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Factors associated with non-fatal heart failure and atrial fibrillation or flutter within the first 30 days post COPD exacerbation: a nested case-control study

Emily L. Graul¹, Clementine Nordon², Kirsty Rhodes², Shruti Menon³, Mahmoud Al Ammouri¹, Constantinos Kallis¹, Anne E. Ioannides¹, Hannah R. Whittaker¹, Nicholas S. Peters⁴ and Jennifer K. Quint^{1*}

Abstract

Background An immediate, temporal risk of heart failure and arrhythmias after a Chronic Obstructive Pulmonary Disease (COPD) exacerbation has been demonstrated, particularly in the first month post-exacerbation. However, the clinical profile of patients who develop heart failure (HF) or atrial fibrillation/flutter (AF) following exacerbation is unclear. Therefore we examined factors associated with people being hospitalized for HF or AF, respectively, following a COPD exacerbation.

Methods We conducted two nested case-control studies, using primary care electronic healthcare records from the Clinical Practice Research Datalink Aurum linked to Hospital Episode Statistics, Office for National Statistics for mortality, and socioeconomic data (2014-2020). Cases had hospitalization for HF or AF within 30 days of a COPD exacerbation, with controls matched by GP practice (HF 2:1;AF 3:1). We used conditional logistic regression to explore demographic and clinical factors associated with HF and AF hospitalization.

Results Odds of HF hospitalization (1,569 cases, 3,138 controls) increased with age, type II diabetes, obesity, HF and arrhythmia history, exacerbation severity (hospitalization), most cardiovascular medications, GOLD airflow obstruction, MRC dyspnea score, and chronic kidney disease. Strongest associations were for severe exacerbations (adjusted odds ratio (aOR)=6.25, 95%CI 5.10-7.66), prior HF (aOR=2.57, 95%CI 1.73-3.83), age \geq 80 years (aOR=2.41, 95%CI 1.88-3.09), and prior diuretics prescription (aOR=2.81, 95%CI 2.29-3.45).

Odds of AF hospitalization (841 cases, 2,523 controls) increased with age, male sex, severe exacerbation, arrhythmia and pulmonary hypertension history and most cardiovascular medications. Strongest associations were for severe exacerbations (aOR=5.78, 95%CI 4.45-7.50), age \geq 80 years (aOR=3.15, 95%CI 2.26-4.40), arrhythmia (aOR=3.55, 95%CI 2.53-4.98), pulmonary hypertension (aOR=3.05, 95%CI 1.21-7.68), and prescription of anticoagulants (aOR=3.81, 95%CI 2.57-5.64), positive inotropes (aOR=2.29, 95%CI 1.41-3.74) and anti-arrhythmic drugs (aOR=2.14, 95%CI 1.10-4.15).

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*Correspondence:

Jennifer K. Quint

j.quint@imperial.ac.uk

Full list of author information is available at the end of the article



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Conclusions Cardiopulmonary factors were associated with hospitalization for HF in the 30 days following a COPD exacerbation, while only cardiovascular-related factors and exacerbation severity were associated with AF hospitalization. Understanding factors will help target people for prevention.

Keywords Chronic Obstructive Pulmonary Disease Exacerbations, Cardiovascular Disease, Heart Failure, Arrhythmia, Atrial Fibrillation, Flutter, Electronic Health Records, Epidemiology

Background

Exacerbations of Chronic Obstructive Pulmonary Disease (COPD) are associated with an increased risk of cardiovascular disease (CVD) [1] likely due to linked pathophysiology, hypoxic state, and an amplified systemic inflammatory response [2, 3]. Previous studies have demonstrated an increased, immediate period of risk for hospitalized cardiovascular events following a COPD exacerbation compared with non-exacerbating patients, [1, 4] with the risk highest within the first month and following a severe (hospitalized) exacerbation [1, 5, 6]. The 30 day risk of arrhythmias and heart failure (HF) following an exacerbation, [6–8] approach [4, 6] or even surpass [7, 9] 3-fold, compared to those who did not have an exacerbation.

Globally, the prevalence of HF in COPD is high, [10] and, of patients hospitalized for exacerbation, 20% have existing, undertreated HF [11]. Incident HF attributed to exacerbations is thought to come from the increase in pulmonary arterial pressures, low blood oxygen levels [12] and activation of adrenoceptors of the autonomic nervous system [12, 13]. However, shared symptomology of HF and COPD exacerbations makes new HF diagnosis difficult, with HF often missed [3, 12, 14] or occurring in tandem; approximately 8% of people primarily diagnosed with HF also have a secondary diagnosis of exacerbation [15]. Studies have investigated COPD progression in HF [12] and conversely, HF progression across COPD phenotypes, [12, 16] but few have focused on exacerbating COPD alone [15] and no studies have examined factors associated with hospitalization with a HF diagnosis following a COPD exacerbation.

Arrhythmias are also common among people with COPD, with prevalence ranging from 5 to 15% globally, [10] and atrial fibrillation (AF) is the most common arrhythmia [17]. AF diagnoses at the time of an exacerbation are also common, with estimates around 17% [18], but due to shared, nonspecific symptoms between AF and COPD, differential diagnosis can be difficult [19]. During a COPD exacerbation, changes in blood gases from hypoxia and rising pulmonary pressure can lead to electrophysiological and structural changes of the atrium, and together are thought to contribute to exacerbation-related disturbances in rhythm and progression of AF [6, 10, 19–21] The understanding of

COPD progression alongside AF progression is unclear [19]. Few studies have examined factors associated with hospitalization for incident AF after an exacerbation, with the focus on the short-term [21, 22]. Several have however investigated factors associated with concurrent AF at time of an exacerbation [18, 23].

Therefore, using a primary-care defined COPD cohort from the Clinical Practice Research Datalink (CPRD) Aurum database linked with hospital, mortality, and socioeconomic deprivation data, we explored factors associated with incident hospitalization for non-fatal HF, or AF or atrial flutter, within the 30 days following a COPD exacerbation.

