (14.6)	66 (9.88)	246 (12.9)
5 – Least deprived	1,764 (24.3)	137 (20.5)	386 (20.2)	Diabetes mellitus	1,883 (26.0)	223 (33.4)	581 (30.4)
GOLD Stage				CVD medications [‡]			
1: Mild	2,545 (35.1)	284 (42.5)	798 (41.7)	ACEi	4,918 (67.8)	380 (56.9)	425 (22.2)
2: Moderate	1,528 (21.1)	169 (25.3)	463 (24.2)	Beta-blockers	2,234 (30.8)	233 (34.9)	669 (35.0)
3: Severe	1,114 (15.4)	101 (15.1)	271 (14.2)	Calcium channel blockers	1,117 (15.4)	127 (19.0)	330 (17.2)
4: Very Severe	305 (4.21)	26 (3.89)	60 (3.13)	Loop diuretics	4,967 (68.5)	449 (67.2)	1,288 (67.3)
Missing	1,761 (24.3)	88 (13.2)	322 (16.8)	MRA	1,536 (21.2)	163 (24.4)	453 (23.7)
				Statins	4,205 (58.0)	434 (65.0)	1,298 (67.8)
				Vasodilators	1,592 (22.0)	179 (26.8)	498 (26.0)

Table E6. Descriptive statistics for non-users, incident users, and prevalent users of angiotensin receptor blockers (ARB) at start of follow-up. Proportions may not sum to 100% due to rounding. Severity of airflow limitation using the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines [1]. Angiotensin converting enzyme inhibitors (ACEi). Beta-blockers (BB). Calcium channel blockers (CCB). Interquartile range (IQR). Long-acting beta agonists (LABA). Inhaled corticosteroids (ICS). Long-acting muscarinic antagonist (LAMA). Mineralocorticoid receptor antagonists (MRA). Short-acting beta agonists (SABA). Short-acting muscarinic antagonist (SAMA). [‡]At least two prescriptions >15 days apart in the year prior to the start of follow-up. [‡]Prior diagnosis of ischaemic heart disease, peripheral artery disease, atrial fibrillation, hypertension, and/or stroke.

