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Title: Impact of COPD and asthma on in-hospital mortality and management of patients with heart failure

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Abstract

Objective: To evaluate the association between having concomitant COPD or asthma, and in-patient mortality and post-discharge management among patients hospitalised for acute HF.

Setting: Data were obtained from patients enrolled in the National Heart Failure Audit.

Participants: 217,329 patients hospitalised for HF in England-Wale between March 2012 and 2018.

Outcomes: In-hospital mortality, referrals to cardiology follow-up and prescriptions for HF medications were compared between patients with comorbid COPD (COPD-HF) or asthma (asthma-HF) versus HF-alone using mixed-effects logistic regression.

Results: Patients with COPD-HF were more likely to die during hospitalisation, and those with asthma-HF had a reduced likelihood of death, compared with patients who had HF-alone. In patients who survived to discharge, referral to HF follow-up services differed between groups: COPD-HF patients had reduced odds of cardiology follow-up, whilst cardiology referral odds for asthma-HF were similar to HF-alone. Overall, proportions of HF medication prescriptions at discharge were low for both COPD-HF and asthma-HF groups, particularly prescriptions for beta-blockers.

Conclusions: In this nationwide analysis, we showed that COPD and asthma significantly impact the clinical course in patients hospitalised for HF. COPD is associated with higher in-patient mortality and lower cardiology referral odds, whilst COPD and asthma are both associated with lower use of prognostic HF therapies on discharge. These data highlight therapeutic gaps and a need for better integration of cardiopulmonary services to improve healthcare provision for patients with HF and coexisting respiratory disease.

Keywords: heart failure, chronic obstructive pulmonary disease, asthma

Strengths and limitations

- This is the first study generalisable to the population of England-Wales which evaluates the effect of respiratory disease on in-hospital mortality and management outcomes in patients hospitalized with HF.
- HF diagnosis was based either on diagnostic tests of clinical investigations which limited misclassification bias.
- The large proportion of missing data regarding bronchodilators and inhaled corticosteroids prescriptions prevented evaluation of whether the impact of COPD and asthma on outcomes in patients with HF is mediated by the treatment for their respiratory disease.

Introduction

COPD and asthma frequently coexist with HF and are independently associated with mortality and increased healthcare use[1 2]. This has been explained by shared systemic inflammation, worsened by the presence of pulmonary disease as well as sub-optimal HF management[3]. Evidence suggests that patients with HF and comorbid COPD are less likely to receive guideline recommended treatment for their HF. For example, beta-blockers which are used in the management of HF with reduced ejection fraction (HFrEF) are often not prescribed to patients with COPD, due to fear of bronchoconstriction, reduced effectiveness of emergency beta-agonist medication or difficulty in discriminating between COPD and asthma.

Less data exist on the relationship between asthma and HF. Some studies have shown that asthma is associated with an increased occurrence of cardiovascular disease whilst others suggest this is limited to women or smokers[4] and depends on age of asthma-onset[5]. This is further complicated by a component of chronic irreversible airflow obstruction in some people with long standing asthma, associated with a reduced response to asthma therapy[6]. This may, in turn, affect treatment choices in this group of patients and increase vulnerability to adverse events, versus either disease occurring alone. The use of beta-agonists or inhaled corticosteroids in both COPD and asthma has been associated with HF-onset, HF-related hospitalisation and increase in cardiovascular events[7], which depend on disease severity and study setting, but nevertheless worsen prognosis[1 5].

Our main aim was to compare in-hospital mortality and post-discharge HF management (referrals to HF services, discharge medication) among patients admitted to hospital with decompensated HF, with and without COPD or asthma in a sample of patients from the

National Heart Failure Audit (NHFA) from England and Wales. We also investigated whether ejection fraction (EF) status affects outcomes in these patient groups.

Methods

We included patients older than 18 years of age admitted to hospital for HF between March 2012 to April 2018 whose data were submitted to the NHFA. We considered their first HF hospitalisation only (**Supplemental Methods**).

Exposures

COPD was defined as having a history of COPD - chronic bronchitis and/or emphysema, confirmed by spirometry or beta agonist/steroid inhaler use.

Asthma was defined as having a history of childhood asthma and atopy or having an asthma diagnosis confirmed by a respiratory physician.

No diagnostic test results were provided for COPD or asthma, and for the purposes of this work were based on being recorded as “yes” (present) or “no” (absent) in the audit data as defined above.

EF status was defined as HFrEF and HF with preserved EF (HFpEF), determined through echocardiography, MRI, nuclear scan, or angiogram. Those with an EF <40% were categorised HFrEF. Due to a lack of information regarding specific diagnostic tests required to make a HFpEF diagnosis, we determined HFpEF as patients not categorised as HFrEF[8].

Covariates were age, sex, New York Heart Association [NYHA] classification and place of care (cardiology ward vs. other place of care [i.e., general ward]) and comorbidities (atrial fibrillation

[AF], ischemic heart disease [IHD], diabetes, valve disease, hypertension [**Supplementary Table 3**]).

Outcomes

Our primary outcome was in-hospital death during the index event (HF admission), defined as a dichotomised variable (died/alive at discharge), according to COPD or asthma status. Secondary analyses included post-discharge referral to HF services (cardiology, HF nurse, HF MDT [multidisciplinary team]) and prescriptions for HF medications at discharge in those with HFrEF.

Statistical analysis

Differences in baseline characteristics between patients with COPD-HF/Asthma-HF and HF alone are presented using percentages for categorial variables and medians and interquartile ranges [IQR]. We assessed differences between groups using chi-square and Kruskall-Wallis tests. We assessed differences in outcomes between patients with COPD-HF compared with HF alone and between asthma-HF compared with HF-alone using multilevel logistic regression with a random effect for hospital, to calculate odds ratios (OR) and 95% confidence intervals (CI) **(Supplemental Methods).** In the main analysis, we adjusted for confounders with less than 20% missing data: age, sex, comorbidities, place of care and NYHA status. The model building process is presented in **Supplementary Table 4**. Analyses of referrals were conducted similarly and excluded patients who died in-hospital. Associations between COPD or asthma and beta-blocker prescriptions at discharge excluded those with HFpEF.

Sensitivity analyses

Due to potential confounding, smoking and Body Mass Index (BMI) were multiply imputed using a multilevel approach (**Supplemental methods**). We also repeated the main analysis in a cohort of patients including only a "confirmed HF diagnosis" (ICD-10 HF diagnosis confirmed by imaging/BNP testing, or adjudicated by a clinician in the absence of echocardiography)[9].

Analyses were performed with R v4.0.3.

Results

Baseline characteristics are presented in **Table 1**. In total, 217,329 patients were admitted to hospital in England-Wales due to decompensated HF between 2012 and 2018, with data on COPD/asthma status available **(Supplemental Figure 1).** The median age was 81 years (IQR 72-87) and 53.7% were male. Death occurred in 12% of patients. COPD was diagnosed in 15% of patients and asthma in 6.6%. Most patients were characterised by either marked or severe breathlessness and half had a recorded HF management plan in place at discharge. Length of stay and deprivation ranking did not differ significantly between patients with COPD-HF, asthma-HF and HF alone. COPD-HF patients were mostly male, were less often admitted to cardiology and were more frequently diagnosed with IHD compared with those with HF alone; hypertension was slightly less common among COPD-HF patients, whereas diabetes was more common. The proportion of patients with HFpEF was marginally higher in the COPD-HF group, compared with the HF-only group. Asthma-HF patients were mostly female, with higher levels of diabetes and hypertension compared to HF-only. Conversely, AF was less common in the asthma-HF compared with the HF-alone group; there were also more patients with HFpEF.

In-hospital death

The association between COPD and in-hospital death, is presented in **Figure 1, Table 2, and Supplementary Table 5.** Overall, COPD was independently associated with increased odds of in-hospital death ([adjusted]OR_{adj}, 95% CI: 1.10, 1.06-1.14). The relationship between COPD and in-hospital death differed according to EF: COPD was associated with an increase in mortality in patients with HFrEF (OR_{adj}: 1.15, 1.09 – 1.21), but not in those with HFpEF (OR_{adj}: 1.05, 0.99–1.10).

Conversely, asthma was associated with a decrease in the odds of in-hospital death compared with HF patients without asthma (OR_{adj}, 95%CI: 0.85, 0.79-0.88). The odds of death did not vary by EF status for patients with asthma-HF **(Figure 1, Table 2).**

Sensitivity analyses where smoking status and BMI were imputed (**Supplementary Table 6**), and where patients with a confirmed HF diagnosis only were included (**Supplementary Table 7**), showed similar results to the main analysis.

Referrals to HF services

In the fully adjusted models, COPD was associated with decreased likelihood of outpatient referral to a cardiologist (OR_{adj}, 95%CI 0.79, 0.77-0.81) and to a HF-MDT (OR_{adj}, 95% CI 0.94, 0.91-0.97). Patients with COPD-HFrEF were less likely to be referred to a cardiologist than those with HFrEF without COPD (OR_{adj}: 0.85, 95% CI 0.81-0.88) while patients with COPD-HFpEF were significantly less likely to be referred, compared to HFpEF without COPD (OR_{adj}, 95CI% 0.73, 0.70-0.76). COPD was associated with a decreased likelihood of documented HF-MDT referral only for patients with HFpEF (OR_{adj}, 95%CI, 0.90, 0.86-0.94).

Overall, referral odds did not differ in patients with asthma-HF compared to those with HF-alone. There was a significant increase in the odds of referral to a cardiologist for those with asthma-HFrEF (OR_{adj}, 95%CI 1.08, 1.03-1.14) and a decreased likelihood of referral for patients with asthma-HFpEF (OR_{adj} 95CI, 0.93, 0.88-0.98), compared to HFrEF, HFpEF-alone, respectively. Referrals to HF nurse or HF MDT were not different between those with HF alone or HF and asthma **(Figure 2).**

HF medication prescription at discharge

Patients with COPD-HF had lower prescription proportions of ACEIs/ARBs, beta-blockers and double (ACEi/ARB+beta-blocker) and triple-therapy (ACEi/ARB+beta-blocker+MRA) compared to those with HF-only. ACEIs/ARBs, MRAs and triple-therapy were prescribed more frequently in the asthma-HF group compared with the HF-alone group; however beta-blockers or double-therapy were less often prescribed for asthma-HF vs. HF-alone **(Figure 3).**

In patients with HFrEF, COPD and asthma were associated with decreased likelihood of beta-blocker prescription at discharge (OR_{adj} 0.66, 95%CI 0.59-0.67, OR_{adj}: 0.57, 95%CI 0.54-0.60). COPD was associated with lower chance or ACEi/ARB prescription, but did not affect MRA prescriptions, while asthma was associated with increased odds of ACEi/ARB and MRA **(Table 3).**

Discussion

This is the first study to provide a large assessment of contemporary HF practice, generalisable to the population of England-Wales, evaluating the effect of COPD and asthma on clinical and management outcomes. We found that patients with COPD-HF were more likely to die during

their HF admission, compared to patients with HF-only; those with asthma-HF had a reduced probability of in-hospital death, compared to patients with HF-alone. Referrals to HF services also differed: COPD was associated with a 21% reduction in post-discharge cardiology referral whilst a diagnosis of asthma did not affect this outcome.

Airways diseases, particularly COPD is associated with adverse events in patients with HF[1-3 10-12], however diagnostic misclassification is under-estimated and studies of the independent effect of asthma are lacking. We report several findings which add to previous literature.

The finding that COPD is associated with in-hospital mortality confirms reports from previous European data which considered longer term follow-ups[13 14]. A greater severity of cardiovascular disease amongst those with COPD-HF may have contributed to the increase in mortality, as indicated by the higher proportions of patients in NYHA classes III and IV, compared with those with HF alone. Further explanations could include admission to non-cardiology wards for COPD-HF patients, which has been linked with poorer outcomes in acute HF[15].

A COPD diagnosis was associated with increased in-hospital death in those with HFrEF, but not in those with HFpEF, which is surprising, given that COPD is suggested to be more severe in the latter group[16]. In contrast with our report, previous studies found that risk of death is increased in those with COPD-HFpEF compared to COPD-HFrEF[17 18], however these may be confounded by a lack of validity of EF status (inferred by ICD codes rather than echocardiography) or spirometry to confirm COPD status, consideration of long-term rather than short term effects on mortality, or by including chronic rather than hospitalised HF. Our result therefore may be explained by poor uptake of disease-modifying treatments available for HFrEF in those with

COPD[13], which has been previously reported and could be more pronounced in a cohort of patients newly admitted for HF.

After adjusting for age, sex and other baseline characteristics including comorbidities, and further adjustments for smoking status and BMI, differences between those with and without COPD, respectively asthma, did not materially change the association between the two lung diseases with in-hospital mortality. This suggests an independent contribution of COPD to increased mortality in patients hospitalised with HF, significant beyond the potential confounders considered in this analysis.

While previous reports suggest asthma is associated with increased risk of developing cardiovascular disease[4], no prior study has reported on the association between asthma and death during acute HF hospitalisation. We found that, on average, asthma was independently associated with a 24% reduction in risk of death in patients with HF. The mechanisms underlying this epidemiological association are unclear. Several factors may explain our result. Asthma management is reliant on anti-inflammatory agents such as inhaled corticosteroids (ICS), which have been linked to cardioprotective effects[19 20] including lower all-cause mortality and lower risk of myocardial infarction ([MI], a precursor to HF). Potential long-term ICS use in our asthma-HF cohort could have diminished patients' baseline mortality risk.

The nature of inflammation is different in COPD compared with asthma, and influences response to medication. One hypothesis which may underlie the diverging findings on the effect of the two lung diseases on outcomes in patients with HF thus relates to differences in management and their subsequent differential cardiovascular risk. Bronchodilator medications, which are central to the symptomatic treatment of COPD, have been associated with increased

cardiovascular risk[7]. While combination treatments such as ICS/LABA may have a good cardiovascular safety profile in asthma, this differs in COPD[6 12]. RCTs have not demonstrated mortality benefits with ICS in individuals with COPD, although some observational studies suggest the opposite. Since both lung diseases were diagnosed prior to HF admission, it would be plausible to assume that any effects of long-term pulmonary medication could influence the chance of death in our cohort. Thus, the heightened risk of in-hospital mortality observed in the COPD-HF group, but not in asthma-HF could be related to more frequent use of bronchodilators and a poorer safety profile of ICS in COPD compared to asthma. Alternatively, COPD-specific characteristics such as such as progressive lung function decline may have influenced in-hospital mortality in those admitted for HF.

The association between COPD/asthma and referral to follow-up cardiology services has not been studied before in hospitalised HF patients. Overall, patients with COPD-HF were less likely to be referred to a cardiology service after hospital discharge, compared with those who had HF-alone. This indicates that a COPD diagnosis may be an obstacle preventing access to HF specialist care. According to NICE, all patients with a HF diagnosis need to be seen by a HF specialist within two weeks of discharge, but data suggest these timelines are not met[21]. The compounded effect of a COPD diagnosis has the potential to further impair the long-term prognosis of these comorbid patients. Our study also indicated EF status mediated the relationship with referrals, as individuals with COPD-HFpEF were less likely to have an appointment compared with their COPD-HFrEF counterparts. This is particularly worrying as HF, irrespective of EF, is best monitored and managed within specialist HF teams.

Asthma did not adversely influence referrals to HF services, but we identified an increased likelihood of referral to cardiology in asthma-HFpEF as compared with asthma-HFrEF. One possible explanation is greater uncertainty in clinical management of patients with HFpEF, leading to increased referral, though this needs to be assessed in future studies. Clarifying these clinical management pathways offers a potential to improve HF prognosis by ensuring access to care is timely and tailored to individual patients' risk, pathology, and health.