Study design and methods

Data source

We obtained pseudonymized, routinely-collected electronic healthcare record data from CPRD Aurum, [24] a primary care database broadly representative by age, sex, deprivation, and regional distribution, [25] and covering approximately 20% of GP-registered patients in England [24]. Primary care data from the May 2022 build [24] were linked to the Office for National Statistics (ONS) for mortality, socioeconomic data from the 2015 Index of Multiple Deprivation (IMD), and secondary care data from NHS England's Hospital Episode Statistics (HES) Admitted Patient Care (APC) database.

Source population

The source population were people with a COPD diagnosis who had been included in the Exacerbations of COPD and their OutcomeS on CardioVascular diseases (EXACOS-CV) observational open cohort study [4]. People were eligible for inclusion in that original cohort study if they met the following criteria: 1) aged 40 years or older, 2) had a COPD diagnosis using a validated algorithm (86.5% PPV) [26] 3) were eligible for linkage with HES, ONS, and IMD data, 4) had a smoking history (i.e., current or ex-smoker), 5) had continuous GP practice registration with acceptable quality data in the year before start of follow up, and 6) had data recorded after 1st of January 2014.

Study design and population

We conducted two nested-case control studies, in parallel. The study population for each study consisted of COPD patients in the EXACOS-CV source population, who 1) experienced an exacerbation within cohort follow-up, 2) among the pool of eligible controls had at least 30 days of contributing data post-exacerbation, and 3) had no evidence of HF or arrhythmias in the year before exacerbation. People were excluded from the AF/flutter study population if, within the 30 days post-exacerbation, they had evidence of other non-AF arrhythmias (e.g., cardiac arrest) (Fig. 1 for study designs; Supplementary Figures 1 and 2 for HF and AF/flutter eligibility diagram respectively).

Cases were individuals with a hospitalized, cardiovascular event (HF or AF/flutter, respectively) within 1-30 days post COPD exacerbation. Cases were determined in the HES database using ICD-10 codes in the primary diagnostic position across all episodes in a single hospitalization. The date of admission was the date of the case (index date, HF or AF/flutter, respectively). Extended case definitions are in Supplementary Table 3.

The set of controls per case was drawn among individuals in the study population who had no in-hospital diagnosis of the cardiovascular event-of-interest (HF or AF/flutter, respectively) and who had 30 days of contributing data post-exacerbation. Controls were assigned a pseudo-end date (i.e., 30 days post-exacerbation) on which to match. Controls were individually matched to cases on GP practice to account for unmeasurable potential clinical differences in disease management by clinicians, within a 30-day window of the index date, and could be used as a control for more than one case. For the HF analysis, controls were matched 2:1 and for the AF/flutter analysis, 3:1.

The choice of matching factors and ratios were chosen based on considerations of 1) maximizing the ratio itself for reasons of power and precision while 2) minimizing cases lost without a full set of controls. Only case sets with the full ratio of controls per case were included for analysis.

Factors

We examined factors potentially associated with hospitalization for HF or AF/flutter in the 30 days

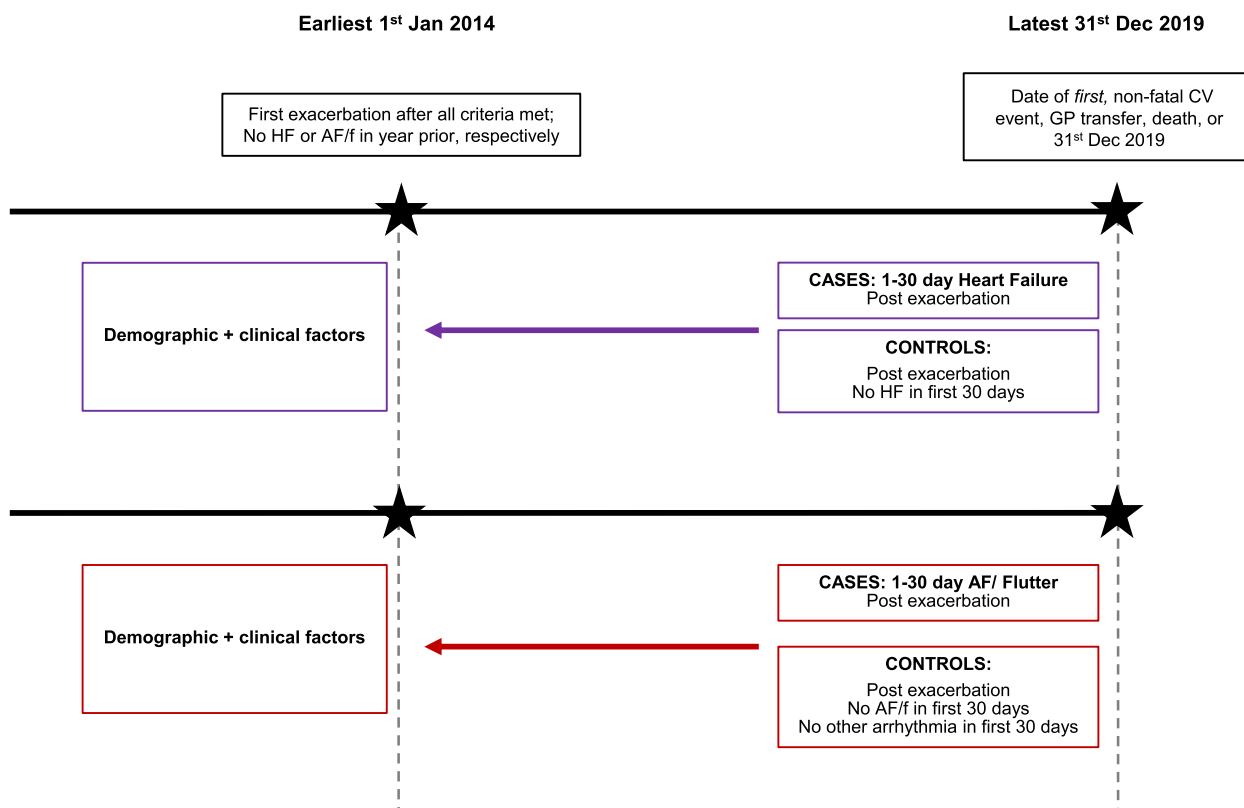


Fig. 1 Study design for the parallel, nested case control studies. Abbreviations: HF=heart failure, AF/f = atrial fibrillation/flutter, GP=general practice, CV=cardiovascular. Two nested case control studies, for HF and AF/f respectively, were conducted among all patients who experienced an exacerbation at start of cohort follow up. Full definitions of demographic and clinical factors of interest are in the [Supplementary materials](#)