	Non-Users of BB	Incident Users of BB (<6 months)	Prevalent Users of BB (≥6 months)		Non-Users of BB	Incident Users of BB (<6 months)	Prevalent Users of BB (≥6 months)
Number of Patients (N)	6,161	1,163	3,259	Exacerbation History (IQR)	2 (1, 3)	2 (1, 4)	2 (1, 4)
Female	2,457 (40.0)	356 (30.6)	985 (30.2)	COPD medications [†]			
Age, years (IQR)	78.4 (71.5, 83.8)	76.9 (70.1, 82.7)	75.7 (68.5, 81.8)	SABA/SAMA	6,161 (100)	1,163 (100)	3,259 (100)
Smoking Status				LABA alone	139 (2.26)	25 (2.15)	62 (1.90)
Current Smoker	1,199 (19.5)	202 (17.4)	723 (22.2)	LAMA alone	389 (6.31)	77 (6.62)	345 (10.6)
Former Smoker	4,962 (80.5)	961 (82.6)	2,536 (77.8)	ICS alone	620 (10.1)	50 (4.30)	189 (5.80)
Body Mass Index				LABA+LAMA	75 (1.22)	9 (0.77)	40 (1.23)
Underweight (< 18.5)	239 (3.88)	31 (2.67)	77 (2.36)	LABA+ICS	1,706 (27.7)	268 (23.0)	627 (19.2)
Healthy Weight (18.5-24.9)	1,783 (28.9)	335 (28.8)	849 (26.1)	LAMA+ICS	106 (1.72)	20 (1.72)	56 (1.72)
Overweight (25.0-29.9)	1,849 (30.0)	351 (30.2)	1,052 (32.3)	Triple	1,519 (24.7)	345 (29.7)	826 (25.4)
Obese (≥ 30)	1,991 (32.3)	432 (37.2)	1,230 (37.7)	No long-acting inhaler	0	0	0
Missing Data	299 (4.85)	14 (1.20)	51 (1.56)	History of Cardiovascular Disease [‡]	5,367 (87.1)	1,095 (94.2)	3,048 (93.5)
Index of Multiple Deprivation				Atrial fibrillation	2,029 (32.9)	535 (46.0)	1,355 (41.6)
1 – Most deprived	831 (13.5)	173 (14.9)	480 (14.7)	Hypertension	3,371 (54.7)	705 (60.6)	1,978 (60.7)
2	1,240 (20.1)	220 (18.9)	637 (19.6)	Ischaemic heart disease	3,115 (50.6)	760 (65.4)	2,090 (64.1)
3	1,228 (19.9)	216 (18.6)	619 (19.0)	Peripheral artery disease	803 (13.0)	183 (15.7)	490 (15.0)
4	1,397 (22.7)	272 (23.4)	768 (23.6)	Stroke	891 (14.5)	186 (16.0)	473 (14.5)
5 – Least deprived	1,465 (23.8)	282 (24.3)	755 (23.2)	Diabetes mellitus	1,517 (24.6)	380 (32.7)	1,017 (31.2)
GOLD Stage				CVD medications [†]			
1: Mild	2,108 (34.2)	462 (39.7)	1,341 (41.2)	ACEi	3,406 (55.3)	700 (60.2)	2,100 (64.4)
2: Moderate	1,263 (20.5)	314 (27.0)	806 (24.7)	ARB	1,144 (18.6)	249 (21.4)	721 (22.1)
3: Severe	970 (15.7)	179 (15.4)	460 (14.1)	Calcium channel blockers	1,155 (18.8)	201 (17.3)	320 (9.82)
4: Very Severe	288 (4.67)	36 (3.10)	79 (2.42)	Loop diuretics	4,178 (67.8)	811 (69.7)	2,295 (70.4)
Missing	1,532 (24.9)	172 (14.8)	573 (17.6)	MRA	1,095 (17.8)	282 (24.3)	994 (30.5)
				Statins	3,322 (53.9)	785 (67.5)	2,346 (72.0)
				Vasodilators	1,378 (22.4)	319 (27.4)	803 (24.6)

Table E7. Descriptive statistics for non-users, incident users, and prevalent users of beta-blockers (BB) at start of follow-up. Proportions may not sum to 100% due to rounding. Severity of airflow limitation using the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines [1]. Angiotensin converting enzyme inhibitors (ACEi). Angiotensin receptor blockers (ARB). Calcium channel blockers (CCB). Interquartile range (IQR). Long-acting beta agonists (LABA). Inhaled corticosteroids (ICS). Long-acting muscarinic antagonist (LAMA). Mineralocorticoid receptor antagonists (MRA). Short-acting beta agonists (SABA). Short-acting muscarinic antagonist (SAMA). [†]At least two prescriptions >15 days apart in the year prior to the start of follow-up. [‡]Prior diagnosis of ischaemic heart disease, peripheral artery disease, atrial fibrillation, hypertension, and/or stroke.