Patients with COPD-HFrEF were 34% less likely to receive a beta-blocker prescription at discharge, compared with patients with HFrEF alone, despite recent data supporting use of these agents in COPD[22 23]. Similar to data on patients post-MI[24], it is worrying that COPD was also associated with decreased likelihood of guideline recommended ACEi/ARB prescription in those with HF, as there is no contraindication for those with pulmonary disease. Efforts need to be made to ensure appropriate therapeutic management of these patients.

Those with asthma-HFrEF had 43% less chance of being prescribed a beta-blocker compared with patients with HF-alone. Current guidelines recommend that asthma patients with chronic HFrEF should not receive disease-modifying beta-blocker treatment due to possible bronchoconstriction, despite evidence to suggest that cardioselective beta-blockade may be used with careful up-titration and monitoring[25 26], where benefits may outweigh risks in individual patients. Based on the low uptake across the whole spectrum of HF medications in patients with additional lung disease (**Figure 3**), we expect these patients would have worse prognosis compared to their more adequately treated counterparts.

Considering these results, management needs to be optimized in patients with COPD or asthma and concurrent HF. The arrival of new treatments such as sodium-glucose co-transporter 2 inhibitors (SGLT2-i) have widened treatment choice in HFrEF, and there is now evidence supporting their use in individuals with COPD[27]. Given the contraindication of beta-blockers in asthma, these new treatments should urgently be assessed in this population, as data are currently lacking.

Strengths and limitations

The main strength of this study is the large sample size and validity of diagnoses used, which were based either on diagnostic tests of clinical investigations. We did not have however have information on duration and severity of asthma or COPD, nor lung function test results and thus we could not verify accuracy of these diagnoses, which are often subject to misclassification, especially in the elderly[28]. We also could not differentiate between childhood asthma or late-onset asthma which may have different implications [29].

HFpEF was determined as a HF diagnosis without systolic dysfunction, which has been used in previous NHFA reports. Nevertheless, there is no consensus gold standard HFpEF diagnosis[8] and it remains difficult to validate. Further work in this area is needed, particularly in accurately distinguishing between HFpEF and COPD, which have similar clinical presentation[3].

There was a considerable proportion of missing data on bronchodilators/inhaled corticosteroids in the dataset which prevented assessment of whether the impact of COPD and asthma on outcomes is mediated, in part, by their treatment.

Smoking status was also characterised by a large percentage of missing data, however an analysis using multiple imputation indicated that even after adjusting for this confounder, the association between both COPD and asthma on in-hospital mortality remained unchanged **(Supplementary Table 6).**

We only focused on decompensated HF and the picture may change when investigating long-term mortality, recurrent admissions, or other aspects of treatment such as medication adherence.

While the referral likelihood estimates provide a first glimpse into the association between COPD/asthma and potential healthcare service provision for HF patients in England-Wales, we did not have access to data on concrete healthcare utilisation amongst our cohort.

Due to lack of data, we could not establish whether cause of death varied amongst the groups and whether the increased mortality associated with COPD was underlined by higher rates of respiratory versus cardiac or other disease.

Conclusion

This analysis adds to the growing body of evidence that COPD and asthma affect outcomes in patients with acute HF. Our data suggest that while COPD is a main contributor to in-hospital mortality and is associated with decreased referral to cardiology services amongst HF patients, asthma does not negatively impact these outcomes. Both lung diseases are however responsible for significant decreases in the prescription of HF treatments at discharge, particularly beta-blockers. These findings highlight a need for better integration of cardiopulmonary services with an aim to tailor healthcare provision for these patients.

Competing interests

CG, CK and RZ have nothing to declare. Prof. Quint's research group has received funds from AZ, GSK, The Health Foundation, MRC, British Lung Foundation, IQVIA, Chiesi, and Asthma UK outside the submitted work; grants and personal fees from GlaxoSmithKline, Boehringer Ingelheim, AstraZeneca, Bayer, Insmed outside the submitted work.

Data availability

The data that support the findings of this study have been provided by the Healthcare Quality Improvement Partnership from the National Heart Failure Audit Programme, but restrictions apply to the availability of these data and so are not publicly available.

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Author contributions

Conceptualization & Methodology: CG, JKQ, CK. Original draft: CG. Editing and final approval: CG, JKQ, RZ, CK; Data curation & Formal data analysis: CG; Data acquisition: JKQ.

Ethics approval

This study involved analysis of pre-existing, de-identified data, thus it was exempt from Institutional Review Board approval.

Patient and public involvement

Patients were not involved in the design and conduct of the study.

Figure legends

Figure 1 - Association between COPD, asthma and in-hospital death, adjusted for age, sex, valve disease; IHD, hypertension, diabetes, AF, NYHA, place of care and EF status; odds ratio with 95% confidence intervals.

Figure 2. Association between COPD, asthma and referrals to HF services, adjusted for age, sex, valve disease; IHD, hypertension, diabetes, AF, NYHA, place of care and EF status.

Figure 3. HF-medication prescription rates according to comorbid respiratory disease status

Table 1. Baseline characteristics according to COPD and asthma status, in patients hospitalised for HF in England-Wales.

	HF alone (N=170297)	COPD + HF (N=32695)	Asthma + HF (N=14400)	Overall (N=217,392)
Age, median [IQR]	81 [72, 88]	79 [72, 85]	79 [69, 86]	81 [72, 87]
Missing	67 (0.1%)	22 (0.1%)	10 (0.1%)	199 (0.1%)
Male	91837 (53.9%)	19072 (58.3%)	5936 (41.2%)	116845 (53.7%)
Missing	74 (0.1%)	44 (0.1%)	21 (0.1%)	239 (0.1%)
Place of admission				
Cardiology	76428 (44.9%)	12361 (37.8%)	6147 (42.7%)	94936 (43.7%)
Other	93358 (54.8%)	20246 (61.9%)	8218 (57.1%)	21822 (56.0%)
Missing	511 (0.3%)	88 (0.3%)	35 (0.2%)	634 (0.3%)
Died in-hospital	20316 (11.9%)	4181 (12.8%)	1337 (9.3%)	25834 (11.9%)
Device therapy				
None	147485 (86.6%)	28962 (88.6%)	12818 (89.0%)	189265 (87.1%)
CRT-D	3047 (1.8%)	496 (1.5%)	189 (1.3%)	3732 (1.7%)
CRT-P	1681 (1%)	296 (0.9%)	142 (1%)	2119 (1.0%)
ICD	3001 (1.8%)	511 (1.6%)	211 (1.5%)	0 (0%)
Missing	15083 (8.9%)	2430 (7.4%)	1040 (7.2%)	18553 (8.5%)
Comorbidities				
Valve disease	38213 (22.4%)	7005 (21.4%)	2906 (20.2%)	48124 (22.1%)
Missing	3426 (2.0%)	822 (2.5%)	335 (2.3%)	4583 (2.1%)
IHD	65992 (38.8%)	14198 (43.4%)	5175 (35.9%)	85365 (39.3%)
Missing	3667 (2.2%)	811 (2.5%)	335 (2.3%)	4813 (2.2%)
Hypertension	91477 (53.7%)	16838 (51.5%)	8208 (57%)	116523 (53.6%)
Missing	1326 (0.8%)	381 (1.2%)	125 (0.9%)	1832 (0.8%)
Diabetes	50194 (29.5%)	10348 (31.7%)	4772 (33.1%)	65314 (30%)

	HF alone (N=170297)	COPD + HF (N=32695)	Asthma + HF (N=14400)	Overall (N=217,392)
Missing	459 (0.3%)	142 (0.4%) 54	54 (0.4%)	655 (0.3%)
AF	72235 (42.4%)	13728 (42%)	5508 (38.2%)	91471 (42.1%)
Breathlessness (NYHA class)				
No limitation of physical activity	12273 (7.2%)	1254 (3.8%)	768 (5.3%)	14295 (6.6%)
Slight Limitation of ordinary physical activity	24541 (14.4%)	3951 (12.1%)	1993 (13.8%)	30485 (14.%)
Marked Limitation of ordinary physical activity	68179 (40%)	13671 (41.8%)	6011 (41.7%)	87861 (40.4%)
Symptoms at rest or minimal activity	54652 (32.1%)	12191 (37.3%)	4809 (33.4%)	71652 (33%)
Missing	10652 (6.3%)	1628 (5.0%)	819 (5.7%)	13099 (6.0%)
Echocardiography performed	137955 (81%)	26165 (80%)	11342 (78.8%)	175462 (80.7%)
Ejection fraction status				
HFrEF	92619 (54.4%)	16408 (50.2%)	7334 (50.9%)	116361 (53.5%)
HFpEF	77678 (45.6%)	16287 (49.8%)	7066 (49.1%)	101031 (46.5%)
HF management plan				
Pre-discharge management plan is in place	11760 (6.9%)	2152 (6.6%)	1002 (7.0%)	14914 (6.9%)
Management plan has been discussed with the patient	10572 (6.2%)	1894 (5.8%)	954 (6.6%)	13420 (6.2%)
Management plan has been communicated to the primary care team	19880 (11.7%)	3963 (12.1%)	1780 (12.4%)	25623 (11.8%)
All of the above	83507 (49%)	15496 (47.4%)	7140 (49.6%)	106143 (48.8%)
No plan	18021 (10.6%)	3937 (12.0%)	1546 (10.7%)	23504 (10.8%)
Missing	26557 (15.6%)	5253 (16.1%)	1978 (13.7%)	33788 (15.5%)
Referral to HF MDT	53898 (31.6%)	9719 (29.7%)	4455 (30.9%)	68072 (31.3%)

	HF alone (N=170297)	COPD + HF (N=32695)	Asthma + HF (N=14400)	Overall (N=217,392)
Missing	29946 (17.6%)	5722 (17.5%)	2216 (15.4%)	37884 (17.4%)
Referral to cardiology follow up	70925 (41.6%)	11875 (36.3%)	6241 (43.3%)	89041 (41%)
Missing	13827 (8.1%)	2882 (8.8%)	984 (6.8%)	17693 (8.1%)
Referral to HF nurse follow-up	76170 (44.7%)	13728 (42.0%)	6249 (43.4%)	96147 (44.2%)
Missing	13442 (7.9%)	2658 (8.1%)	952 (6.6%)	17052 (7.8%)
LOS				
Median [IQR]	8 [3, 15]	8 [4, 16]	7 [3, 14]	8 [4, 15]
IMD Wales (quartile)	**N=8205**	**N=1889**	**N=776**	**N= N=10870**
1st (most deprived)	2126 (25.9%)	371 (19.6%)	188 (24.2%)	2685 (24.7%)
2nd	2058 (25.1%) 396	(21.0%) 190	(24.5%) 83	2644 (24.3%)
3rd	1977 (24.1%)	459 (24.3%)	196 (25.3%)	2632 (24.2%)
4th (least deprived)	1824 (22.2%)	607 (32.1%)	185 (23.8%)	2616 (24.1%)
Missing (not shown due to small numbers)	-	-	-	-
IMD England (quartile)	**N=159540**	**N=30352**	**N=13433**	**N=203325**
1st (most deprived)	35836 (22.5%)	9338 (30.8%)	3449 (25.7%)	48623 (23.9%)
2nd	38347 (24.0%)	7762 (25.6%)	3403 (25.3%)	49512 (24.4%)
3rd	40131 (25.2%)	6848 (22.6%)	3166 (23.6%)	50145 (24.7%)
4th (least deprived)	41387 (25.9%)	5615 (18.5%)	3072 (22.9%)	50074 (24.6%)
Missing	3839 (2.4%)	789 (2.6%)	343 (2.6%)	4971 (2.4%)

Abbreviations
AF= atrial fibrillation; COPD= chronic obstructive pulmonary disease; CRT-P= cardiac resynchronisation therapy pacemaker; CRT-D= cardiac resynchronisation therapy defibrillator, HF= heart failure; HFrEF= heart failure with reduced ejection fraction; HFpEF= heart failure with preserved ejection fraction; ICD= implantable cardioverter defibrillator; IMD= indices of multiple deprivation; LOS= length of stay; MDT= multi-disciplinary team; NYHA = New York Heart Association

Table 2 – Association between COPD, asthma and outcomes in patients hospitalised for HF in England-Wales

	Fully adjusted[a] interaction model COPD*EF OR (95% CI)		Fully adjusted[b] interaction model Asthma*EF OR (95% CI)	
Outcome	COPD * HFrEF	COPD* HFpEF	Asthma * HFrEF	Asthma * HFpEF
In-hospital death (N= 194,156[c])	Interaction *P*-value = 0.01		Interaction *P*-value = 0.842	
Fixed-effects	1.15 (1.09 – 1.21, p=0.294*10^{-10})	1.05 (0.99 – 1.10, p=0.081)	-	-
Random effects (hospitals, n=216)				
Variance	*0.201*		-	
LR test P-value[d]	*P=0.22*10^{-16}*		-	-
Referral to cardiology follow-up (N= 166,658[c])	Interaction *P*-value= 0.288*10^{-7}		Interaction *P*-value=0.0001	
Fixed effects	0.85 (0.81, 0.88, p=0.2*10^{-16})	0.73 (0.70, 0.76, p=0.2*10^{-16})	1.08 (1.03-1.14, p=0.2*10^{-16})	0.93 (0.88- 0.98, p=0.003)
Random effects (hospitals, n=216)				
Variance	*0.512*		*0.512*	
LR test p-value[d]	*0.22*10^{-16}*		*P=0.22*10^{-16}*	
Referral to HF MDT (N=149,098[c])	Interaction *P*-value = 0.017		Interaction *P*-value=0.095	
Fixed effects	0.97 (0.93, 1.02, p=0.263)	0.90 (0.86, 0.94, p=0.265*10^{-5})	-	-
Random effects (hospitals, n=216)				
Variance	*2.139*		-	-
LR test p-value[d]	*0.22*10^{-16}*		-	-
Referral to HF nurse (N= 166,723[c])	Interaction *P*-value = 0.249		Interaction *P*-value = 0.450	

Abbreviations
COPD= chronic obstructive pulmonary disease; HF= heart failure; HFrEF= heart failure with reduced ejection fraction; HFpEF= heart failure with preserved ejection fraction; LR= likelihood ratio; MDT= multidisciplinary team; OR= odds ratio; CI= confidence interval

[a] Adjusted for age, sex, diabetes, hypertension, ischemic heart disease, atrial fibrillation, asthma, place of care and New York Heart Association status

[b] Adjusted for age, sex, diabetes, hypertension, ischemic heart disease, atrial fibrillation, COPD, place of care and New York Heart Association status

[c] Excludes patients with missing data on covariates included in model

[d] Likelihood ratio test comparing fixed to random effects for hospital model fit, significant indicates random effects model performed better than fixed effects model

Table 3. Association between COPD, asthma and HF medication prescription at discharge, in patients with HFrEF

Medication prescription at discharge	COPD unadjusted OR (95%CI)	COPD fully adjusted[a] OR (95%CI)	Asthma unadjusted OR (95%CI)	Asthma fully adjusted[b] OR (95%CI)
Beta-blockers (N= 86449[a,b])				
Fixed effects	0.61 (0.58, 0.64, p=$0.22*10^{-16}$)	0.66 (0.64, 0.68, P=$0.22*10^{-16}$)	0.63 (0.59, 0.67, p=$0.22*10^{-16}$)	0.57 (0.54 0.60, p=$0.22*10^{-16}$)
Random effects				
Variance	*0.553*	*0.578*	*0.549*	*0.578*
LR test p-value	$0.22*10^{-16}$	$0.22*10^{-16}$	$0.22*10^{-16}$	$0.22*10^{-16}$
ACEis/ARBs (N=96080 [a,b])				
Fixed effects	0.87 (0.84, 0.90, p=$0.139*10^{-13}$)	0.91 (0.87-0.95, p=$0.256*10^{-6}$)	1.13 (1.07, 1.19, p=$0.16*10^{-6}$)	1.07 (1.01, 1.13, p=0.0143)
Random effects				
Variance	*0.149*	*0.130*	*0.148*	*0.130*
LR test p-value	$0.22*10^{-16}$	$0.22*10^{-16}$	$0.22*10^{-16}$	$0.22*10^{-16}$
MRA (N=96080 [a,b])				
Fixed effects	0.97 (0.94, 1.01, p=0.114)	1.02 (0.98, 1.06, p=0.268)	1.08 (1.04, 1.13, p=0.00043)	1.07 (1.02, 1.12, p= 0.0084)
Random effects				
Variance	*0.232*	*0.195*	*0.226*	*0.195*
LR test p-value	$0.22*10^{-16}$	$0.22*10^{-16}$	$0.22*10^{-16}$	$0.22*10^{-16}$