following an exacerbation of COPD. Factors included demographic characteristics: age (categorized into four age bands; 40-69, 70-74, 75-79, ≥ 80), sex, IMD quintiles, and ethnicity; and smoking status. Comorbidities included (hypertension, anxiety, depression and depressive symptoms, type II diabetes, chronic kidney disease (CKD), BMI [body mass index; using World Health Organization classification]). COPD factors included GOLD grade of airflow limitation (defined as 1 mild, 2 moderate, 3-4 severe/very severe), Medical Research Council (MRC) dyspnea score (1-2; 3; 4-5), exacerbation severity at cohort entry (moderate/severe) prior exacerbation frequency (infrequent (≤ 1) versus frequent (≥ 2) history in a year window preceding one year to cohort entry). Prior CVD history was evidence of the following anytime preceding the year before exacerbation date [acute coronary syndrome (ACS), arrhythmias, HF, ischemic stroke, pulmonary hypertension PH], COPD inhaled therapies, and major classes of cardiovascular medications (prescriptions defined two years before cohort entry). Covariate definitions are in Supplementary Table 4.

We used validated definitions for COPD exacerbations. A moderate exacerbation was defined as a COPD-related primary care (GP) visit with either a code for exacerbation (including Lower Respiratory Tract Infection (LRTI) SNOMED-CT codes) and/or prescription for respiratory antibiotics and oral systemic corticosteroids not on the same day as an annual review, as validated in CPRD [27]. A severe exacerbation was defined as a hospitalization with an acute respiratory event code including COPD or bronchitis as a primary diagnosis, or a secondary diagnosis of COPD, as validated in HES [28]. We considered exacerbations to be the same event if recorded within 14 days in which case the highest level of severity was chosen.

We checked covariate missingness to assess use in adjusted models. Imputation was not considered for covariates with missing data, given the missingness mechanism was Missing-Not-At-Random (MNAR), violating the Missing-Completely-At-Random (MCAR) assumption premising imputation [29].

Codelists

Codelists for primary care factors were generated using SNOMED-CT and British National Formulary ontologies; we used our standardizable, reproducible methodology, available on GitHub: for [drug](#) [30] and [medical/phenotype codelists](#), respectively. Codelists for hospitalizations used ICD-10 codes. Codelists are available on our EXACOS-CV [GitHub repository](#).

Statistical analysis

We compared separately the odds of hospitalization for HF or AF/flutter between the comparator groups for each factor, using conditional logistic regression. Our final model was adjusted for all covariates without substantial amount of missing data, including demographic factors, comorbidities, and COPD inhaled therapies and cardiovascular medications. In three sensitivity analyses, we repeated main analyses additionally adjusting for variables-of-interest with substantial missing data, respectively: GOLD, MRC, and CKD.

Analyses were performed using STATA v17.

Ethics

These data were collected and provided by CPRD. Ethical approval was obtained through CPRD's Research Data Governance Process (protocol number: 22_002377). The RECORD checklist for observational studies is in Supplementary Table 5.

Results

Characteristics of study participants

The HF dataset consisted of 1,569 cases experiencing an HF event within the first 30 days post-exacerbation, matched to 3,138 controls. The AF/flutter dataset consisted of 841 cases experiencing an AF/flutter event within the first 30 days post-exacerbation, matched to 2,523 controls. Tables 1 and 2 show the characteristics of the participants for HF and AF/flutter, respectively.

Across both study populations, cases tended to have had a severe exacerbation, were more likely to be older, male, an ex-smoker, have comorbidities including prior prevalent cardiovascular disease, and be prescribed cardiovascular medications. Cases and controls both tended to have infrequent exacerbation history, have prescriptions for long-acting therapies, but tended to not have prescriptions for short-acting inhaled therapies.

Factors associated with HF hospitalization 1-30 days post exacerbation

Age, type II diabetes, obesity, prior HF diagnosis, prior arrhythmia diagnosis, having a severe exacerbation, and most cardiovascular medications were associated with increased odds of being hospitalized for HF within 30 days of a COPD exacerbation (Table 1). The factors most strongly associated with HF were exacerbation severity (aOR=6.25, 95%CI 5.10-7.66), a prior HF diagnosis (aOR=2.57, 95%CI 1.73-3.83), age at least 80 years (≥ 80 vs. 40-69; aOR=2.41, 95%CI 1.88-3.09), and, of the cardiovascular medications, diuretics (aOR=2.81, 95%CI 2.29-3.45).