	Non-Users of LD	Incident Users of LD (<6 months)	Prevalent Users of LD (≥6 months)		Non-Users of LD	Incident Users of LD (<6 months)	Prevalent Users of LD (≥6 months)
Number of Patients (N)	3,037	2,105	6,334	Exacerbation History (IQR)	1 (0, 3)	2 (1, 4)	2 (1, 4)
Female	1,025 (33.8)	746 (35.4)	2,428 (38.3)	COPD medications [†]			
Age, years (IQR)	76.2 (69.1, 82.3)	78.1 (71.4, 83.6)	78.2 (71.4, 83.7)	SABA/SAMA	3,037 (100)	2,105 (100)	6,334 (100)
Smoking Status				LABA alone	67 (2.21)	34 (1.63)	136 (2.15)
Current Smoker	747 (24.6)	402 (19.1)	1,186 (18.7)	LAMA alone	262 (8.63)	153 (7.27)	474 (7.48)
Former Smoker	2,290 (75.4)	1,703 (80.9)	5,148 (81.3)	ICS alone	248 (8.17)	166 (7.89)	544 (8.59)
Body Mass Index				LABA+LAMA	35 (1.15)	30 (1.43)	76 (1.20)
Underweight (< 18.5)	135 (4.45)	83 (3.94)	186 (2.94)	LABA+ICS	695 (22.9)	525 (24.9)	1,606 (25.4)
Healthy Weight (18.5-24.9)	935 (30.8)	592 (28.1)	1,703 (26.9)	LAMA+ICS	52 (1.71)	45 (2.14)	105 (1.66)
Overweight (25.0-29.9)	964 (31.7)	647 (30.7)	1,935 (30.6)	Triple	688 (22.7)	579 (27.5)	1,678 (26.5)
Obese (≥ 30)	891 (29.3)	717 (34.1)	2,271 (35.9)	No long-acting inhaler	0	0	0
Missing Data	112 (3.69)	66 (3.14)	239 (3.77)	History of Cardiovascular Disease [‡]	2,649 (87.2)	1,908 (90.6)	5,702 (90.0)
Index of Multiple Deprivation				Atrial fibrillation	875 (28.8)	827 (39.3)	2,468 (39.0)
1 – Most deprived	450 (14.8)	308 (14.6)	842 (13.3)	Hypertension	1,624 (53.5)	1,225 (58.2)	3,696 (58.4)
2	576 (19.0)	430 (20.4)	1,283 (20.3)	Ischaemic heart disease	1,625 (53.5)	1,167 (55.4)	3,524 (55.6)
3	610 (20.1)	424 (20.1)	1,256 (19.8)	Peripheral artery disease	413 (13.6)	292 (13.9)	873 (13.8)
4	709 (23.4)	286 (23.1)	1,444 (22.8)	Stroke	414 (13.6)	322 (15.3)	938 (14.8)
5 – Least deprived	692 (22.8)	457 (21.7)	1,509 (23.8)	Diabetes mellitus	667 (22.0)	554 (26.3)	1,817 (28.7)
GOLD Stage				CVD medications [†]			
1: Mild	1,146 (37.7)	785 (37.3)	2,272 (35.9)	ACEi	1,684 (55.5)	1,159 (55.1)	3,728 (58.9)
2: Moderate	664 (21.9)	481 (22.9)	1,397 (22.1)	ARB	566 (18.6)	466 (22.1)	1,295 (20.5)
3: Severe	439 (14.5)	341 (16.2)	1,005 (15.9)	Beta-blockers	941 (31.0)	616 (29.3)	2,054 (32.4)
4: Very Severe	110 (3.62)	92 (4.37)	260 (4.10)	Calcium channel blockers	501 (16.5)	353 (16.8)	983 (15.5)
Missing	678 (22.3)	406 (19.3)	1,400 (22.1)	MRA	367 (12.1)	402 (19.1)	1,643 (25.9)
				Statins	1,781 (58.6)	1,227 (58.3)	3,810 (60.2)
				Vasodilators	591 (19.5)	507 (24.1)	1,553 (24.5)

Table E8. Descriptive statistics for non-users, incident users, and prevalent users of loop diuretics (LD) at start of follow-up. Proportions may not sum to 100% due to rounding. Severity of airflow limitation using the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines [1]. Angiotensin converting enzyme inhibitors (ACEi). Angiotensin receptor blockers (ARB). Calcium channel blockers (CCB). Interquartile range (IQR). Long-acting beta agonists (LABA). Inhaled corticosteroids (ICS). Long-acting muscarinic antagonist (LAMA). Mineralocorticoid receptor antagonists (MRA). Short-acting beta agonists (SABA). Short-acting muscarinic antagonist (SAMA). [†]At least two prescriptions >15 days apart in the year prior to the start of follow-up. [‡]Prior diagnosis of ischaemic heart disease, peripheral artery disease, atrial fibrillation, hypertension, and/or stroke.