Abbreviations
COPD= chronic obstructive pulmonary disease; OR= odd ratio; CI= confidence intervals; LR= likelihood ratio
[a]Adjusted for age, sex, diabetes, hypertension, ischemic heart disease, atrial fibrillation, asthma, place of care and New York Heart Association status
[b]Adjusted for age, sex, diabetes, hypertension, ischemic heart disease, atrial fibrillation, COPD, place of care and New York Heart Association status
Likelihood ratio test comparing fixed to random effects for hospital model fit, significant indicates random effects model performed better than fixed effects model

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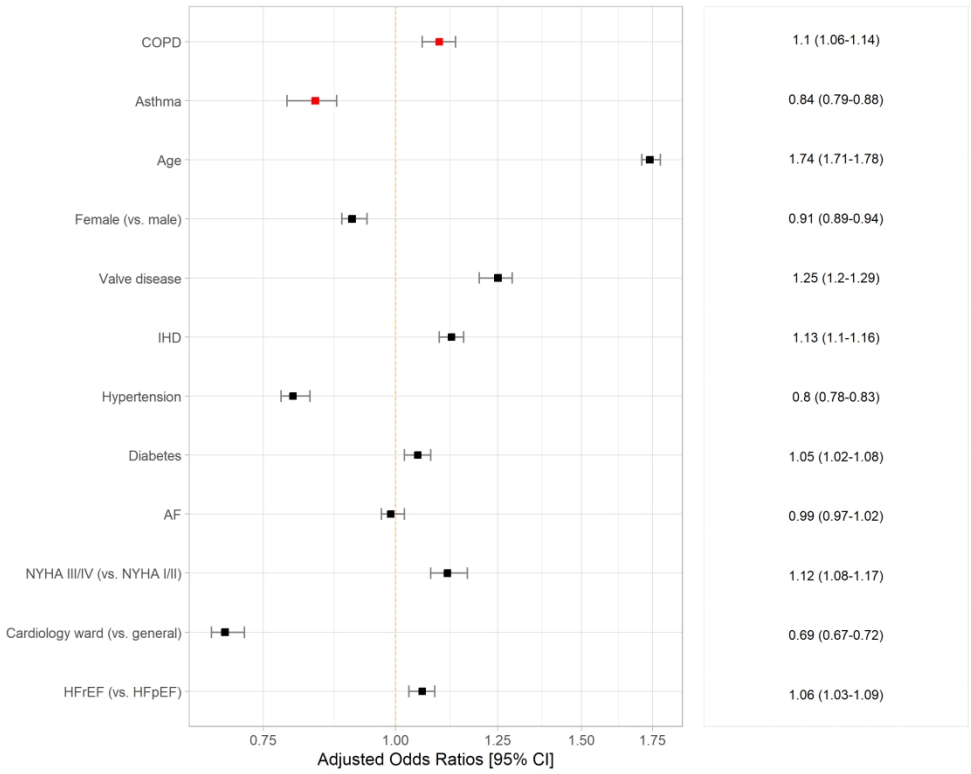

Figure 1 - Association between COPD, asthma and in-hospital death, adjusted for age, sex, valve disease; IHD, hypertension, diabetes, AF, NYHA, place of care and EF status; odds ratio with 95% confidence intervals.

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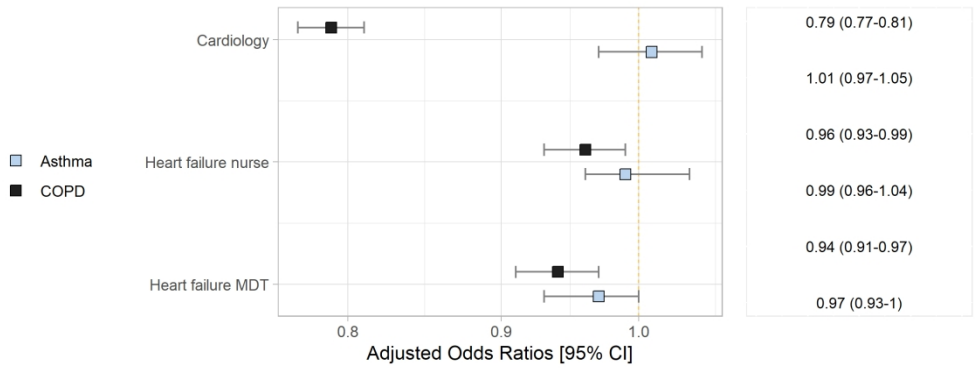


Figure 2. Association between COPD, asthma and referrals to HF services, adjusted for age, sex, valve disease; IHD, hypertension, diabetes, AF, NYHA, place of care and EF status.

516x193mm (118 x 118 DPI)

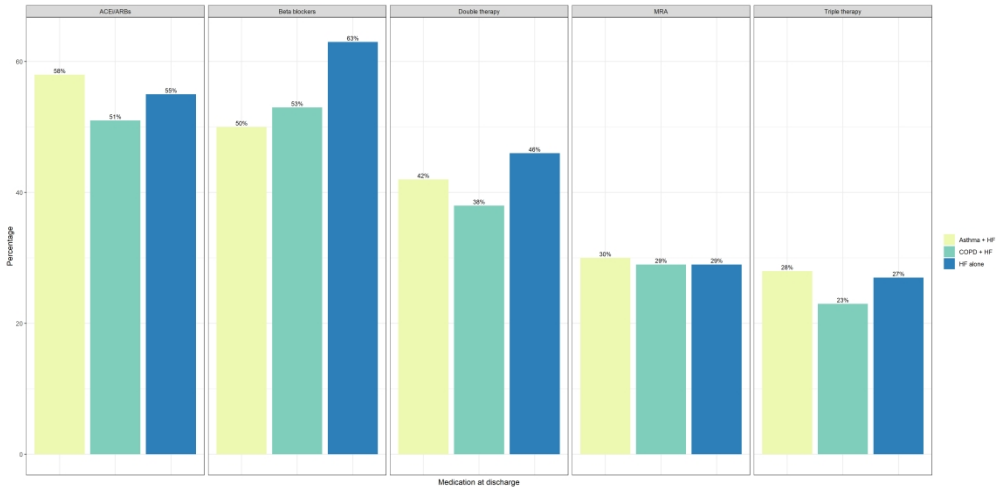


Figure 3. HF-medication prescription rates at discharge, according to comorbid respiratory disease status

1291x645mm (118 x 118 DPI)

Supplemental Material

Supplemental Methods

Data source

The NHFA was established in 2007 for hospitals in England-Wales to assess the quality of care and outcomes of hospitalised patients with a HF diagnosis in the first position at death or discharge, identified using ICD-10 codes (**Supplementary Table 1**). Admissions coded in the audit are compared to HF episodes in the Hospital Episode Statistics (HES) in England and the Patient Episode Database of Wales (PEDW) to determine the case ascertainment rate. The number of participating NHS trusts fluctuated from 145 in 2012–13 (97%) to 136 (82%) in 2017/2018. This corresponds to an increase from capturing 60% of national HF admissions in 2012, to 76% at the end of April 2018. Data are entered into the audit by hospital staff, using case ascertainment forms and data are categorised as mandatory (main indicators such as HF treatments, comorbidities, echocardiography) or non-mandatory (i.e., smoking status, pulmonary oedema, ethnicity). Since non-mandatory data elements are not expected to be included, there are considerable proportions of missing data across these variables (**Supplemental Table 2**). Some mandatory variables also have significant amounts of missing data (e.g., more than 70% missing data on BNP measurements, weight, height). The breadth of variables collected varied throughout the history of the audit, to reflect changes in HF guidelines and quality standards, which evolved over time. For example, haemoglobin and serum creatinine were collected routinely only after 2012[1].

Statistical analysis

The analysis for the main outcome was implemented in a stepwise manner. First, an unconditional model including, COPD was considered. In a second step we added asthma. Third, we added an interaction term between COPD and asthma, to assess whether both diagnoses had a significant contribution to the model. In lack of statistical significance these patients were not considered in further analyses. We then evaluated effect modification by EF status (HFrEF/HFpEF) by including separately an interaction term between COPD and EF, then asthma and EF.

Handling of missing data

Sensitivity analysis – missing data imputation

While the proportions of missing data (see above) were considerable, we deemed necessary to investigate further two important factors: “smoking status” and “Body Mass Index (BMI)”. In particular, we were interested in assessing whether COPD has an independent association with death in patients with HF, when controlling for smoking status, or whether the relationship is influenced by this factor.

We assumed data on smoking and BMI to be missing at random in our cohort, as the distribution in observed cases was similar to other UK cohorts of patients with HF[2 3]. We then used a multi-level approach[4] which takes into consideration the hierarchical data structure, clustered at hospital level. A Gibbs sampling procedure was used to generate 20 imputed data sets after a burn-in of 1000 iterations.

Table 1. Inclusion criteria for National Heart Failure Audit

ICD-10 code	Diagnosis
I11.0	Hypertensive heart disease with (congestive) heart failure
I25.5	Ischaemic cardiomyopathy
I42.0	Dilated cardiomyopathy
I42.9	Cardiomyopathy, unspecified
I50.0	Congestive heart failure
I50.1	Left ventricular failure
I50.9	Heart failure, unspecified
ICD= International Statistical Classification of Diseases and Related Health Problems	

Table 2. Variables with considerable missingness in the National Heart Failure Audit 2012-2018

	HF alone (N=170297)	COPD + HF (N=32695)	Asthma + HF (N=14400)	Overall (N=217392)
Cerebrovascular accident	2882 (1.7%)	582 (1.8%)	244 (1.7%)	3708 (1.7%)
Missing	145636 (85.5%)	28115 (86.0%)	12279 (85.3%)	186030 (85.6%)
Alcohol units/week				
Median [Q1, Q3]	0 [0, 1.00]	0 [0, 2.00]	0 [0, 0]	0 [0, 1.00]
Missing	159233 (93.5%)	30570 (93.5%)	13314 (92.5%)	203117 (93.4%)
Smoking status				
Current smoker	1869 (1.1%)	911 (2.8%)	143 (1.0%)	2923 (1.3%)
Ex-smoker	8371 (4.9%)	2505 (7.7%)	715 (5.0%)	11591 (5.3%)
Never-smoker	8823 (5.2%)	673 (2.1%)	896 (6.2%)	10392 (4.8%)
Missing	151234 (88.8%)	28606 (87.5%)	12646 (87.8%)	192486 (88.5%)
Chest X-ray (pulmonary oedema)	3954 (2.3%)	692 (2.1%)	334 (2.3%)	4980 (2.3%)
Missing	157253 (92.3%)	30528 (93.4%)	13311 (92.4%)	201092 (92.5%)
Medications at admission				
ACEi	6316 (3.7%)	1116 (3.4%)	513 (3.6%)	7945 (3.7%)
Contraindicated	592 (0.3%)	140 (0.4%)	59 (0.4%)	791 (0.4%)
Missing	152642 (89.6%)	29598 (90.5%)	12903 (89.6%)	195143 (89.8%)
ARB	2392 (1.4%)	453 (1.4%)	305 (2.1%)	3150 (1.4%)
Not applicable	2570 (1.5%)	513 (1.6%)	240 (1.7%)	3323 (1.5%)
Stopped	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Contraindicated	338 (0.2%)	88 (0.3%)	32 (0.2%)	458 (0.2%)
Missing	151870 (89.2%)	29463 (90.1%)	12781 (88.8%)	194114 (89.3%)
Beta-blocker	9516 (5.6%)	1446 (4.4%)	598 (4.2%)	11560 (5.3%)
Not applicable	762 (0.4%)	144 (0.4%)	88 (0.6%)	994 (0.5%)
Contraindicated	153 (0.1%)	136 (0.4%)	74 (0.5%)	363 (0.2%)
Missing	151820 (89.2%)	29481 (90.2%)	12831 (89.1%)	194132 (89.3%)
Loop diuretic	5519 (3.2%)	1202 (3.7%)	490 (3.4%)	7211 (3.3%)

Missing	160255 (94.1%)	30820 (94.3%)	13532 (94.0%)	204607 (94.1%)
Thiazide or Metolazone	925 (0.5%)	140 (0.4%)	81 (0.6%)	1146 (0.5%)
Stopped*	-	-	-	-
Missing	152559 (89.6%)	29604 (90.5%)	12891 (89.5%)	195054 (89.7%)
MRA	2356 (1.4%)	502 (1.5%)	221 (1.5%)	3079 (1.4%)
Not applicable	225 (0.1%)	45 (0.1%)	27 (0.2%)	297 (0.1%)
Contraindicated	36 (0.0%)	*	*	42 (0.0%)
Missing	152494 (89.5%)	29570 (90.4%)	12885 (89.5%)	194949 (89.7%)
Digoxin	1700 (1.0%)	399 (1.2%)	168 (1.2%)	2267 (1.0%)
Missing	152631 (89.6%)	29622 (90.6%)	12874 (89.4%)	195127 (89.8%)
CCB	2847 (1.7%)	479 (1.5%)	280 (1.9%)	3606 (1.7%)
Missing	155279 (91.2%)	30261 (92.6%)	13150 (91.3%)	198690 (91.4%)
Bronchodilators	919 (0.5%)	1390 (4.3%)	750 (5.2%)	3059 (1.4%)
Missing	155316 (91.2%)	30248 (92.5%)	13136 (91.2%)	198700 (91.4%)
Ivabradine	186 (0.1%)	64 (0.2%)	31 (0.2%)	281 (0.1%)
Missing	153320 (90%)	29666 (90.7%)	12845 (89.2%)	195831 (90.1%)
BMI				
Median [Q1, Q3]	26.5 [22.9, 31.1]	27.1 [22.8, 32.2]	28.0 [23.6, 33.7]	26.7 [22.9, 31.4]
Missing	125287 (73.6%)	23693 (72.5%)	10274 (71.3%)	159254 (73.3%)
BNP				
Median [Q1, Q3]	428 [1.00, 1100]	350 [1.00, 985]	353 [1.00, 871]	412 [1.00, 1070]
Missing	153043 (89.9%)	29385 (89.9%)	12978 (90.1%)	195406 (89.9%)
NT_proBNP				
Median [Q1, Q3]	2790 [404, 7530]	2490 [349, 6820]	2440 [426, 6330]	2700 [393, 7320]
Missing	153022 (89.9%)	29161 (89.2%)	12818 (89.0%)	195001 (89.7%)
*not shown due to small numbers policy				

Table 3. Comorbidity definitions, according to NHFA dataset[1], variables recorded from patient history

COPD	History of COPD - chronic bronchitis, emphysema or their cooccurrence. Must be indicated by pulmonary function testing evidence .ie FEV1<75% predicted value or use of beta agonist/steroid inhalers.
Asthma	History of childhood asthma and atopy, or asthma confirmed by respiratory physician for adult onset.
Diabetes	Diagnosis of diabetes prior to admission. This includes a confirmed diagnosis of diabetes and/or the use of an oral hypoglycaemic agent or insulin, and/or a fasting blood glucose >6.7, and/or a random blood glucose >11.
Hypertension	Recorded Blood Pressure >140/90 on at least two occasions prior to admission, or already receiving treatment (drug, dietary or lifestyle) for hypertension
Ischemic heart disease	History of myocardial infarction, angina, ECG evidence of MI, CABG or angiogram documenting coronary artery disease.
Cerebrovascular accident	A past neurological deficit of cerebrovascular cause, including episodes that persist beyond 24 hours and transient ischaemic attacks lasting less than 24 hours.
Atrial fibrillation	An ECG was performed showing atrial fibrillation.
Valve disease	History of clinically diagnosed valve disease, moderate or severe stenosis or regurgitation on imaging, or an operative valve replacement/repair

[1] Available: https://www.nicor.org.uk/national-cardiac-audit-programme/datasets/

Table 4. Model building - association between COPD, asthma (including interaction with ejection fraction group) and in-hospital death in patients hospitalised for heart failure.