Table 1 Factors associated with hospitalizations for heart failure within the first 30 days post acute exacerbation of COPD

Characteristic N (%)	Controls (N=3,138)	Cases (Non-fatal HF) (N=1,569)	aOR (95% CI) ^a (N=4,312)	
Age				
40-69	1,432 (45.6)	327 (20.8)	1.00 (ref)	
70-74	560 (17.9)	233 (14.9)	1.40 (1.07-1.84)	
75-79	480 (15.3)	312 (19.9)	1.97 (1.50-2.60)	
80+	666 (21.2)	697 (44.4)	2.41 (1.88-3.09)	
Male sex	1,594 (50.8)	890 (56.7)	1.13 (0.93-1.37)	
Smoking status				
Ex-smoker	1,845 (58.8)	1,105 (70.4)	1.00 (ref)	
Current smoker	1,293 (41.2)	464 (29.6)	0.94 (0.77-1.15)	
Index of Multiple Deprivation (IMD) quintile				
Least Deprived	433 (13.8)	222 (14.2)	1.00 (ref)	
2	547 (17.4)	279 (17.8)	1.12 (0.79-1.58)	
3	581 (18.5)	286 (18.2)	1.23 (0.86-1.74)	
4	674 (21.5)	352 (22.4)	1.13 (0.79-1.62)	
Most Deprived	898 (28.6)	429 (27.3)	1.22 (0.84-1.77)	
Missing	5 (0.2)	1 (0.1)	-	
Ethnicity				
White	2,409 (76.8)	1,199 (76.4)	-	
South Asian	38 (1.2)	19 (1.2)	-	
Black	<15 (suppressed)	<15 (suppressed)	-	
Other	<15 (suppressed)	<15 (suppressed)	-	
Mixed	<15 (suppressed)	<15 (suppressed)	-	
Missing	659 (21.0)	340 (21.7)	-	
Comorbidities				
Type II Diabetes	622 (19.8)	503 (32.1)	1.40 (1.12-1.75)	
Depression / depressive symptoms	2,287 (72.9)	1,247 (79.5)	0.95 (0.74-1.21)	
Anxiety	878 (28.0)	374 (23.8)	0.80 (0.64-0.99)	
Hypertension	1,645 (52.4)	1,078 (68.7)	0.85 (0.68-1.08)	
BMI				
Normal (18.5 to <25)	967 (30.8)	416 (26.5)	1.00 (ref)	
Underweight (<18.5)	152 (4.84)	79 (5.0)	1.32 (0.86-2.03)	
Overweight (25 to <30)	926 (29.5)	451 (28.7)	1.17 (0.92-1.48)	
Obese (30+)	929 (29.6)	545 (34.7)	1.37 (1.07-1.75)	
Missing/Unknown	164 (5.2)	78 (5.0)	-	
Chronic Kidney Disease				
No (eGFR >60% or uAlb<3mg/mmol)	2,131 (67.9)	806 (51.4)	-	
Yes	457 (14.6)	621 (39.6)	-	
Missing	550 (17.5)	142 (9.1)	-	
COPD prognosis				
Exacerbation severity at start of follow-up				
Moderate	2,482 (79.1)	652 (41.6)	1.00 (ref)	
Severe	656 (20.9)	917 (58.4)	6.25 (5.10-7.66)	
Exacerbation frequency in the 1-year window preceding 1-year-to-start of cohort follow-up				
Infrequent exacerbator (≤1)	2,660 (84.8)	1,333 (85.0)	1.00 (ref)	
Frequent exacerbator (≥2)	478 (15.2)	236 (15.0)	0.94 (0.72-1.23)	
GOLD grade of airflow limitation				
1 (Mild)	698 (22.2)	232 (14.8)	-	
2 (Moderate)	1,282 (40.9)	556 (35.4)	-	
3-4 (Severe or Very Severe)	669 (21.3)	370 (23.6)	-	
Missing/Unknown	489 (15.6)	411 (26.2)	-	
MRC dyspnea score				
1-2	1,423 (45.4)	416 (26.5)	-	
3	785 (25.0)	438 (27.9)	-	
4-5	556 (17.7)	473 (30.2)	-	
Missing/Unknown	374 (11.9)	242 (15.4)	-	
Prior prevalent CVD				
Acute Coronary Syndrome (ACS)	285 (9.1)	334 (21.3)	0.99 (0.75-1.30)	
Arrhythmias	420 (13.4)	542 (34.5)	1.40 (1.07-1.83)	
Heart Failure (HF)	66 (2.1)	201 (12.8)	2.57 (1.73-3.83)	
Pulmonary Hypertension (PH)	30 (1.0)	47 (3.0)	0.90 (0.49-1.68)	
Ischemic Stroke	218 (7.0)	189 (12.1)	1.04 (0.76-1.43)	
COPD Medications				
Long-acting, inhaled therapies				
No long-acting therapies	459 (14.6)	246 (15.7)	1.00 (ref)	
LABA/LAMA mono/dual	530 (16.9)	246 (15.7)	0.84 (0.60-1.16)	
ICS-based mono/dual/triple	2,149 (68.5)	1,077 (68.6)	0.80 (0.61-1.04)	
Short-acting, inhaled therapies				
No short-acting therapies	2,651 (84.5)	1,351 (86.1)	1.00 (ref)	
SABA/SAMA mono/dual	487 (15.5)	218 (13.9)	0.83 (0.63-1.09)	
CVD medications				
Positive inotropes	99 (3.2)	219 (14.0)	1.52 (1.03-2.25)	
Diuretics	1,005 (32.0)	1,122 (71.5)	2.81 (2.29-3.45)	
Anti-arrhythmic drugs	39 (1.2)	88 (5.6)	1.46 (0.87-2.45)	
Beta blockers	575 (18.3)	677 (43.2)	1.65 (1.33-2.06)	
Hypertension and heart failure drugs	1,398 (44.6)	1,071 (68.3)	1.43 (1.15-1.79)	
Nitrates, CCBs, other antianginals	1,205 (38.4)	852 (54.3)	1.05 (0.86-1.29)	
Anticoagulants	294 (9.37)	459 (29.3)	1.57 (1.16-2.13)	
Antiplatelets	1,020 (32.5)	807 (51.4)	1.60 (1.28-2.00)	
Statins	1,568 (50.0)	1,012 (64.5)	0.77 (0.61-0.96)	

eGFR Estimated glomerular filtration rate, uAlb Urine albumin, CVD Cardiovascular disease, ICS Inhaled corticosteroid, LABA Long-acting beta agonist, LAMA Long-acting muscarinic antagonist, SABA Short-acting beta agonist, SAMA Short-acting muscarinic antagonist, CCB Calcium channel blocker. n(%) described for the COPD and CV prescription categories may be mutually exclusive, as they can be taken in combination elsewhere in the table (e.g., patient prescribed a long-acting inhaler, short-acting inhaler, oral therapy, and a cardiovascular medication)