	Non-Users of MRA	Incident Users of MRA (<6 months)	Prevalent Users of MRA (≥6 months)		Non-Users of MRA	Incident Users of MRA (<6 months)	Prevalent Users of MRA (≥6 months)
Number of Patients (N)	7,146	1,335	2,244	Exacerbation History (IQR)	2 (0, 3)	3 (1, 5)	2 (1, 4)
Female	2,674 (37.4)	428 (32.1)	731 (32.6)	COPD medications [†]			
Age, years (IQR)	77.6 (71.1, 83.5)	77.3 (70.8, 83.4)	75.9 (68.6, 81.9)	SABA/SAMA	7,146 (100)	1,335 (100)	2,244 (100)
Smoking Status				LABA alone	155 (2.17)	27 (2.02)	46 (2.05)
Current Smoker	1,468 (20.5)	239 (17.9)	460 (20.5)	LAMA alone	561 (7.85)	80 (5.99)	169 (7.53)
Former Smoker	5,678 (79.5)	1,096 (82.1)	1,784 (79.5)	ICS alone	629 (8.80)	78 (5.84)	158 (7.04)
Body Mass Index				LABA+LAMA	89 (1.25)	17 (1.27)	24 (1.07)
Underweight (< 18.5)	265 (3.71)	32 (2.40)	53 (2.36)	LABA+ICS	1,764 (24.7)	325 (24.3)	558 (24.9)
Healthy Weight (18.5-24.9)	2,048 (28.7)	354 (26.5)	554 (24.7)	LAMA+ICS	119 (1.67)	26 (1.95)	39 (1.74)
Overweight (25.0-29.9)	2,234 (31.3)	409 (30.6)	702 (31.3)	Triple	1,698 (23.8)	458 (34.3)	683 (30.4)
Obese (≥ 30)	2,316 (32.4)	491 (36.8)	863 (38.5)	No long-acting inhaler	0	0	0
Missing Data	283 (3.96)	49 (3.67)	71 (3.21)	History of Cardiovascular Disease [‡]	6,355 (88.9)	1,230 (92.1)	2,028 (90.4)
Index of Multiple Deprivation				Atrial fibrillation	2,458 (34.4)	615 (46.1)	942 (42.0)
1 – Most deprived	998 (14.0)	179 (13.4)	301 (13.4)	Hypertension	4,064 (56.9)	780 (58.4)	1,275 (56.8)
2	1,425 (19.9)	285 (21.4)	436 (19.4)	Ischaemic heart disease	3,861 (54.0)	813 (60.9)	1,333 (59.4)
3	1,416 (19.8)	278 (20.8)	453 (20.2)	Peripheral artery disease	983 (13.8)	196 (14.7)	298 (13.3)
4	1,635 (22.9)	319 (23.9)	531 (23.7)	Stroke	1,052 (14.7)	200 (15.0)	302 (13.5)
5 – Least deprived	1,672 (23.4)	274 (20.5)	523 (23.3)	Diabetes mellitus	1,827 (25.6)	418 (31.3)	701 (31.2)
GOLD Stage				CVD medications [†]			
1: Mild	2,591 (36.3)	469 (35.1)	820 (36.5)	ACEi	4,104 (57.4)	773 (57.9)	1,354 (60.3)
2: Moderate	1,531 (21.4)	321 (24.0)	524 (23.4)	ARB	1,349 (18.9)	342 (25.6)	537 (23.9)
3: Severe	1,061 (14.9)	261 (19.6)	385 (17.2)	Beta-blockers	2,030 (28.4)	475 (35.6)	989 (44.1)
4: Very Severe	276 (3.86)	64 (4.79)	103 (4.59)	Calcium channel blockers	1,217 (17.0)	200 (15.0)	263 (11.7)
Missing	1,687 (23.6)	220 (16.5)	412 (18.4)	Loop diuretics	4,657 (65.2)	1,076 (80.6)	1,818 (81.0)
				Statins	4,186 (58.6)	833 (62.4)	1,433 (63.9)
				Vasodilators	1,589 (22.2)	369 (27.6)	584 (26.0)