Predictors	Model 1	Model 2	Model 3	Model 4	Model 5a	Model 5b	Model 6
Fixed effects [coefficient estimate, SE]							
COPD	0.064 [0.017, p<0.001]	0.0706 [0.0174, p<0.001]	0.060 [0.018, p<0.001]	-0.0445 [0.0256, p=0.081]	0.064 [0.017, p<0.001]	-0.029 [0.0242, p=0232]	0.0468 [0.026, p=0.081]
Asthma	-	-0.263 [0.0255, p<0.001]	-0.287 [0.029, p<0.001]	-0.302 [0.040, p<0.001]	-0.2719 [0.034, p<0.001]	-0.266 [0.0255, p<0.001]	-0.179 [0.028, p<0.001]
COPD*Asthma	-	-	**0.098 [0.0573, p=0.087]**	0.149 [0.076, p=0.051]	-	-	-
EF	-	-	-	-0.208 [0.015, p<0.001]	-0.173 [0.014, p<0.001]	-0.207 [0.0149, p<0.001]	0.0410 [0.017, p<0.05]
COPD *EF	-	-	-	**0.205 [0.036, p<0.001]**	**-**	**0.195 [0.034, p<0.001]**	**0.096 [0.037, p<0.05]**
Asthma*EF	-	-	-	**0.018 [0.058, p=0.753]**	**0.013 [0.05, p=0.797]**	-	-
COPD*Asthma*EF	-	-	-	**-0.093 [0.112, p=0.402]**	-	-	-
Age	-	-	-	-	-	-	0.553 [0.0101, p<0.001]

Female (vs. male)	-	-	-	-	-	-	-0.0922 [0.0150, p<0.001]
Valve disease	-	-	-	-	-	-	0.219 [0.0169, p<0.001]
IHD	-	-	-	-	-	-	0.1204 [0.015, p<0.001]
Hypertension	-	-	-	-	-	-	-0.220 [0.0148, p<0.001]
Diabetes	-	-	-	-	-	-	0.0489 [0.0164, p<0.01]
AF	-	-	-	-	-	-	-0.0056 [0.0147, p=0.703]
NYHA	-	-	-	-	-	-	0.116 [0.018, p<0.001]
Place of care (cardiology vs not cardiology)	-	-	-	-	-	-	-0.363 [0.0168, p<0.001]
Random effects (hospitals, n=219)							
Variance	0.205	0.208	0.208	0.201	0.201	0.201	0.159
SD	0.453	0.456	0.456	0.448	0.449	0.449	0.399
AIC	160533.4	158837.1	158836.2	158652.0	158681.2	158649.7	133038.5

Abbreviations
AIC= Akaike information criterion; AF= atrial fibrillation; COPD= chronic obstructive pulmonary disease; CI=confidence intervals; EF= ejection fraction; NYHA= New York Heart Association; IHD= ischemic heart disease; SD= standard deviation; SE= standard error

Results from a 2-level unconditional model that included COPD as fixed-effect and hospital as random effect suggested COPD was associated with an increase in the estimate for in-hospital mortality. The addition of asthma to this model indicated it had an inverse relationship with likelihood of death. A test for the interaction between COPD and asthma was not significant, thus, it was not considered in subsequent analyses. Further, we wanted to assess whether the effects of COPD, respectively asthma on in-hospital death are different with respect to EF status group therefore, we added a three-way interaction between COPD, asthma and EF to

the model. We detected a significant interaction between COPD and EF only, suggesting the effect of COPD only, not asthma would be differential according to the EF status. In the final model, we estimated the association between COPD and mortality in HFrEF and in HFpEF and adjusted for baseline covariates.

Table 5. Association between COPD, asthma and in-hospital death

Predictors	**COPD only (95% CI)**	**COPD + asthma**	**Fully adjusted model**	**Model with COPD and EF interaction, fully adjusted OR (95% CI)**
Fixed effects (95% CI)				P-value for interaction =0.01
COPD	**1.07 (1.03 – 1.10)**	**1.07 (1.04-1.11)**	**1.10 (1.06 – 1.14)**	1.04 (0.99-1.10)
Asthma	-	**0.77 (0.73 – 0.80)**	**0.84 (0.79, 0.88)**	0.83 (0.79-0.88)
COPD (Yes vs. No): HFpEF	-	-	-	**1.05 (0.99 – 1.10)**
COPD (Yes vs. No): HFrEF	-	-	-	**1.15 (1.09 – 1.21)**
Age	-		1.74 (1.71 -1.78)	1.74 (1.71-1.77)
Female (vs. male)	-		0.91 (0.89-0.94)	0.91 (0.89-0.94)
Valve disease	-		1.25 (1.20-1.29)	1.25 (1.20-1.29)
IHD	-		1.12 (1.10-1.16)	1.13 (1.10-1.16)
Hypertension	-		0.8 (0.78-0.83)	0.80 (0.78-0.83)
Diabetes	-		1.05 (1.02-1.08)	1.05 (1.02-1.08)
AF	-		0.99 (0.97-1.02)	0.99 (0.96-1.02)
NYHA (III/IV vs. I/II)	-		1.12 (1.08-1.17)	1.12 (1.08-1.17)
Place of care (not cardiology vs. cardiology ward)	-		0.69 (0.67-0.72)	0.69 (0.67-0.71)
Random effects (Variance)				
LR test p-value	P<0.001	P<0.001	P<0.001	P<0.001
Likelihood ratio test comparing fixed to random effects for hospital model fit, significant indicates random effects model performed better than fixed effects model Abbreviations				

AF= atrial fibrillation; COPD= chronic obstructive pulmonary disease; CI=confidence intervals; EF= ejection fraction; NYHA= New York Heart Association; IHD= ischemic heart disease; SD= standard deviation.

Table 6. Association between COPD and in-hospital mortality in patients hospitalised with heart failure. Results from 20 models using imputed smoking status and BMI (estimates combined using Rubin's rule).

	Fully adjusted model, OR (95% CI)
Fixed effects (95% CI)	
COPD	1.12 (1.07 – 1.17)
Asthma	0.84 (0.80 – 0.90)
Age	1.67 (1.62 – 1.71)
Female (vs. male)	0.89 (0.86 – 0.92)
Valve disease	1.22 (1.18 – 1.26)
IHD	1.13 (1.10 – 1.17)
Hypertension	0.82 (0.89 – 0.85)
Diabetes	1.12 (1.08 – 1.15)
AF	1.01 (0.98 – 1.04)
NYHA (III/IV vs. I/II)	1.15 (1.10 – 1.20)
Place of care (cardiology vs. no cardiology ward)	0.70 (0.69 – 0.73)
EF	1.03 (0.99 – 1.06)
Smoking status (ref: Current smoker)	
Ex-smoker	0.90 (0.77 – 1.06)
Never	1 (0.84 – 1.19)
BMI (ref: normal weight)	
Underweight	1.31 (1.21 – 1.43)
Overweight	0.86 (0.81 – 0.91)
Obese	0.77 (0.73 – 0.81)
Random effects (Variance)	
LR test p-value	P<0.001

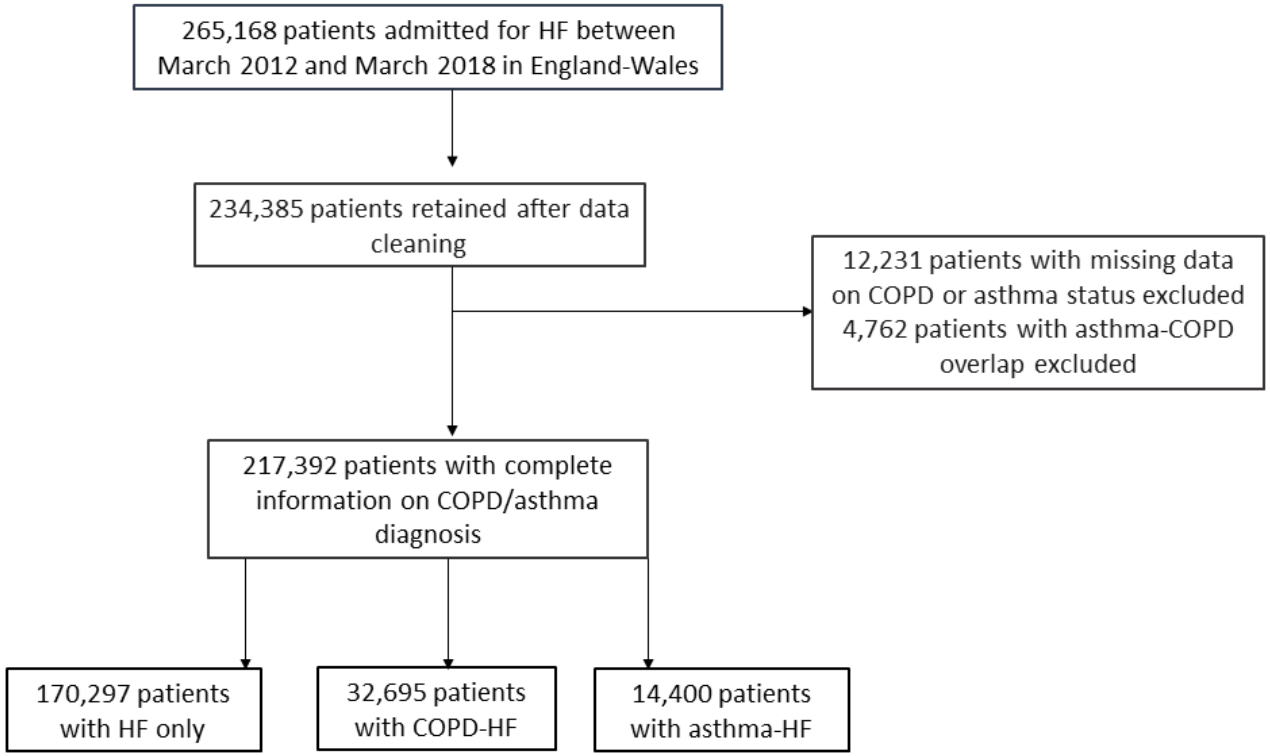
Abbreviations
AF= atrial fibrillation; BMI= Body Mass index; CI= confidence intervals; COPD= chronic obstructive pulmonary disease; EF= ejection fraction; IHD= ischemic heart disease; NYHA= New York Heart Association; OR= Odds ratio; ref= reference

Table 7. Association between COPD and in-hospital mortality in patients hospitalised with a confirmed diagnosis of HF.

	Fully adjusted model, OR (95% CI)
Fixed effects (95% CI)	
COPD	1.11 (1.07 - 1.16)
Asthma	0.84 (0.79 - 0.89)
Age	1.04 (1.04 - 1.05)
Female (vs. male)	0.91 (0.88 - 0.94)
Valve disease	1.26 (1.22 - 1.30)
IHD	1.15 (1.11 - 1.18)
Hypertension	0.81 (0.79 - 0.84)
Diabetes	1.06 (1.03 - 1.10)
AF	0.98 (0.95 - 1.01)
NYHA (III/IV vs. I/II)	1.13 (1.08 - 1.18)
Place of care (cardiology vs. no cardiology ward)	0.69 (0.66 - 0.71)
EF	1.04 (1.01 - 1.08)
Random effects (Variance)	0.166
LR test p-value	p<0.001
Abbreviations AF= atrial fibrillation; BMI= Body Mass index; CI= confidence intervals; COPD= chronic obstructive pulmonary disease; EF= ejection fraction; IHD= ischemic heart disease; NYHA= New York Heart Association; OR= Odds ratio; ref= reference	

Figure 1. Study flow

HF= heart failure; COPD=chronic obstructive pulmonary disease



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STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2,3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5,6
Objectives	3	State specific objectives, including any pre-specified hypotheses	5,6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6, 7, Supplement
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6, 7, Supplement
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7, 8, Supplement
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6, 7, Supplement*
Bias	9	Describe any efforts to address potential sources of bias	7, 8, 9, Supplement
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8, 9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8,9, Supplement
		(*b*) Describe any methods used to examine subgroups and interactions	8,9, Supplement
		(*c*) Explain how missing data were addressed	9, Supplement
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	6

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	9, Supplement
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6, Supplement flow chart
		(b) Give reasons for non-participation at each stage	Supplement flow chart
		(c) Consider use of a flow diagram	Supplement flow chart
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9, 10
		(b) Indicate number of participants with missing data for each variable of interest	20-22, Supplement
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	10-12
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	23, Supplement
		(*b*) Report category boundaries when continuous variables were categorized	9, 20-22
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10, Supplement
Discussion			
Key results	18	Summarise key results with reference to study objectives	12-16
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	18
Generalisability	21	Discuss the generalisability (external validity) of the study results	18
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	19

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Impact of COPD and asthma on in-hospital mortality and management of patients with heart failure in England and Wales: an observational analysis

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Title: Impact of COPD and asthma on in-hospital mortality and management of patients with heart failure in England and Wales: an observational analysis

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Abstract

Objective: To evaluate the association between having concomitant COPD or asthma, and in-patient mortality and post-discharge management among patients hospitalised for acute HF.

Setting: Data were obtained from patients enrolled in the National Heart Failure Audit.

Participants: 217,329 patients hospitalised for HF in England-Wales between March 2012 and 2018.

Outcomes: In-hospital mortality, referrals to cardiology follow-up and prescriptions for HF medications were compared between patients with comorbid COPD (COPD-HF) or asthma (asthma-HF) versus HF-alone using mixed-effects logistic regression.

Results: Patients with COPD-HF were more likely to die during hospitalisation, and those with asthma-HF had a reduced likelihood of death, compared with patients who had HF-alone ([adjusted]OR_{adj}, 95% CI: 1.10, 1.06-1.14 and OR_{adj}, 95%CI: 0.85, 0.79-0.88). In patients who survived to discharge, referral to HF follow-up services differed between groups: COPD-HF patients had reduced odds of cardiology follow-up (OR_{adj}, 95%CI 0.79, 0.77-0.81), whilst cardiology referral odds for asthma-HF were similar to HF-alone. Overall, proportions of HF medication prescriptions at discharge were low for both COPD-HF and asthma-HF groups, particularly prescriptions for beta-blockers.

Conclusions: In this nationwide analysis, we showed that COPD and asthma significantly impact the clinical course in patients hospitalised for HF. COPD is associated with higher in-patient mortality and lower cardiology referral odds, whilst COPD and asthma are both associated with lower use of prognostic HF therapies on discharge. These data highlight therapeutic gaps and a

need for better integration of cardiopulmonary services to improve healthcare provision for patients with HF and coexisting respiratory disease.

Keywords: heart failure, chronic obstructive pulmonary disease, asthma

Strengths and limitations

- This study evaluates the association between respiratory disease and in-hospital mortality and management outcomes in patients hospitalized with HF in a representative population from England and Wales.
- HF diagnosis was based either on diagnostic tests or clinical investigations which limited misclassification bias
- HF with preserved ejection fraction was an exclusion diagnosis (i.e., defined as HF in patients who did not have reduced ejection fraction) due to lack of information regarding specific diagnostic tests to confirm preserved ejection fraction status.
- There was a large proportion of missing data regarding bronchodilators and inhaled corticosteroids prescriptions which prevented evaluation of their impact on outcomes.