^a The final model was adjusted for socioeconomic status (IMD), smoking status, and comorbidities: BMI, Type II diabetes, depression and depressive symptoms, exacerbation severity, exacerbation frequency and prior prevalent CVD (hypertension, acute coronary syndrome, arrhythmia, heart failure, pulmonary hypertension, ischemic stroke), and COPD medications (short-acting and long-acting COPD inhaled therapies) and major classes of CVD medications according to the British National Formulary (BNF)

Table 2 Factors associated with hospitalizations for atrial fibrillation or flutter within the first 30 days post acute exacerbation of COPD

Characteristic N (%)	Controls (N=2,523)	Cases (Non-fatal AF/flutter) (N=841)	aOR (95% CI) ^a (N=3,096)	
Age				
40-69	1,097 (43.5)	138 (16.4)	1.00 (ref)	
70-74	458 (18.2)	120 (14.3)	1.21 (0.85-1.73)	
75-79	463 (18.4)	196 (23.3)	1.82 (1.28-2.58)	
80+	505 (20.0)	387 (46.0)	3.15 (2.26-4.40)	
Male sex	1,226 (48.6)	496 (59.0)	1.50 (1.18-1.91)	
Smoking status				
Ex-smoker	1,502 (59.5)	571 (67.9)	1.00 (ref)	
Current smoker	1,021 (40.5)	270 (32.1)	1.17 (0.90-1.51)	
Index of Multiple Deprivation (IMD) quintile				
Least Deprived	354 (14.0)	129 (15.3)	1.00 (ref)	
2	418 (16.6)	170 (20.2)	1.35 (0.88-2.06)	
3	448 (17.8)	155 (18.4)	0.98 (0.63-1.53)	
4	593 (23.5)	153 (18.2)	0.81 (0.51-1.28)	
Most Deprived	710 (28.1)	234 (27.8)	1.10 (0.68-1.79)	
Ethnicity				
White	1,896 (75.2)	624 (74.2)	-	
South Asian	26 (1.0)	<15 (suppressed)	-	
Black	<15 (suppressed)	<15 (suppressed)	-	
Other	<15 (suppressed)	<15 (suppressed)	-	
Mixed	<15 (suppressed)	<15 (suppressed)	-	
Missing	585 (23.2)	212 (25.2)	-	
Comorbidities				
Type II Diabetes	474 (18.8)	223 (26.5)	1.02 (0.76-1.37)	
Depression / depressive symptoms	1,844 (73.1)	667 (79.3)	1.04 (0.76-1.41)	
Anxiety	655 (26.0)	185 (22.0)	1.04 (0.78-1.39)	
Hypertension	1,339 (53.2)	569 (67.7)	1.03 (0.77-1.37)	
BMI				
Normal (18.5 to <25)	775 (30.7)	279 (33.2)	1.00 (ref)	
Underweight (<18.5)	122 (4.8)	42 (4.99)	1.16 (0.69-1.94)	
Overweight (25 to <30)	755 (29.9)	254 (30.2)	0.94 (0.70-1.26)	
Obese (30+)	741 (29.4)	229 (27.2)	0.97 (0.71-1.32)	
Missing/Unknown	130 (5.2)	37 (4.4)	-	
Chronic Kidney Disease				
No (eGFR >60% or uAlb<3mg/mmol)	1,694 (67.1)	476 (56.6)	-	
Yes	372 (14.7)	288 (34.2)	-	
Missing	457 (18.1)	77 (9.2)	-	
COPD prognosis				
Exacerbation severity at start of follow-up				
Moderate	2,081 (82.5)	434 (51.6)	1.00 (ref)	
Severe	442 (17.5)	407 (48.4)	5.78 (4.45-7.50)	
Exacerbation frequency in the 1-year window preceding 1-year-to-start of cohort follow-up				
Infrequent exacerbator (≤1)	2,006 (79.5)	669 (80.0)	1.00 (ref)	
Frequent exacerbator (≥2)	517 (20.5)	17 (20.5)	0.81 (0.60-1.10)	
GOLD grade of airflow limitation				
1 (Mild)	561 (22.2)	144 (17.1)	-	
2 (Moderate)	975 (38.6)	293 (34.8)	-	
3-4 (Severe or Very Severe)	603 (23.9)	224 (26.6)	-	
Missing/Unknown	384 (15.2)	180 (21.4)	-	
MRC dyspnea score				
1-2	1,111 (44.0)	255 (30.3)	-	
3	687 (27.2)	232 (27.6)	-	
4-5	471 (18.7)	251 (29.9)	-	
Missing/Unknown	254 (10.1)	103 (12.3)	-	
Prior prevalent CVD				
Acute Coronary Syndrome (ACS)	216 (8.6)	147 (17.5)	0.76 (0.53-1.11)	
Arrhythmias	239 (9.5)	425 (50.5)	3.55 (2.53-4.98)	
Heart Failure (HF)	65 (2.6)	73 (8.7)	1.17 (0.70-1.98)	
Pulmonary Hypertension (PH)	<15 (suppressed)	31 (3.7)	3.05 (1.21-7.68)	
Ischemic Stroke	152 (6.0)	101 (12.0)	0.87 (0.57-1.32)	
COPD Medications				
Long-acting, inhaled therapies				
No long-acting therapies	302 (12.0)	104 (12.4)	1.00 (ref)	
LABA/LAMA mono/dual	317 (12.6)	88 (10.5)	1.14 (0.70-1.87)	
ICS-based mono/dual/triple	1,904 (75.5)	649 (77.2)	1.23 (0.85-1.79)	
Short-acting, inhaled therapies				
No short-acting therapies	2,095 (83.0)	705 (83.8)	1.00 (ref)	
SABA/SAMA mono/dual	428 (17.0)	136 (16.2)	1.17 (0.84-1.62)	
CVD medications				
Positive inotropes	45 (1.78)	184 (21.9)	2.29 (1.41-3.74)	
Diuretics	875 (34.7)	523 (62.2)	1.36 (1.04-1.77)	
Anti-arrhythmic drugs	28 (1.1)	63 (7.5)	2.14 (1.10-4.15)	
Beta blockers	395 (15.7)	342 (40.7)	1.52 (1.14-2.03)	
Hypertension and HF drugs	1,121 (44.4)	522 (62.1)	0.91 (0.69-1.21)	
Nitrates, CCBs, other antianginals	987 (39.1)	435 (51.7)	1.04 (0.80-1.34)	
Anticoagulants	153 (6.1)	323 (38.4)	3.81 (2.57-5.64)	
Antiplatelets	840 (33.3)	402 (47.8)	1.46 (1.10-1.93)	
Statins	1,239 (49.1)	531 (63.1)	0.95 (0.72-1.26)	