Table E9. Descriptive statistics for non-users, incident users, and prevalent users of mineralocorticoid receptor antagonists (MRA) at start of follow-up. Proportions may not sum to 100% due to rounding. Severity of airflow limitation using the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines [1]. Angiotensin converting enzyme inhibitors (ACEi). Angiotensin receptor blockers (ARB). Beta-blockers (BB). Calcium channel blockers (CCB). Interquartile range (IQR). Long-acting beta agonists (LABA). Inhaled corticosteroids (ICS). Long-acting muscarinic antagonist (LAMA). Short-acting beta agonists (SABA). Short-acting muscarinic antagonist (SAMA). [†]At least two prescriptions >15 days apart in the year prior to the start of follow-up. [‡]Prior diagnosis of ischaemic heart disease, peripheral artery disease, atrial fibrillation, hypertension, and/or stroke.

Exposure	Adjusted Hazard Ratio (95% confidence interval)
ACEi	5.38 (4.79, 6.05)
ARB	5.99 (5.08, 7.07)
BB	5.65 (4.92, 6.49)
LD	4.76 (4.31, 5.25)
MRA	6.01 (5.31, 6.80)

Table E10. Adjusted hazard ratios comparing incident-use to non-use of heart failure medications. Angiotensin converting enzyme inhibitors (ACEi). Angiotensin receptor blockers (ARB). Beta-blockers (BB). Loop diuretics (LD). Mineralocorticoid receptor antagonists (MRA).

Exposure	Adjusted Hazard Ratio (95% confidence interval)
ACEi	1.11 (1.03, 1.19)
ARB	1.22 (1.12, 1.32)
BB	1.41 (1.32, 1.51)
LD	1.12 (1.05, 1.20)
MRA	1.61 (1.48, 1.74)

Table E11. Adjusted hazard ratios comparing prevalent-use to non-use of heart failure medications. Angiotensin converting enzyme inhibitors (ACEi). Angiotensin receptor blockers (ARB). Beta-blockers (BB). Loop diuretics (LD). Mineralocorticoid receptor antagonists (MRA).

Exposure	Adjusted Hazard Ratio (95% confidence interval)
ACEi	0.24 (0.22, 0.27)
ARB	0.23 (0.20, 0.26)
BB	0.27 (0.25, 0.30)
LD	0.25 (0.23, 0.27)
MRA	0.32 (0.28, 0.35)

Table E12. Adjusted hazard ratios comparing prevalent-use to incident-use of heart failure medications. Angiotensin converting enzyme inhibitors (ACEi). Angiotensin receptor blockers (ARB). Beta-blockers (BB). Loop diuretics (LD). Mineralocorticoid receptor antagonists (MRA).