Introduction

COPD and asthma frequently coexist with HF and are independently associated with mortality and increased healthcare use[1 2]. This has been explained by shared systemic inflammation, worsened by the presence of pulmonary disease as well as sub-optimal HF management[3]. Evidence suggests that patients with HF and comorbid COPD are less likely to receive guideline recommended treatment for their HF. For example, beta-blockers which are used in the management of HF with reduced ejection fraction (HFrEF) are often not prescribed to patients with COPD, due to fear of bronchoconstriction[4], reduced effectiveness of emergency beta-agonist medication or difficulty in discriminating between COPD and asthma[5].

Less data exist on the relationship between asthma and HF. Some studies have shown that asthma is associated with an increased occurrence of cardiovascular disease whilst others suggest this is limited to women or smokers[6] and depends on age of asthma-onset[7]. This is further complicated by a component of chronic irreversible airflow obstruction in some people with long standing asthma, associated with a reduced response to asthma therapy[8]. This may, in turn, affect treatment choices in this group of patients and increase vulnerability to adverse events, versus either disease occurring alone. The use of beta-agonists or inhaled corticosteroids in both COPD and asthma has been associated with HF-onset, HF-related hospitalisation and increase in cardiovascular events[9], which depend on disease severity and study setting, but nevertheless worsen prognosis[1 7].

Our main aim was to compare in-hospital mortality and post-discharge HF management (referrals to HF services, discharge medication) among patients admitted to hospital with decompensated HF, with and without COPD or asthma in a sample of patients from the

National Heart Failure Audit (NHFA) from England and Wales. We also investigated whether ejection fraction (EF) status affects outcomes in these patient groups.

Methods

We included patients older than 18 years of age admitted to hospital for HF between March 2012 to April 2018 whose data were submitted to the NHFA. We considered their first HF hospitalisation only (**Supplemental Methods, Supplemental Table 1**).

Exposures

COPD was defined as having a history of COPD - chronic bronchitis and/or emphysema, confirmed by spirometry or beta agonist/steroid inhaler use.

Asthma was defined as having a history of childhood asthma and atopy or having an asthma diagnosis confirmed by a respiratory physician.

No diagnostic test results were provided for COPD or asthma (**Supplemental Table 2**), and for the purposes of this work were based on being recorded as "yes" (present) or "no" (absent) in the audit data as defined above.

EF status was defined as HFrEF and HF with preserved EF (HFpEF), determined through echocardiography, MRI, nuclear scan, or angiogram. Those with an EF <40% were categorised HFrEF. Due to a lack of information regarding specific diagnostic tests required to make a HFpEF diagnosis, we determined HFpEF as patients not categorised as HFrEF[10].

Covariates were age, sex, New York Heart Association [NYHA] classification and place of care (cardiology ward vs. other place of care [i.e., general ward]) and comorbidities (atrial fibrillation

[AF], ischemic heart disease [IHD], diabetes, valve disease, hypertension [**Supplementary Table 2**]).

Outcomes

Our primary outcome was in-hospital death during the index event (HF admission), defined as a dichotomised variable (died/alive at discharge), according to COPD or asthma status. Secondary analyses included post-discharge referral to HF services (cardiology, HF nurse, HF MDT [multidisciplinary team]) and prescriptions for HF medications at discharge in those with HFrEF.

Statistical analysis

Differences in baseline characteristics between patients with COPD-HF/Asthma-HF and HF alone are presented using percentages for categorial variables and medians and interquartile ranges [IQR] for continuous variables. We assessed differences between groups using chi-square and Kruskall-Wallis tests. We assessed differences in outcomes between patients with COPD-HF compared with HF alone and between asthma-HF compared with HF-alone using multilevel logistic regression with a random effect for hospital, to calculate odds ratios (OR) and 95% confidence intervals (CI) **(Supplemental Methods).** In the main analysis, we adjusted for confounders with less than 20% missing data: age, sex, comorbidities, place of care and NYHA status. The model building process is presented in **Supplementary Table 3**. Analyses of referrals were conducted similarly and excluded patients who died in-hospital. Associations between COPD or asthma and HF medication prescriptions at discharge (beta blockers, angiotensin-converting-enzyme inhibitors [ACEis], angiotensin receptor blockers [ARBs] and mineralocorticoid receptor antagonists [MRAs]) excluded those with HFpEF.

Sensitivity analyses

Due to potential confounding, smoking and Body Mass Index (BMI) were multiply imputed using a multilevel approach (**Supplemental methods**). We also repeated the main analysis in a cohort of patients including only a "confirmed HF diagnosis" (ICD-10 HF diagnosis confirmed by imaging/BNP testing, or adjudicated by a clinician in the absence of echocardiography)[11].

Analyses were performed with R v4.0.3.

Results

Baseline characteristics are presented in **Table 1**. In total, 217,329 patients were admitted to hospital in England-Wales due to decompensated HF between 2012 and 2018, with data on COPD/asthma status available **(Supplemental Figure 1).** The median age was 81 years (IQR 72-87) and 53.7% were male. In-hospital death occurred in 12% of patients. COPD was diagnosed in 15% of patients and asthma in 6.6%. Most patients were characterised by either marked or severe breathlessness and half had a recorded HF management plan in place at discharge. Length of stay and deprivation ranking did not differ significantly between patients with COPD-HF, asthma-HF and HF alone. COPD-HF patients were mostly male, were less often admitted to cardiology and were more frequently diagnosed with IHD compared with those with HF alone; hypertension was slightly less common among COPD-HF patients, whereas diabetes was more common. The proportion of patients with HFpEF was marginally higher in the COPD-HF group, compared with the HF-only group. Asthma-HF patients were mostly female, with higher levels of diabetes and hypertension compared to HF-only. Conversely, AF was less common in the asthma-HF compared with the HF-alone group; there were also more patients with HFpEF.

In-hospital death

The association between COPD and in-hospital death, is presented in **Figure 1, Table 2, and Supplementary Table 4.** Overall, COPD was independently associated with increased odds of in-hospital death ([adjusted]OR_{adj}, 95% CI: 1.10, 1.06-1.14). The relationship between COPD and in-hospital death differed according to EF: COPD was associated with an increase in mortality in patients with HFrEF (OR_{adj}: 1.15, 1.09 – 1.21), but not in those with HFpEF (OR_{adj}: 1.05, 0.99–1.10).

Conversely, asthma was associated with a decrease in the odds of in-hospital death compared with HF patients without asthma (OR_{adj}, 95%CI: 0.85, 0.79-0.88). The odds of death did not vary by EF status for patients with asthma-HF **(Figure 1, Table 2).**

Sensitivity analyses where smoking status and BMI were imputed due to missing data (**Supplementary Table 5**), and where patients with a confirmed HF diagnosis only were included (**Supplementary Table 6**), showed similar results to the main analysis.

Referrals to HF services

In the fully adjusted models, COPD was associated with decreased likelihood of outpatient referral to a cardiologist (OR_{adj}, 95%CI 0.79, 0.77-0.81) and to a HF-MDT (OR_{adj}, 95% CI 0.94, 0.91-0.97). Patients with COPD-HFrEF were less likely to be referred to a cardiologist than those with HFrEF without COPD (OR_{adj}: 0.85, 95% CI 0.81-0.88) while patients with COPD-HFpEF were significantly less likely to be referred, compared to HFpEF without COPD (OR_{adj}, 95CI% 0.73, 0.70-0.76). COPD was associated with a decreased likelihood of documented HF-MDT referral only for patients with HFpEF (OR_{adj}, 95%CI, 0.90, 0.86-0.94).

Overall, referral odds did not differ in patients with asthma-HF compared to those with HF-alone. There was a significant increase in the odds of referral to a cardiologist for those with asthma-HFrEF (OR_{adj}, 95%CI 1.08, 1.03-1.14) and a decreased likelihood of referral for patients with asthma-HFpEF (OR_{adj} 95CI, 0.93, 0.88-0.98), compared to HFrEF, HFpEF-alone, respectively. Referrals to HF nurse or HF MDT were not different between those with HF alone or HF and asthma **(Figure 2).**

HF medication prescription at discharge

Patients with COPD-HF had lower prescription proportions of ACEIs/ARBs, beta-blockers and double (ACEi/ARB+beta-blocker) and triple-therapy (ACEi/ARB+beta-blocker+MRA) compared to those with HF-only. ACEIs/ARBs, MRAs and triple-therapy were prescribed more frequently in the asthma-HF group compared with the HF-alone group; however beta-blockers or double-therapy were less often prescribed for asthma-HF vs. HF-alone **(Figure 3).**

In patients with HFrEF, COPD and asthma were associated with decreased likelihood of beta-blocker prescription at discharge (OR_{adj} 0.66, 95%CI 0.59-0.67, OR_{adj}: 0.57, 95%CI 0.54-0.60). COPD was associated with lower chance or ACEi/ARB prescription, but did not affect MRA prescriptions, while asthma was associated with increased odds of ACEi/ARB and MRA **(Table 3).**

Discussion

This is the first study to provide a large assessment of contemporary HF practice, generalisable to the population of England-Wales, evaluating the effect of COPD and asthma on clinical and management outcomes. We found that patients with COPD-HF were more likely to die during

their HF admission, compared to patients with HF-only; those with asthma-HF had a reduced probability of in-hospital death, compared to patients with HF-alone. Referrals to HF services also differed: COPD was associated with a 21% reduction in post-discharge cardiology referral whilst a diagnosis of asthma did not affect this outcome.

Airways diseases, particularly COPD is associated with adverse events in patients with HF[1-3 12-14], however diagnostic misclassification is under-estimated and studies of the independent effect of asthma are lacking. We report several findings which add to previous literature.

The finding that COPD is associated with in-hospital mortality confirms reports from previous European data which considered longer term follow-ups[15 16]. A greater severity of cardiovascular disease amongst those with COPD-HF may have contributed to the increase in mortality, as indicated by the higher proportions of patients in NYHA classes III and IV, compared with those with HF alone. Further explanations could include admission to non-cardiology wards for COPD-HF patients, which has been linked with poorer outcomes in acute HF[17].

A COPD diagnosis was associated with increased in-hospital death in those with HFrEF, but not in those with HFpEF, which is surprising, given that COPD is suggested to be more severe in the latter group[18]. In contrast with our report, previous studies found that risk of death is increased in those with COPD-HFpEF compared to COPD-HFrEF[19 20], however these may be confounded by a lack of validity of EF status (inferred by ICD codes rather than echocardiography) or spirometry to confirm COPD status, consideration of long-term rather than short term effects on mortality, or by including chronic rather than hospitalised HF. Our result therefore may be explained by poor uptake of disease-modifying treatments available for HFrEF in those with

COPD[15], which has been previously reported and could be more pronounced in a cohort of patients newly admitted for HF.

After adjusting for age, sex and other baseline characteristics including comorbidities, and further adjustments for smoking status and BMI, differences between those with and without COPD, respectively asthma, did not materially change the association between the two lung diseases with in-hospital mortality. This suggests an independent contribution of COPD to increased mortality in patients hospitalised with HF, significant beyond the potential confounders considered in this analysis.

While previous reports suggest asthma is associated with increased risk of developing cardiovascular disease[6], no prior study has reported on the association between asthma and death during acute HF hospitalisation. We found that, on average, asthma was independently associated with a 24% reduction in risk of death in patients with HF. The mechanisms underlying this epidemiological association are unclear. Several factors may explain our result. Asthma management is reliant on anti-inflammatory agents such as inhaled corticosteroids (ICS), which have been linked to cardioprotective effects[21 22] including lower all-cause mortality and lower risk of myocardial infarction ([MI], a precursor to HF). Potential long-term ICS use in our asthma-HF cohort could have diminished patients' baseline mortality risk.

The nature of inflammation is different in COPD compared with asthma, and influences response to medication. One hypothesis which may underlie the diverging findings on the effect of the two lung diseases on outcomes in patients with HF thus relates to differences in management and their subsequent differential cardiovascular risk. Bronchodilator medications, which are central to the symptomatic treatment of COPD, have been associated with increased

cardiovascular risk[9]. While combination treatments such as ICS/LABA may have a good cardiovascular safety profile in asthma, this differs in COPD[8 14]. RCTs have not demonstrated mortality benefits with ICS in individuals with COPD, although some observational studies suggest the opposite. The largest trial[23] examining all-cause mortality in 16,000 patients with COPD and risk of cardiovascular disease showed the treatments evaluated (long-acting beta-agonists and/or inhaled corticosteroids) were well tolerated by patients, however the effect on patients with existing HF remains under debate.

Since both lung diseases were diagnosed prior to HF admission, it would be plausible to assume that any effects of long-term pulmonary medication could influence the chance of death in our cohort. Thus, the heightened risk of in-hospital mortality observed in the COPD-HF group, but not in asthma-HF could be related to more frequent use of bronchodilators and a poorer safety profile of ICS in COPD compared to asthma. Alternatively, COPD-specific characteristics such as such as progressive lung function decline may have influenced in-hospital mortality in those admitted for HF.

However, due to large amounts of missing data on respiratory disease medication prescription in our cohort (**Supplemental Table 7**), we could not verify these assumptions in our dataset. Future studies incorporating accurate information on bronchodilator use in patients with concomitant HF and respiratory disease should be conducted.

The association between COPD/asthma and referral to follow-up cardiology services has not been studied before in hospitalised HF patients. Overall, patients with COPD-HF were less likely to be referred to a cardiology service after hospital discharge, compared with those who had

HF-alone. This indicates that a COPD diagnosis may be an obstacle preventing access to HF specialist care. According to NICE, all patients with a HF diagnosis need to be seen by a HF specialist within two weeks of discharge, but data suggest these timelines are not met[24]. The compounded effect of a COPD diagnosis has the potential to further impair the long-term prognosis of these comorbid patients. Further, more than 60% of patients with COPD and HF were admitted to a general ward rather than a specialised cardiology ward, which may also explain the low likelihood of cardiology referrals in this group.

Our study also indicated EF status mediated the relationship with referrals, as individuals with COPD-HFpEF were less likely to have an appointment compared with their COPD-HFrEF counterparts. This is particularly worrying as HF, irrespective of EF, is best monitored and managed within specialist HF teams.

Asthma did not adversely influence referrals to HF services, but we identified an increased likelihood of referral to cardiology in asthma-HFpEF as compared with asthma-HFrEF. One possible explanation is greater uncertainty in clinical management of patients with HFpEF, leading to increased referral, though this needs to be assessed in future studies. Clarifying these clinical management pathways offers a potential to improve HF prognosis by ensuring access to care is timely and tailored to individual patients' risk, pathology, and health.

Patients with COPD-HFrEF were 34% less likely to receive a beta-blocker prescription at discharge, compared with patients with HFrEF alone, despite recent data supporting use of these agents in COPD[25 26]. Similar to data on patients post-MI[27], it is worrying that COPD was also associated with decreased likelihood of guideline recommended ACEi/ARB prescription in

those with HF, as there is no contraindication for those with pulmonary disease. Efforts need to be made to ensure appropriate therapeutic management of these patients.

Those with asthma-HFrEF had 43% less chance of being prescribed a beta-blocker compared with patients with HF-alone. Current guidelines recommend that asthma patients with chronic HFrEF should not receive disease-modifying beta-blocker treatment due to possible bronchoconstriction, despite evidence to suggest that cardioselective beta-blockade may be used with careful up-titration and monitoring[28 29], where benefits may outweigh risks in individual patients. Based on the low uptake across the whole spectrum of HF medications in patients with additional lung disease (**Figure 3**), we expect these patients would have worse prognosis compared to their more adequately treated counterparts.