eGFR Estimated glomerular filtration rate, uAlb Urine albumin, CVD Cardiovascular disease, ICS Inhaled corticosteroid, LABA Long-acting beta agonist, LAMA Long-acting muscarinic antagonist, SABA Short-acting beta agonist, SAMA Short-acting muscarinic antagonist, CCB Calcium channel blocker. n(%) described for the COPD and CV prescription categories may be mutually exclusive, as they can be taken in combination elsewhere in the table (e.g., patient prescribed a long-acting inhaler, short-acting inhaler, oral therapy, and a cardiovascular medication)

^a The final model was adjusted for socioeconomic status (IMD), smoking status, and comorbidities: BMI, Type II diabetes, depression and depressive symptoms, exacerbation severity, exacerbation frequency and prior prevalent CVD (hypertension, acute coronary syndrome, arrhythmia, heart failure, pulmonary hypertension, ischemic stroke), and COPD medications (short-acting and long-acting COPD inhaled therapies) and major classes of CVD medications according to the British National Formulary (BNF)

In sensitivity analyses, GOLD grade, MRC score, and history of CKD were all associated with an increased odds of being hospitalized for HF within the month post exacerbation. (Supplementary Table 1) The strongest associations were for CKD (aOR=1.85, 95%CI 1.46-2.35) and higher levels of airflow limitation and breathlessness (GOLD grade 3-4 Severe/Very Severe aOR=1.83, 95%CI 1.32-2.54, versus GOLD grade 1 Mild) (Score 4-5 MRC aOR=1.87, 95%CI 1.42-2.46, versus MRC 1-2).

Factors associated with AF/flutter hospitalization 1-30 days post exacerbation

Age, male sex, prior arrhythmia, prior PH, and having a severe exacerbation were associated with AF/flutter in the 30 days following an exacerbation. Most cardiovascular medications were also associated with AF/flutter (Table 2). The factors most strongly associated with AF were exacerbation severity (aOR=5.78 95%CI 4.45-7.50), age ≥ 80 years (aOR=3.15 95%CI 2.26-4.40), prior arrhythmia and PH (aOR=3.55, 95%CI 2.53-4.98; aOR=3.05, 95%CI 1.21-7.68), and of the cardiovascular medications, anticoagulants (aOR=3.81, 95%CI 2.57-5.64), positive inotropes (aOR=2.29, 95%CI 1.41-3.74) and anti-arrhythmic drugs (aOR=2.14, 95%CI 1.10-4.15).

In sensitivity analyses, GOLD grade, MRC score, and CKD had no association with AF/flutter (Supplementary Table 2).

Discussion

In a primary care defined COPD population, this study examined the clinical profiles of people hospitalized for HF and for AF within a month post exacerbation. We observed that the odds of HF and of AF hospitalization were higher for people with severe, hospitalized exacerbations and with cardiovascular-related history. For HF analyses only, the odds of HF were also higher for people with microvascular factors (i.e., type II diabetes; obesity; CKD) and for people with pulmonary factors, namely those with worse GOLD grade of airflow limitation and higher levels of MRC breathlessness scores.

Heart failure

The pathophysiological links between COPD exacerbations and HF are recognized [31–33]. Upon exacerbation, dynamic lung hyperinflation from airflow limitation alongside heightened inflammation and hypoxia, can lead to increased strain on both the lungs and heart. The increased cardiopulmonary pressure can then lead to impaired contraction or filling of the left ventricle, namely HF with preserved or with reduced ejection fraction, respectively [31–33].

Few studies have investigated factors associated with HF in COPD alone, [15, 34–36] of which only one [15] investigated hospitalized exacerbation with concurrent HF, but did not quantify this relationship with ORs, and was conducted in the US National Inpatient Sample (NIS) database. The remaining were post-hoc analyses of trials focused on stable COPD [34–36].

The strong magnitude of the association for exacerbation severity (hospitalization) but not for exacerbation frequency, suggests two points. First, from a healthcare service-level standpoint, patients hospitalized for exacerbations are more likely to be hospitalized for a future HF (i.e., re-admission) compared with patients whose exacerbation was managed in primary care. Second, clinically, exacerbation severity (e.g., greater intensity of inflammation) has a greater indication of a patients' future cardiac state, rather than past exacerbation occurrence and management. Findings for older age were anticipated and align with previous studies [15, 34–36].

The associations for history of HF, arrhythmia, type II diabetes, and CKD with post-exacerbation HF are unsurprising given their known independent relationships each with HF and exacerbations alone. Chronic, unmanaged HF can lead to future health service utilization for HF [16, 37]. Arrhythmia-attributed cardiac remodeling can contribute to development of cardiomyopathy [38]. Diabetes is a risk factor for substantial HF progression [16, 39], and separately a population-based study in COPD patients demonstrated an increased risk of cardiovascular mortality with type II diabetes [40]. Impaired renal hemodynamics and activation of the renin-angiotensin-aldosterone system (RAAS) can lead to HF, [41] and separately reduced kidney function is associated with future HF [42].