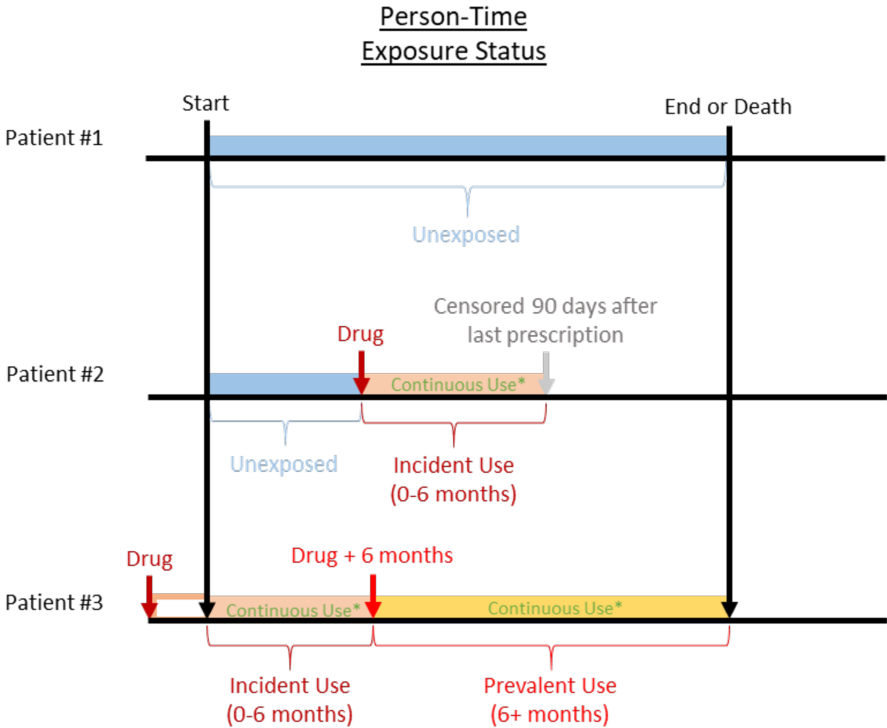


Figure E1. Example of person-time based follow-up.

Patient #1 enters the study at their start of follow-up unexposed, they remain unexposed until their end of follow-up. **Patient #2** enters the study at their start of follow-up unexposed. They become exposed to incident drug use upon first prescription of the drug of interest and remain exposed throughout continuous use of the drug. They are censored 90 days after their last prescription within continuous use, which occurs within 6 months of their first prescription. **Patient #3** enters the study at their start of follow-up exposed to incident continuous drug use, whereby their first prescription of the drug of interest was within 6 months of their start of follow-up. They remain exposed to incident continuous drug use until 6 months after their first prescription, thereafter they are exposed to prevalent continuous drug use until their end of follow-up. *Continuous drug use was defined as at least two prescriptions of the drug of interest and gaps between prescriptions were no more than 90 days. Patients were censored 90 days after their last prescription in a continuous run.

A) ACEi				B) ARB				C) BB			
		End of Follow-up				End of Follow-up				End of Follow-up	
		Non-User	Incident User	Prevalent User			Non-User	Incident User	Prevalent User		
Start of Follow-up	Non-User	3,497 (39.3)	213 (2.39)	426 (4.79)	Start of Follow-up	Non-User	6,851 (77.0)	99 (1.11)	303 (3.40)	Start of Follow-up	Non-User
	Incident User		136 (1.53)	462 (5.19)		Incident User		37 (0.42)	229 (2.57)		Incident User
	Prevalent User			4,167 (46.8)		Prevalent User			1,382 (15.5)		Prevalent User
		D) LD		E) MRA							
		End of Follow-up		End of Follow-up							
		Non-User	Incident User	Prevalent User			Non-User	Incident User	Prevalent User		
Start of Follow-up	Non-User	1,884 (21.2)	430 (4.83)	723 (8.12)	Start of Follow-up	Non-User	6,231 (70.0)	325 (3.65)	590 (6.63)	Start of Follow-up	Non-User
	Incident User		253 (2.84)	699 (7.85)		Incident User		101 (1.13)	319 (3.58)		Incident User
	Prevalent User			4,912 (55.2)		Prevalent User			1,335 (15.0)		Prevalent User

Figure E2. Cardiovascular medication exposure status for chronic obstructive pulmonary disease (COPD) patients with heart failure (HF) at start and end of follow-up for A) angiotensin converting enzyme inhibitors (ACEi), (B) angiotensin receptor blockers (ARB), (C) beta-blockers (BB), (D) LDs (LD), and (E) mineralocorticoid receptor antagonists (MRA). Population size: N = 8,901. Count (%).

References

1. GOLD. Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2017. [Webpage] 2017 [cited 10 Jan 2018]; Available from: <http://goldcopd.org/gold-2017-global-strategy-diagnosis-management-prevention-copd/>