Considering these results, management needs to be optimized in patients with COPD or asthma and concurrent HF. The arrival of new treatments such as sodium-glucose co-transporter 2 inhibitors (SGLT2-i) have widened treatment choice in HFrEF, and there is now evidence supporting their use in individuals with COPD[30]. Given beta-blockers are avoided in asthma, these new treatments should urgently be assessed in this population, as data are currently lacking.

Strengths and limitations

The main strength of this study is the large sample size and representativeness of a hospitalised population with HF from England and Wales. We did not have however have information on duration and severity of asthma or COPD, nor lung function test results and thus we could not verify accuracy of these diagnoses, which are often subject to misclassification, especially in the

elderly[31]. Data on bronchodilator use was largely missing for our cohort (**Supplemental Table 7**), limiting assessment of both diagnostic accuracy of the respiratory diseases, and association with outcomes evaluated in this study. We also could not differentiate between childhood asthma or late-onset asthma which may have different implications [32].

HFpEF was determined as a HF diagnosis without systolic dysfunction, which has been used in previous NHFA reports. Nevertheless, there is no consensus gold standard HFpEF diagnosis[10] and it remains difficult to validate. Further work in this area is needed, particularly in accurately distinguishing between HFpEF and COPD, which have similar clinical presentation.

There was a considerable proportion of missing data on bronchodilators/inhaled corticosteroids in the dataset which prevented assessment of whether the impact of COPD and asthma on outcomes is mediated, in part, by their treatment. Future studies incorporating accurate information on bronchodilator use in patients with concomitant HF and respiratory disease should be conducted.

Smoking status was also characterised by a large percentage of missing data, however an analysis using multiple imputation indicated that even after adjusting for this confounder in the imputed dataset, the association between both COPD and asthma on in-hospital mortality remained unchanged. **(Supplementary Table 5).**

We only focused on decompensated HF and the picture may change when investigating long-term mortality, recurrent admissions, or other aspects of treatment such as medication adherence.

While the referral likelihood estimates provide a first glimpse into the association between COPD/asthma and potential healthcare service provision for HF patients in England-Wales, we did not have access to data on concrete healthcare utilisation amongst our cohort.

Due to lack of data, we could not establish whether cause of death varied amongst the groups and whether the increased mortality associated with COPD was underlined by higher rates of respiratory versus cardiac or other disease.

Conclusion

This analysis adds to the growing body of evidence that COPD and asthma affect outcomes in patients with acute HF. Our data suggest that while COPD is a main contributor to in-hospital mortality and is associated with decreased referral to cardiology services amongst HF patients, asthma does not negatively impact these outcomes. Both lung diseases are however responsible for significant decreases in the prescription of HF treatments at discharge, particularly beta-blockers. These findings highlight a need for better integration of cardiopulmonary services with an aim to tailor healthcare provision for these patients.

Competing interests

CG, CK and RZ have nothing to declare. Prof. Quint's research group has received funds from AZ, GSK, The Health Foundation, MRC, British Lung Foundation, IQVIA, Chiesi, and Asthma UK outside the submitted work; grants and personal fees from GlaxoSmithKline, Boehringer Ingelheim, AstraZeneca, Bayer, Insmed outside the submitted work.

Data availability

The data that support the findings of this study have been provided by the Healthcare Quality Improvement Partnership from the National Heart Failure Audit Programme, but restrictions apply to the availability of these data and so are not publicly available.

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Author contributions

Conceptualization & Methodology: CG, JKQ, CK. Original draft: CG. Editing and final approval: CG, JKQ, RZ, CK; Data curation & Formal data analysis: CG; Data acquisition: JKQ.

Ethics approval

This study involved analysis of pre-existing, de-identified data, thus it was exempt from Institutional Review Board approval.

Patient and public involvement

Patients were not involved in the design and conduct of the study.

Figure legends

Figure 1 - Association between COPD, asthma and in-hospital death, adjusted for age, sex, valve disease; IHD, hypertension, diabetes, AF, NYHA, place of care and EF status; odds ratio with 95% confidence intervals.

Figure 2. Association between COPD, asthma and referrals to HF services, adjusted for age, sex, valve disease; IHD, hypertension, diabetes, AF, NYHA, place of care and EF status.

Figure 3. HF-medication prescription rates at discharge, according to comorbid respiratory disease status

Table 1. Baseline characteristics according to COPD and asthma status, in patients hospitalised for HF in England-Wales.

	HF alone (N=170297)	COPD + HF (N=32695)	Asthma + HF (N=14400)	Overall (N=217,392)
Age, median [IQR]	81 [72, 88]	79 [72, 85]	79 [69, 86]	81 [72, 87]
Missing	67 (0.1%)	22 (0.1%)	10 (0.1%)	199 (0.1%)
Male	91837 (53.9%)	19072 (58.3%)	5936 (41.2%)	116845 (53.7%)
Missing	74 (0.1%)	44 (0.1%)	21 (0.1%)	239 (0.1%)
Place of admission				
Cardiology	76428 (44.9%)	12361 (37.8%)	6147 (42.7%)	94936 (43.7%)
Other	93358 (54.8%)	20246 (61.9%)	8218 (57.1%)	21822 (56.0%)
Missing	511 (0.3%)	88 (0.3%)	35 (0.2 %)	634 (0.3%)
Died in-hospital	20316 (11.9%)	4181 (12.8%)	1337 (9.3%)	25834 (11.9%)
Device therapy				
None	147485 (86.6%)	28962 (88.6%)	12818 (89.0%)	189265 (87.1%)
CRT-D	3047 (1.8%)	496 (1.5%)	189 (1.3%)	3732 (1.7%)
CRT-P	1681 (1%)	296 (0.9%)	142 (1%)	2119 (1.0%)
ICD	3001 (1.8%)	511 (1.6%)	211 (1.5%)	0 (0%)
Missing	15083 (8.9%)	2430 (7.4%)	1040 (7.2%)	18553 (8.5%)
Comorbidities				
Valve disease	38213 (22.4%)	7005 (21.4%)	2906 (20.2%)	48124 (22.1%)
Missing	3426 (2.0%)	822 (2.5%)	335 (2.3%)	4583 (2.1%)
IHD	65992 (38.8%)	14198 (43.4%)	5175 (35.9%)	85365 (39.3%)
Missing	3667 (2.2%)	811 (2.5%)	335 (2.3%)	4813 (2.2%)
Hypertension	91477 (53.7%)	16838 (51.5%)	8208 (57%)	116523 (53.6%)
Missing	1326 (0.8%)	381 (1.2%)	125 (0.9%)	1832 (0.8%)
Diabetes	50194 (29.5%)	10348 (31.7%)	4772 (33.1%)	65314 (30%)
Missing	459 (0.3%)	142 (0.4%)	54 (0.4%)	655 (0.3%)
AF	72235 (42.4%)	13728 (42%)	5508 (38.2%)	91471 (42.1%)
Breathlessness (NYHA)				
No limitation of physical activity	12273 (7.2%)	1254 (3.8%)	768 (5.3%)	14295 (6.6%)
Slight Limitation of ordinary physical activity	24541 (14.4%)	3951 (12.1%)	1993 (13.8%)	30485 (14.%)
Marked Limitation of ordinary physical activity	68179 (40%)	13671 (41.8%)	6011 (41.7%)	87861 (40.4%)
Symptoms at rest or minimal activity	54652 (32.1%)	12191 (37.3%)	4809 (33.4%)	71652 (33%)
Missing	10652 (6.3%)	1628 (5.0%)	819 (5.7%)	13099 (6.0%)
Echocardiography performed	137955 (81%)	26165 (80%)	11342 (78.8%)	175462 (80.7%)
Ejection fraction status				
HFrEF	92619 (54.4%)	16408 (50.2%)	7334 (50.9%)	116361 (53.5%)

	HF alone (N=170297)	COPD + HF (N=32695)	Asthma + HF (N=14400)	Overall (N=217,392)
HFpEF	77678 (45.6%)	16287 (49.8%)	7066 (49.1%)	101031 (46.5%)
HF management plan				
Pre-discharge management plan in place	11760 (6.9%)	2152 (6.6%)	1002 (7.0%)	14914 (6.9%)
Management plan has been discussed with the patient	10572 (6.2%)	1894 (5.8%)	954 (6.6%)	13420 (6.2%)
Management plan has been communicated to the primary care team	19880 (11.7%)	3963 (12.1%)	1780 (12.4%)	25623 (11.8%)
All of the above	83507 (49%)	15496 (47.4%)	7140 (49.6%)	106143 (48.8%)
No plan	18021 (10.6%)	3937 (12.0%)	1546 (10.7%)	23504 (10.8%)
Missing	26557 (15.6%)	5253 (16.1%)	1978 (13.7%)	33788 (15.5%)
Referral to HF MDT	53898 (31.6%)	9719 (29.7%)	4455 (30.9%)	68072 (31.3%)
Missing	29946 (17.6%)	5722 (17.5%)	2216 (15.4%)	37884 (17.4%)
Referral to cardiology follow up	70925 (41.6%)	11875 (36.3%)	6241 (43.3%)	89041 (41%)
Missing	13827 (8.1%)	2882 (8.8%)	984 (6.8%)	17693 (8.1%)
Referral to HF nurse follow-up	76170 (44.7%)	13728 (42.0%)	6249 (43.4%)	96147 (44.2%)
Missing	13442 (7.9%)	2658 (8.1%)	952 (6.6%)	17052 (7.8%)
LOS				
Median [IQR]	8 [3, 15]	8 [4, 16]	7 [3, 14]	8 [4, 15]
IMD Wales (quartile)	**N=8205**	**N=1889**	**N=776**	**N= N=10870**
1st (most deprived)	2126 (25.9%)	371 (19.6%)	188 (24.2%)	2685 (24.7%)
2nd	2058 (25.1%) 396	(21.0%) 190	(24.5%) 83	2644 (24.3%)
3rd	1977 (24.1%)	459 (24.3%)	196 (25.3%)	2632 (24.2%)
4th (least deprived)	1824 (22.2%)	607 (32.1%)	185 (23.8%)	2616 (24.1%)
Missing*	-	-	-	-
IMD England (quartile)	**N=159540**	**N=30352**	**N=13433**	**N=203325**
1st (most deprived)	35836 (22.5%)	9338 (30.8%)	3449 (25.7%)	48623 (23.9%)
2nd	38347 (24.0%)	7762 (25.6%)	3403 (25.3%)	49512 (24.4%)
3rd	40131 (25.2%)	6848 (22.6%)	3166 (23.6%)	50145 (24.7%)
4th (least deprived)	41387 (25.9%)	5615 (18.5%)	3072 (22.9%)	50074 (24.6%)
Missing	3839 (2.4%)	789 (2.6%)	343 (2.6%)	4971 (2.4%)

AF= atrial fibrillation; COPD= chronic obstructive pulmonary disease; CRT-P= cardiac resynchronisation therapy pacemaker; CRT-D= cardiac resynchronisation therapy defibrillator, HF= heart failure; HFrEF= heart failure with reduced ejection fraction; *HFpEF= heart failure with preserved ejection fraction; ICD= implantable cardioverter defibrillator; IHD= ischemic heart; disease; IMD= indices of multiple deprivation; LOS= length of stay; MDT= multi-disciplinary team; NYHA = New York Heart Association; * not shown due to small numbers.

Table 2 – Association between COPD, asthma and outcomes in patients hospitalised for HF in England-Wales

	Fully adjusted[a] interaction model COPD*EF OR (95% CI)		Fully adjusted[b] interaction model Asthma*EF OR (95% CI)	
Outcome	COPD * HFrEF	COPD* HFpEF	Asthma * HFrEF	Asthma * HFpEF
In-hospital death (N= 194,156[c])	Interaction *P*-value = 0.01		Interaction *P*-value = 0.842	
Fixed-effects	1.15 (1.09 – 1.21, p=0.294*10^{-10})	1.05 (0.99 – 1.10, p=0.081)	-	-
Random effects (hospitals, n=216)				
Variance	*0.201*		-	
LR test P-value[d]	*P=0.22*10^{-16}*		-	-
Referral to cardiology follow-up (N= 166,658[c])	Interaction *P*-value= 0.288*10^{-7}		Interaction *P*-value=0.0001	
Fixed effects	0.85 (0.81, 0.88, p=0.2*10^{-16})	0.73 (0.70, 0.76, p=0.2*10^{-16})	1.08 (1.03-1.14, p=0.2*10^{-16})	0.93 (0.88- 0.98, p=0.003)
Random effects (hospitals, n=216)				
Variance	*0.512*		*0.512*	
LR test p-value[d]	*0.22*10^{-16}*		*P=0.22*10^{-16}*	
Referral to HF MDT (N=149,098[c])	Interaction *P*-value = 0.017		Interaction *P*-value=0.095	
Fixed effects	0.97 (0.93, 1.02, p=0.263)	0.90 (0.86, 0.94, p=0.265*10^{-5})	-	-
Random effects (hospitals, n=216)				
Variance	*2.139*		-	-
LR test p-value[d]	*0.22*10^{-16}*		-	-
Referral to HF nurse (N= 166,723[c])	Interaction *P*-value = 0.249		Interaction *P*-value = 0.450	

COPD= chronic obstructive pulmonary disease; HF= heart failure; HFrEF= heart failure with reduced ejection fraction; HFpEF= heart failure with preserved ejection fraction; LR= likelihood ratio; MDT= multidisciplinary team; OR= odds ratio; CI= confidence interval

[a] Adjusted for age, sex, diabetes, hypertension, ischemic heart disease, atrial fibrillation, asthma, place of care and New York Heart Association status

[b] Adjusted for age, sex, diabetes, hypertension, ischemic heart disease, atrial fibrillation, COPD, place of care and New York Heart Association status

[c] Excludes patients with missing data on covariates included in model

[d] Likelihood ratio test comparing fixed to random effects for hospital model fit, significant indicates random effects model performed better than fixed effects model

Table 3. Association between COPD, asthma and HF medication prescription at discharge, in patients with HFrEF

Medication prescription at discharge	COPD unadjusted OR (95%CI)	COPD fully adjusted[a] OR (95%CI)	Asthma unadjusted OR (95%CI)	Asthma fully adjusted[b] OR (95%CI)
Beta-blockers (N= 86449[a,b])				
Fixed effects	0.61 (0.58, 0.64, p=$0.22*10^{-16}$)	0.66 (0.64, 0.68, P=$0.22*10^{-16}$)	0.63 (0.59, 0.67, p=$0.22*10^{-16}$)	0.57 (0.54 0.60, p=$0.22*10^{-16}$)
Random effects				
Variance	*0.553*	*0.578*	*0.549*	*0.578*
LR test p-value	$0.22*10^{-16}$	$0.22*10^{-16}$	$0.22*10^{-16}$	$0.22*10^{-16}$
ACEis/ARBs (N=96080 [a,b])				
Fixed effects	0.87 (0.84, 0.90, p=$0.139*10^{-13}$)	0.91 (0.87-0.95, p=$0.256*10^{-6}$)	1.13 (1.07, 1.19, p=$0.16*10^{-6}$)	1.07 (1.01, 1.13, p=0.0143)
Random effects				
Variance	*0.149*	*0.130*	*0.148*	*0.130*
LR test p-value	$0.22*10^{-16}$	$0.22*10^{-16}$	$0.22*10^{-16}$	$0.22*10^{-16}$
MRA (N=96080 [a,b])				
Fixed effects	0.97 (0.94, 1.01, p=0.114)	1.02 (0.98, 1.06, p=0.268)	1.08 (1.04, 1.13, p=0.00043)	1.07 (1.02, 1.12, p= 0.0084)
Random effects				
Variance	*0.232*	*0.195*	*0.226*	*0.195*
LR test p-value	$0.22*10^{-16}$	$0.22*10^{-16}$	$0.22*10^{-16}$	$0.22*10^{-16}$