Our findings for cardiovascular medications indicate a certain treatment profile in primary care, leading up to the post-exacerbation HF hospitalization. The strongest association for diuretics suggests that leading up to future HF, patients perhaps are receiving treatment indicated for uncontrolled edema from existing HF, diabetic cardiomyopathy, or CKD for example.

GOLD and MRC as factors for post-exacerbation HF likewise were expected. Increased breathlessness and reduced lung function are not only symptoms of an imminent exacerbation or HF; equally, these factors can also indicate delayed diagnosis of unstable COPD or HF, [16, 43] given their shared symptomology [3, 12, 14]. Reduced lung function can contribute to worsening prognosis and precipitate a future exacerbation or HF [16, 43].

Atrial fibrillation

The pathophysiological mechanisms implicating AF post COPD exacerbation are also established [19, 44]. At time of exacerbation, drastic increases in lung hyperinflation and impaired intrathoracic pressures can cause increased pulmonary vascular resistance and damage, leading to alterations to atrial electrophysiology [19, 44]. Compromised gas exchange in the lungs can induce systemic inflammation and oxidative stress too, and also put strain on pulmonary vasculature, leading to abnormal atrial structure and ion-channel remodeling, [19, 44] while certain treatments prescribed upon exacerbation are arrhythmogenic [19, 44].

Only four studies have investigated patient profiles for AF development in unstable COPD, all hospital-based [18, 21–23], of which two conducted in the US National Inpatient Sample (NIS) database [18, 22]. Two examined factors associated with AF diagnosis after exacerbation [21, 22] one of which patients had existing AF [21]. Two failed to quantify with ORs, only comparing baseline characteristics of exacerbating patients by status of concurrent AF [18, 23].

Our findings for older age and male gender are not unexpected; studies similarly found these associations in exacerbating [18, 22] and in stable COPD [45]. Unsurprisingly, exacerbation severity associated with future AF, again adding to the existing evidence of stronger associations for hospitalized exacerbation [1, 6] and again, likewise to HF, suggests a distinction between health-care service-level patient pathways, and intensity versus frequency.

The associations we found for history of PH and arrhythmias aligns with what was anticipated clinically. Electrophysiological and structural changes to the atrium over time, from either AF itself [20] or from chronic atrial stretching and fibrosis attributed to PH, [46] can lead to future AF. While a study using Euro Heart Survey data showed COPD as a factor for progression of paroxysmal to persistent AF (aOR=1.51, 95%CI 0.95-2.39) [20], neither of the two studies looking at patient profiles for post-exacerbation AF, looked at chronic, prevalent arrhythmias itself as a factor [21, 22]. No studies have looked at PH, although the study among end-stage COPD patients in the NIS database found a weak association for pulmonary circulatory disorders (aOR=1.44, 95%CI 1.37-1.52) [22], compared the OR of about 3 for PH. A study found raised pulmonary artery pressure to be associated with AF ($p<0.05$), but failed to quantify, and it was small, underpowered, and not generalizable as it restricted to hospitalized COPD patients with existing AF [21].

The lack of associations for prior ACS, ischemic stroke, HF, and hypertension somewhat contradict the study among hospitalized, end-stage COPD patients, [22] where

an association was found for HF (aOR=2.42; 95%CI: 2.36-2.48) and coagulopathy (aOR=1.23; 95%CI:1.16-1.31), but again this may reflect the more severe prognosis of these patients versus those in our study.

Likewise to HF, findings for cardiovascular medications indicate a certain treatment profile in primary care, leading up to the post-exacerbation AF hospitalization. Although we were unable to adjudicate by specific subtype of AF (e.g., paroxysmal, persistent) the strongest associations for positive inotropes, anti-arrhythmic drugs, and anticoagulants may suggest that leading up to future AF, patients perhaps are receiving treatment to manage abnormal heart rate and/or rhythm, and/or to prevent clotting. Future research could investigate the respective treatment profile relative to paroxysmal AF and to persistent AF [47] to confirm and extend our findings.

Our null results for other comorbidities (i.e., depression and depressive symptoms, anxiety, BMI, CKD, and type-II diabetes) goes against studies finding an association for diabetes, [18, 22] mixed findings for depression, [18, 22] among other comorbidities. Yet these observed associations could be due to differing context; using the NIS database in a study population of only hospitalized, exacerbating, insured payors. GOLD airflow obstruction and MRC dyspnea score were not associated with post-exacerbation AF hospitalization, possibly as AF is often associated with vague symptoms of onset and not necessarily immediately thought about as a cause of increasing breathlessness in someone with COPD [44, 48, 49].

Methodological considerations

A key strength is our generalizable COPD cohort, defined within the electronic healthcare record with detailed data to examine and adjust for a range of factors. Unlike other studies, this allowed us to look at two patient pathways: cardiovascular-related hospitalizations post primary-care exacerbation, and re-admissions post hospitalized exacerbation. Our exclusion criteria allowed us to quantify the odds of new onset HF and AF hospitalizations following exacerbation, by ensuring no evidence of AF or HF in the year prior to exacerbation. We chose to study two common cardiovascular conditions in COPD, AF and HF. We could not subdivide HF and AF more granularly, because of insufficient statistical power and the inability to obtain electrocardiogram or echocardiogram results to adjudicate.

We used validated codes to define COPD [26] and COPD exacerbations [27, 28] so misclassification is unlikely. Where possible, we used previously tested methods [30] and codes to define our factors-of-interest and codes were checked by a pulmonologist and/or cardiologist. The nested case control matched design

allowed us to control for unmeasurable potential clinical differences in disease management by clinicians, by matching patients on GP practice.

To minimize selection bias among patients with measured factors only, we adjusted only for covariates without substantial missing data. We reserved GOLD, MRC, and CKD for sensitivity analyses; the associations of these factors with HF are generalizable only to patients with measurements (e.g., patients with greater health-care monitoring, provision, or access). For this reason, the relationship for ethnicity could not be quantified, and given the data sparsity. For the HF analysis, we were unable to quantify B-type natriuretic peptide testing as a factor (BNP or NT-proBNP) because of 90% missing data for BNP (data not shown).