Abbreviations
COPD= chronic obstructive pulmonary disease; OR= odd ratio; CI= confidence intervals; LR= likelihood ratio
[a]Adjusted for age, sex, diabetes, hypertension, ischemic heart disease, atrial fibrillation, asthma, place of care and New York Heart Association status
[b]Adjusted for age, sex, diabetes, hypertension, ischemic heart disease, atrial fibrillation, COPD, place of care and New York Heart Association status
Likelihood ratio test comparing fixed to random effects for hospital model fit, significant indicates random effects model performed better than fixed effects model

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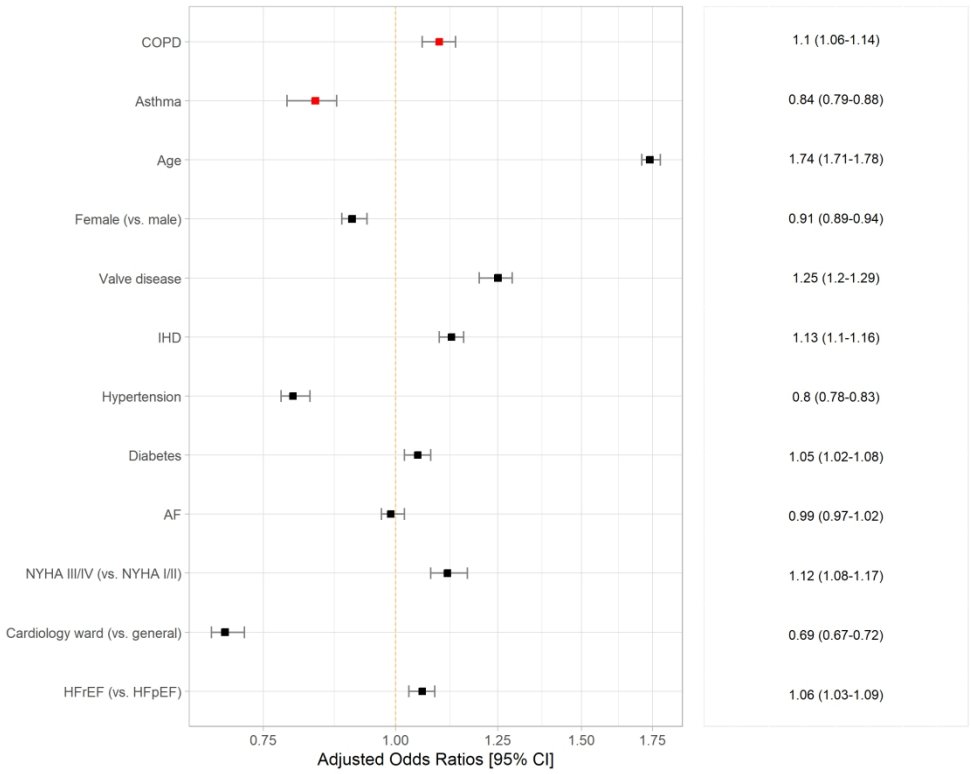

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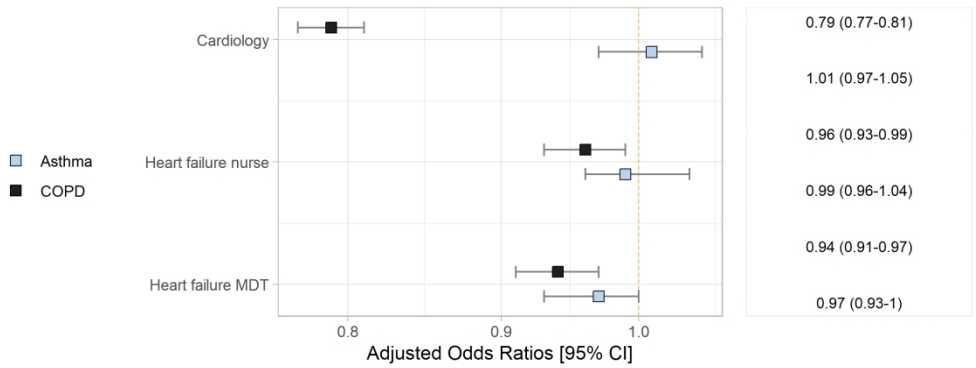

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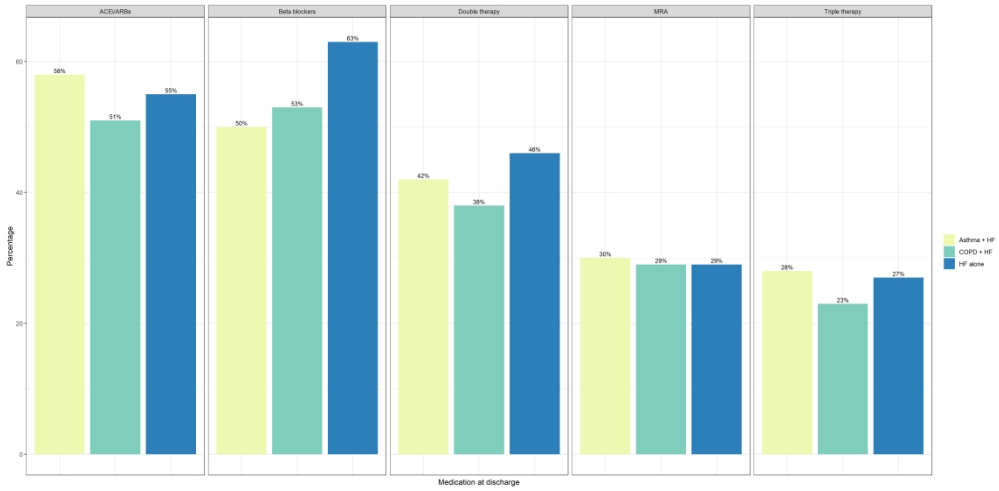

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Supplemental Material

Supplemental Methods

Data source

The NHFA was established in 2007 for hospitals in England-Wales to assess the quality of care and outcomes of hospitalised patients with a HF diagnosis in the first position at death or discharge, identified using ICD-10 codes (**Supplementary Table 1**). Admissions coded in the audit are compared to HF episodes in the Hospital Episode Statistics (HES) in England and the Patient Episode Database of Wales (PEDW) to determine the case ascertainment rate. The number of participating NHS trusts fluctuated from 145 in 2012–13 (97%) to 136 (82%) in 2017/2018. This corresponds to an increase from capturing 60% of national HF admissions in 2012, to 76% at the end of April 2018. Data are entered into the audit by hospital staff, using case ascertainment forms and data are categorised as mandatory (main indicators such as HF treatments, comorbidities, echocardiography) or non-mandatory (i.e., smoking status, pulmonary oedema, ethnicity). Since non-mandatory data elements are not expected to be included, there are considerable proportions of missing data across these variables (**Supplemental Table 2**). Some mandatory variables also have significant amounts of missing data (e.g., more than 70% missing data on BNP measurements, weight, height). The breadth of variables collected varied throughout the history of the audit, to reflect changes in HF guidelines and quality standards, which evolved over time. For example, haemoglobin and serum creatinine were collected routinely only after 2012[1].

Statistical analysis

The analysis for the main outcome was implemented in a stepwise manner. First, an unconditional model including, COPD was considered. In a second step we added asthma. Third, we added an interaction term between COPD and asthma, to assess whether both diagnoses had a significant contribution to the model. In lack of statistical significance these patients were not considered in further analyses. We then evaluated effect modification by EF status (HFrEF/HFpEF) by including separately an interaction term between COPD and EF, then asthma and EF.

Handling of missing data

Sensitivity analysis – missing data imputation

While the proportions of missing data (see above) were considerable, we deemed necessary to investigate further two important factors: “smoking status” and “Body Mass Index (BMI)”. In particular, we were interested in assessing whether COPD has an independent association with death in patients with HF, when controlling for smoking status, or whether the relationship is influenced by this factor.

We assumed data on smoking and BMI to be missing at random in our cohort, as the distribution in observed cases was similar to other UK cohorts of patients with HF[2 3]. We then used a multi-level approach[4] which takes into consideration the hierarchical data structure, clustered at hospital level. A Gibbs sampling procedure was used to generate 20 imputed data sets after a burn-in of 1000 iterations.

Table 1. Inclusion criteria for National Heart Failure Audit

ICD-10 code	Diagnosis
I11.0	Hypertensive heart disease with (congestive) heart failure
I25.5	Ischaemic cardiomyopathy
I42.0	Dilated cardiomyopathy
I42.9	Cardiomyopathy, unspecified
I50.0	Congestive heart failure
I50.1	Left ventricular failure
I50.9	Heart failure, unspecified
ICD= International Statistical Classification of Diseases and Related Health Problems	

Table 2. Comorbidity definitions, according to NHFA dataset[1], variables recorded from patient history

COPD	History of COPD - chronic bronchitis, emphysema or their cooccurrence. Must be indicated by pulmonary function testing evidence .ie FEV1<75% predicted value or use of beta agonist/steroid inhalers.
Asthma	History of childhood asthma and atopy, or asthma confirmed by respiratory physician for adult onset.
Diabetes	Diagnosis of diabetes prior to admission. This includes a confirmed diagnosis of diabetes and/or the use of an oral hypoglycaemic agent or insulin, and/or a fasting blood glucose >6.7, and/or a random blood glucose >11.
Hypertension	Recorded Blood Pressure >140/90 on at least two occasions prior to admission, or already receiving treatment (drug, dietary or lifestyle) for hypertension
Ischemic heart disease	History of myocardial infarction, angina, ECG evidence of MI, CABG or angiogram documenting coronary artery disease.
Cerebrovascular accident	A past neurological deficit of cerebrovascular cause, including episodes that persist beyond 24 hours and transient ischaemic attacks lasting less than 24 hours.
Atrial fibrillation	An ECG was performed showing atrial fibrillation.
Valve disease	History of clinically diagnosed valve disease, moderate or severe stenosis or regurgitation on imaging, or an operative valve replacement/repair

[1] Available: https://www.nicor.org.uk/national-cardiac-audit-programme/datasets/

Table 3. Model building - association between COPD, asthma (including interaction with ejection fraction group) and in-hospital death in patients hospitalised for heart failure.

Predictors	Model 1	Model 2	Model 3	Model 4	Model 5a	Model 5b	Model 6
Fixed effects [coefficient estimate, SE]							
COPD	0.064 [0.017, p<0.001]	0.0706 [0.0174, p<0.001]	0.060 [0.018, p<0.001]	-0.0445 [0.0256, p=0.081]	0.064 [0.017, p<0.001]	-0.029 [0.0242, p=0232]	0.0468 [0.026, p=0.081]
Asthma	-	-0.263 [0.0255, p<0.001]	-0.287 [0.029, p<0.001]	-0.302 [0.040, p<0.001]	-0.2719 [0.034, p<0.001]	-0.266 [0.0255, p<0.001]	-0.179 [0.028, p<0.001]
COPD*Asthma	-	-	**0.098 [0.0573, p=0.087]**	0.149 [0.076, p=0.051]	-	-	-
EF	-	-	-	-0.208 [0.015, p<0.001]	-0.173 [0.014, p<0.001]	-0.207 [0.0149, p<0.001]	0.0410 [0.017, p<0.05]
COPD *EF	-	-	-	**0.205 [0.036, p<0.001]**	**-**	**0.195 [0.034, p<0.001]**	**0.096 [0.037, p<0.05]**
Asthma*EF	-	-	-	**0.018 [0.058, p=0.753]**	**0.013 [0.05, p=0.797]**	-	-
COPD*Asthma*EF	-	-	-	**-0.093 [0.112, p=0.402]**	-	-	-
Age	-	-	-	-	-	-	0.553 [0.0101, p<0.001]
Female (vs. male)	-	-	-	-	-	-	-0.0922 [0.0150, p<0.001]

Valve disease	-	-	-	-	-	-	0.219 [0.0169, p<0.001]
IHD	-	-	-	-	-	-	0.1204 [0.015, p<0.001]
Hypertension	-	-	-	-	-	-	-0.220 [0.0148, p<0.001]
Diabetes	-	-	-	-	-	-	0.0489 [0.0164, p<0.01]
AF	-	-	-	-	-	-	-0.0056 [0.0147, p=0.703]
NYHA	-	-	-	-	-	-	0.116 [0.018, p<0.001]
Place of care (cardiology vs not cardiology)	-	-	-	-	-	-	-0.363 [0.0168, p<0.001]
Random effects (hospitals, n=219)							
Variance	0.205	0.208	0.208	0.201	0.201	0.201	0.159
SD	0.453	0.456	0.456	0.448	0.449	0.449	0.399
AIC	160533.4	158837.1	158836.2	158652.0	158681.2	158649.7	133038.5

Abbreviations
AIC= Akaike information criterion; AF= atrial fibrillation; COPD= chronic obstructive pulmonary disease; CI=confidence intervals; EF= ejection fraction; NYHA= New York Heart Association; IHD= ischemic heart disease; SD= standard deviation; SE= standard error

Results from a 2-level unconditional model that included COPD as fixed-effect and hospital as random effect suggested COPD was associated with an increase in the estimate for in-hospital mortality. The addition of asthma to this model indicated it had an inverse relationship with likelihood of death. A test for the interaction between COPD and asthma was not significant, thus, it was not considered in subsequent analyses. Further, we wanted to assess whether the effects of COPD, respectively asthma on in-hospital death are different with respect to EF status group therefore, we added a three-way interaction between COPD, asthma and EF to the model. We detected a significant interaction between COPD and EF only, suggesting the effect of COPD only, not asthma would

be differential according to the EF status. In the final model, we estimated the association between COPD and mortality in HFrEF and in HFpEF and adjusted for baseline covariates.

Table 4. Association between COPD, asthma and in-hospital death

Predictors	**COPD only (95% CI)**	**COPD + asthma**	**Fully adjusted model**	**Model with COPD and EF interaction, fully adjusted OR (95% CI)**
Fixed effects (95% CI)				P-value for interaction =0.01
COPD	**1.07 (1.03 – 1.10)**	**1.07 (1.04-1.11)**	**1.10 (1.06 – 1.14)**	1.04 (0.99-1.10)
Asthma	**-**	**0.77 (0.73 – 0.80)**	**0.84 (0.79, 0.88)**	0.83 (0.79-0.88)
COPD (Yes vs. No): HFpEF	-	-	**-**	**1.05 (0.99 – 1.10)**
COPD (Yes vs. No): HFrEF	-	-	**-**	**1.15 (1.09 – 1.21)**
Age	-		1.74 (1.71 -1.78)	1.74 (1.71-1.77)
Female (vs. male)	-		0.91 (0.89-0.94)	0.91 (0.89-0.94)
Valve disease	-		1.25 (1.20-1.29)	1.25 (1.20-1.29)
IHD	-		1.12 (1.10-1.16)	1.13 (1.10-1.16)
Hypertension	-		0.8 (0.78-0.83)	0.80 (0.78-0.83)
Diabetes	-		1.05 (1.02-1.08)	1.05 (1.02-1.08)
AF	-		0.99 (0.97-1.02)	0.99 (0.96-1.02)
NYHA (III/IV vs. I/II)	-		1.12 (1.08-1.17)	1.12 (1.08-1.17)
Place of care (not cardiology vs. cardiology ward)	-		0.69 (0.67-0.72)	0.69 (0.67-0.71)
Random effects (Variance)				
LR test p-value	P<0.001	P<0.001	P<0.001	P<0.001
Likelihood ratio test comparing fixed to random effects for hospital model fit, significant indicates random effects model performed better than fixed effects model Abbreviations				

AF= atrial fibrillation; COPD= chronic obstructive pulmonary disease; CI=confidence intervals; EF= ejection fraction; LR= Likelihood ratio test; NYHA= New York Heart Association; IHD= ischemic heart disease; SD= standard deviation.