Confounding by indication is possible, particularly for the associations observed for cardiovascular medications (cases could have been more likely prescribed cardiovascular medications to manage a prevalent co-morbidity (perhaps with delayed diagnosis) that posed future cardiovascular risk, compared with controls) [50]. For example, although 12.8% of HF cases had prevalent HF diagnoses at baseline (201/1569), over 70% of HF cases were prescribed diuretics (1122/1569). Diuretics, particularly extended use of loop diuretics, can indicate possible, pre-HF diagnoses [51], given HF diagnoses tend to be delayed in COPD patients [14, 37, 51]. Taking this information together, this suggests a substantial proportion of cases could have been prescribed diuretics to manage possible-yet-undiagnosed HF, in which case, the later case-defining hospitalization was the delayed, first-time diagnosis of HF.

Our results for cardiovascular medications do not imply these medications are increasing the cardiovascular risk, rather they add to an understanding of the exacerbating patient profile. Furthermore, although these medications could indicate delayed CVD diagnosis, alternatively they could be medically indicated for management of a co-morbidity we did not adjust for, e.g., beta-blockers can be prescribed for thyroid conditions [52].

Implications for clinical practice

Within the month-window following an exacerbation, largely exacerbation intensity and cardiovascular-related management and disease history were associated with odds of incident HF and AF. For HF specifically, existing type II diabetes, CKD, lung function (GOLD grade), and levels of breathlessness (MRC) had an association too—but not for AF. These factors can help better identify patients most at-risk for HF and AF, to streamline efforts to allocate screening, vigilant monitoring, and prevention.

At the time of a COPD exacerbation, particularly hospitalized exacerbation, we recommend preemptively

monitoring markers of possible HF, through taking medication history of loop diuretics, [51] and through BNP testing [53]. At present however, HF prevention is narrow in scope, with guidelines for early identification of HF not explicitly considering unstable COPD [53, 54]. Our results suggest that HF monitoring should widen to include patients with COPD exacerbations.

Upon exacerbation, particularly hospitalized exacerbation, we recommend proactively screening for AF (e.g., electrocardiogram) [19] as AF commonly presents subclinically [17]. Still, at present, AF screening is narrow in scope; it is primarily conducted in patients with existing or suspected AF with the goal of preventing stroke, with AF guidelines not explicitly considering unstable COPD [17, 55]. Our results suggest that AF screening should widen to include patients with COPD exacerbations, to help prevent future AF—even before stroke.

Conclusions

Cardiopulmonary factors were associated with hospitalization for HF in the 30 days following a COPD exacerbation, while only cardiovascular-related factors and exacerbation severity were associated with AF hospitalization. Understanding risk factors will help to target people for prevention. Future studies with the intent of improving risk prediction for HF and AF should consider exacerbations of COPD.

Abbreviations

COPD	Chronic Obstructive Pulmonary Disease
CPRD	Clinical Practice Research Datalink
CVD	Cardiovascular Disease
GP	General practice
HES	Hospital Episode Statistics
IMD	Index of Multiple Deprivation
MRC	Medical Research Council
HF	Heart Failure
AF	Atrial Fibrillation
CKD	Chronic Kidney Disease

Supplementary Information

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Supplementary Material 1.

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Authors' contributions

JQ takes responsibility for the content of the manuscript, including the data and analysis. EG, JQ, CN, KR, and SM conceptualized the study and designed the protocol. JQ, NP and EG contributed to the development of the codelists that defined the study variables. EG, CK contributed to the methodology. EG, HW, CK and AI accessed and verified the data. EG, CK and AI were responsible for data curation and management. EG, CK were responsible for formal

analysis. EG wrote the original draft of the manuscript. EG, MA, JQ contributed to the literature review and clinical implications. All authors contributed and approved the final manuscript. All authors had final responsibility for the decision to submit for publication.

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Availability of data and materials

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 CPRD Aurum version collected in May 2022 and have clearly specified the data selected within the Methods section, and linked data in the [Supplementary Materials](#). 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.

Declarations

Ethics approval and consent to participate

CPRD has NHS Health Research Authority (HRA) Research Ethics Committee (REC) approval to allow the collection and release of anonymized primary care data for observational research [NHS HRA REC reference number: 05/MRE04/87]. Each year CPRD obtains Section 251 regulatory support through the HRA Confidentiality Advisory Group (CAG), to enable patient identifiers, without accompanying clinical data, to flow from CPRD contributing GP practices in England to NHS Digital, for the purposes of data linkage [CAG reference number: 21/CAG/0008]. The protocol for this research was approved by CPRD's Research Data Governance (RDG) Process (protocol number: **22_002377**) and the approved protocol is available upon request. Linked pseudonymized data was provided for this study by CPRD. Data is 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.

Patient consent for publication

Not applicable.

Competing interests

JQ reports grants from GlaxoSmithKline, Health Data Research UK, MRC, Asthma+Lung UK, Bayer, BI, AZ and Chiesi, outside this work and AZ for the conduct of this study. JQ has received personal fees for advisory board participation, consultancy or speaking fees from GlaxoSmithKline, Evidera, AstraZeneca, and Insmad. CN, KR, and SM are employees of AZ and hold stock and/or options in the company. HW reports grants from Health Data Research UK outside the submitted work. EG, CK, AI, and MA have nothing to disclose.

Author details

¹School of Public Health, Imperial College London, 86 Wood Lane, London W12 0BZ, UK. ²Biopharmaceuticals Medical, AstraZeneca, Academy House, 136 Hills Rd, Cambridge CB2 8PA, UK. ³Medical and Scientific Affairs, AstraZeneca, 2 Pancras Sq, London N1C 4AG, UK. ⁴National Heart and Lung Institute, Imperial College London, 86 Wood Lane, London W12 0BZ, UK.

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