Table 5. Association between COPD and in-hospital mortality in patients hospitalised with heart failure. Results from 20 models using imputed smoking status and BMI (estimates combined using Rubin's rule).

	Fully adjusted model, OR (95% CI)
Fixed effects (95% CI)	
COPD	1.12 (1.07 – 1.17)
Asthma	0.84 (0.80 – 0.90)
Age	1.67 (1.62 – 1.71)
Female (vs. male)	0.89 (0.86 – 0.92)
Valve disease	1.22 (1.18 – 1.26)
IHD	1.13 (1.10 – 1.17)
Hypertension	0.82 (0.89 – 0.85)
Diabetes	1.12 (1.08 – 1.15)
AF	1.01 (0.98 – 1.04)
NYHA (III/IV vs. I/II)	1.15 (1.10 – 1.20)
Place of care (cardiology vs. no cardiology ward)	0.70 (0.69 – 0.73)
EF	1.03 (0.99 – 1.06)
Smoking status (ref: Current smoker)	
Ex-smoker	0.90 (0.77 – 1.06)
Never	1 (0.84 – 1.19)
BMI (ref: normal weight)	
Underweight	1.31 (1.21 – 1.43)
Overweight	0.86 (0.81 – 0.91)
Obese	0.77 (0.73 – 0.81)
Random effects (Variance)	
LR test p-value	P<0.001

Abbreviations
AF= atrial fibrillation; BMI= Body Mass index; CI= confidence intervals; COPD= chronic obstructive pulmonary disease; EF= ejection fraction; IHD= ischemic heart disease; NYHA= New York Heart Association; OR= Odds ratio; ref= reference

Table 6. Association between COPD and in-hospital mortality in patients hospitalised with a confirmed diagnosis of HF.

	Fully adjusted model, OR (95% CI)
Fixed effects (95% CI)	
COPD	1.11 (1.07 - 1.16)
Asthma	0.84 (0.79 - 0.89)
Age	1.04 (1.04 - 1.05)
Female (vs. male)	0.91 (0.88 - 0.94)
Valve disease	1.26 (1.22 - 1.30)
IHD	1.15 (1.11 - 1.18)
Hypertension	0.81 (0.79 - 0.84)
Diabetes	1.06 (1.03 - 1.10)
AF	0.98 (0.95 - 1.01)
NYHA (III/IV vs. I/II)	1.13 (1.08 - 1.18)
Place of care (cardiology vs. no cardiology ward)	0.69 (0.66 - 0.71)
EF	1.04 (1.01 - 1.08)
Random effects (Variance)	0.166
LR test p-value	p<0.001

Abbreviations
AF= atrial fibrillation; BMI= Body Mass index; CI= confidence intervals; COPD= chronic obstructive pulmonary disease; EF= ejection fraction; IHD= ischemic heart disease; LR= Likelihood ratio test; NYHA= New York Heart Association; OR= Odds ratio; ref= reference

Table 7. Variables with considerable missingness in the National Heart Failure Audit 2012-2018

	HF alone (N=170297)	COPD + HF (N=32695)	Asthma + HF (N=14400)	Overall (N=217392)
Cerebrovascular accident	2882 (1.7%)	582 (1.8%)	244 (1.7%)	3708 (1.7%)
Missing	145636 (85.5%)	28115 (86.0%)	12279 (85.3%)	186030 (85.6%)
Alcohol units/week				
Median [Q1, Q3]	0 [0, 1.00]	0 [0, 2.00]	0 [0, 0]	0 [0, 1.00]
Missing	159233 (93.5%)	30570 (93.5%)	13314 (92.5%)	203117 (93.4%)
Smoking status				
Current smoker	1869 (1.1%)	911 (2.8%)	143 (1.0%)	2923 (1.3%)
Ex-smoker	8371 (4.9%)	2505 (7.7%)	715 (5.0%)	11591 (5.3%)
Never-smoker	8823 (5.2%)	673 (2.1%)	896 (6.2%)	10392 (4.8%)
Missing	151234 (88.8%)	28606 (87.5%)	12646 (87.8%)	192486 (88.5%)
Chest X-ray (pulmonary oedema)	3954 (2.3%)	692 (2.1%)	334 (2.3%)	4980 (2.3%)
Missing	157253 (92.3%)	30528 (93.4%)	13311 (92.4%)	201092 (92.5%)
Medications at admission				
ACEi	6316 (3.7%)	1116 (3.4%)	513 (3.6%)	7945 (3.7%)
Contraindicated	592 (0.3%)	140 (0.4%)	59 (0.4%)	791 (0.4%)
Missing	152642 (89.6%)	29598 (90.5%)	12903 (89.6%)	195143 (89.8%)
ARB	2392 (1.4%)	453 (1.4%)	305 (2.1%)	3150 (1.4%)
Not applicable	2570 (1.5%)	513 (1.6%)	240 (1.7%)	3323 (1.5%)
Stopped	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Contraindicated	338 (0.2%)	88 (0.3%)	32 (0.2%)	458 (0.2%)
Missing	151870 (89.2%)	29463 (90.1%)	12781 (88.8%)	194114 (89.3%)
Beta-blocker	9516 (5.6%)	1446 (4.4%)	598 (4.2%)	11560 (5.3%)
Not applicable	762 (0.4%)	144 (0.4%)	88 (0.6%)	994 (0.5%)
Contraindicated	153 (0.1%)	136 (0.4%)	74 (0.5%)	363 (0.2%)
Missing	151820 (89.2%)	29481 (90.2%)	12831 (89.1%)	194132 (89.3%)
Loop diuretic	5519 (3.2%)	1202 (3.7%)	490 (3.4%)	7211 (3.3%)

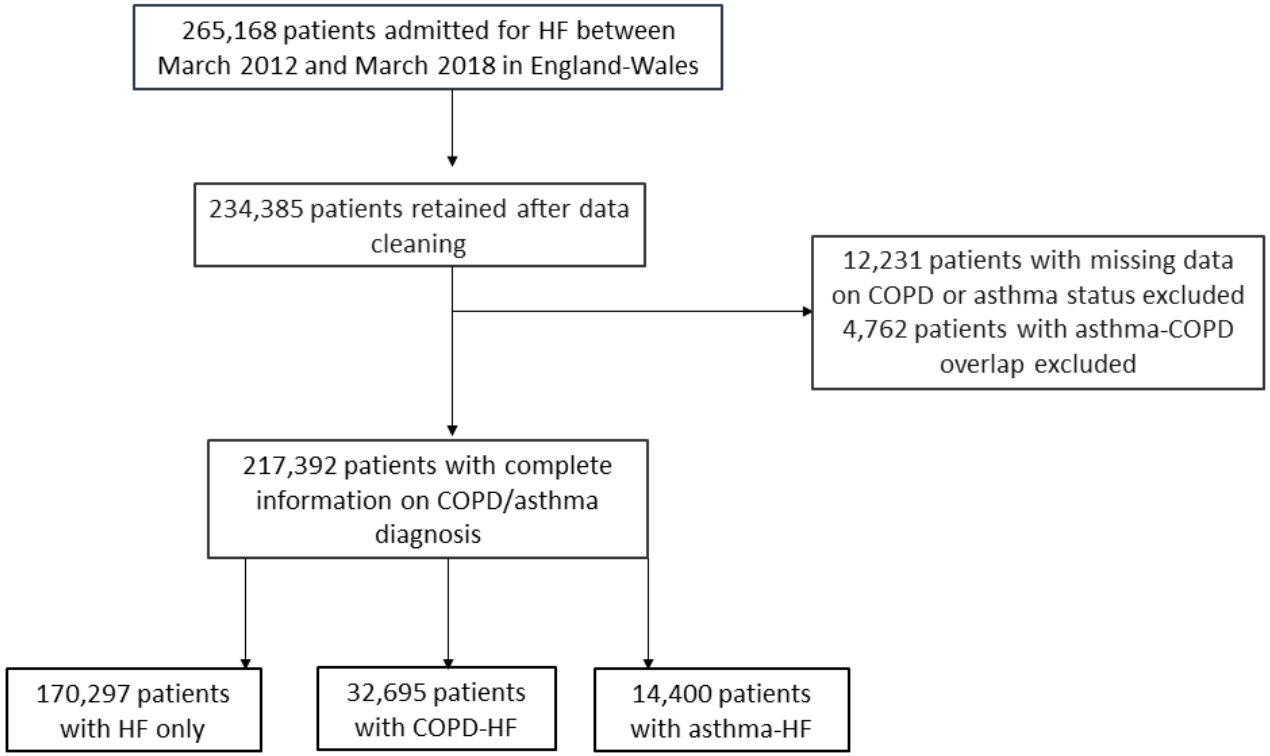
Missing	160255 (94.1%)	30820 (94.3%)	13532 (94.0%)	204607 (94.1%)
Thiazide or Metolazone	925 (0.5%)	140 (0.4%)	81 (0.6%)	1146 (0.5%)
Stopped*	-	-	-	-
Missing	152559 (89.6%)	29604 (90.5%)	12891 (89.5%)	195054 (89.7%)
MRA	2356 (1.4%)	502 (1.5%)	221 (1.5%)	3079 (1.4%)
Not applicable	225 (0.1%)	45 (0.1%)	27 (0.2%)	297 (0.1%)
Contraindicated	36 (0.0%)	*	*	42 (0.0%)
Missing	152494 (89.5%)	29570 (90.4%)	12885 (89.5%)	194949 (89.7%)
Digoxin	1700 (1.0%)	399 (1.2%)	168 (1.2%)	2267 (1.0%)
Missing	152631 (89.6%)	29622 (90.6%)	12874 (89.4%)	195127 (89.8%)
CCB	2847 (1.7%)	479 (1.5%)	280 (1.9%)	3606 (1.7%)
Missing	155279 (91.2%)	30261 (92.6%)	13150 (91.3%)	198690 (91.4%)
Bronchodilators	919 (0.5%)	1390 (4.3%)	750 (5.2%)	3059 (1.4%)
Missing	155316 (91.2%)	30248 (92.5%)	13136 (91.2%)	198700 (91.4%)
Ivabradine	186 (0.1%)	64 (0.2%)	31 (0.2%)	281 (0.1%)
Missing	153320 (90%)	29666 (90.7%)	12845 (89.2%)	195831 (90.1%)
BMI				
Median [Q1, Q3]	26.5 [22.9, 31.1]	27.1 [22.8, 32.2]	28.0 [23.6, 33.7]	26.7 [22.9, 31.4]
Missing	125287 (73.6%)	23693 (72.5%)	10274 (71.3%)	159254 (73.3%)
BNP				
Median [Q1, Q3]	428 [1.00, 1100]	350 [1.00, 985]	353 [1.00, 871]	412 [1.00, 1070]
Missing	153043 (89.9%)	29385 (89.9%)	12978 (90.1%)	195406 (89.9%)
NT_proBNP				
Median [Q1, Q3]	2790 [404, 7530]	2490 [349, 6820]	2440 [426, 6330]	2700 [393, 7320]
Missing	153022 (89.9%)	29161 (89.2%)	12818 (89.0%)	195001 (89.7%)

*not shown due to small numbers policy

ACEi= angiotensin-converting-enzyme inhibitors; ARB= angiotensin receptor blockers; BMI= Body mass index; BNP= brain natriuretic peptide; NT_proBNP= N-terminal (NT)-pro hormone BNP; MRA=mineralocorticoid receptor antagonist

Figure 1. Study flow

HF= heart failure; COPD=chronic obstructive pulmonary disease



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STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2,3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5,6
Objectives	3	State specific objectives, including any pre-specified hypotheses	5,6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6, 7, Supplement
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6, 7, Supplement
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7, 8, Supplement
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6, 7, Supplement*
Bias	9	Describe any efforts to address potential sources of bias	7, 8, 9, Supplement
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8, 9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8,9, Supplement
		(*b*) Describe any methods used to examine subgroups and interactions	8,9, Supplement
		(*c*) Explain how missing data were addressed	9, Supplement
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	6

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	9, Supplement
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6, Supplement flow chart
		(b) Give reasons for non-participation at each stage	Supplement flow chart
		(c) Consider use of a flow diagram	Supplement flow chart
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9, 10
		(b) Indicate number of participants with missing data for each variable of interest	20-22, Supplement
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	10-12
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	23, Supplement
		(*b*) Report category boundaries when continuous variables were categorized	9, 20-22
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10, Supplement
Discussion			
Key results	18	Summarise key results with reference to study objectives	12-16
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	18
Generalisability	21	Discuss the generalisability (external validity) of the study results	18
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	19

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Impact of COPD and asthma on in-hospital mortality and management of patients with heart failure in England and Wales: an observational analysis

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Title: Impact of COPD and asthma on in-hospital mortality and management of patients with heart failure in England and Wales: an observational analysis

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Abstract

Objective: To evaluate the association between having concomitant COPD or asthma, and in-patient mortality and post-discharge management among patients hospitalised for acute HF.

Setting: Data were obtained from patients enrolled in the National Heart Failure Audit.

Participants: 217,329 patients hospitalised for HF in England-Wales between March 2012 and 2018.

Outcomes: In-hospital mortality, referrals to cardiology follow-up and prescriptions for HF medications were compared between patients with comorbid COPD (COPD-HF) or asthma (asthma-HF) versus HF-alone using mixed-effects logistic regression.

Results: Patients with COPD-HF were more likely to die during hospitalisation, and those with asthma-HF had a reduced likelihood of death, compared with patients who had HF-alone ([adjusted]OR_{adj}, 95% CI: 1.10, 1.06-1.14 and OR_{adj}, 95%CI: 0.85, 0.79-0.88). In patients who survived to discharge, referral to HF follow-up services differed between groups: COPD-HF patients had reduced odds of cardiology follow-up (OR_{adj}, 95%CI 0.79, 0.77-0.81), whilst cardiology referral odds for asthma-HF were similar to HF-alone. Overall, proportions of HF medication prescriptions at discharge were low for both COPD-HF and asthma-HF groups, particularly prescriptions for beta-blockers.

Conclusions: In this nationwide analysis, we showed that COPD and asthma significantly impact the clinical course in patients hospitalised for HF. COPD is associated with higher in-patient mortality and lower cardiology referral odds, whilst COPD and asthma are both associated with lower use of prognostic HF therapies on discharge. These data highlight therapeutic gaps and a

need for better integration of cardiopulmonary services to improve healthcare provision for patients with HF and coexisting respiratory disease.

Keywords: heart failure, chronic obstructive pulmonary disease, asthma

Strengths and limitations

- This study evaluates the association between respiratory disease and in-hospital mortality and management outcomes in patients hospitalized with HF in a representative population from England and Wales.
- HF diagnosis was based either on diagnostic tests or clinical investigations which limited misclassification bias
- HF with preserved ejection fraction was an exclusion diagnosis (i.e., defined as HF in patients who did not have reduced ejection fraction) due to lack of information regarding specific diagnostic tests to confirm preserved ejection fraction status.
- There was a large proportion of missing data regarding bronchodilators and inhaled corticosteroids prescriptions which prevented evaluation of their impact on outcomes.

Introduction

COPD and asthma frequently coexist with HF and are independently associated with mortality and increased healthcare use[1 2]. This has been explained by shared systemic inflammation, worsened by the presence of pulmonary disease as well as sub-optimal HF management[3]. Evidence suggests that patients with HF and comorbid COPD are less likely to receive guideline recommended treatment for their HF. For example, beta-blockers which are used in the management of HF with reduced ejection fraction (HFrEF) are often not prescribed to patients with COPD, due to fear of bronchoconstriction[4], reduced effectiveness of emergency beta-agonist medication or difficulty in discriminating between COPD and asthma[5].

Less data exist on the relationship between asthma and HF. Some studies have shown that asthma is associated with an increased occurrence of cardiovascular disease whilst others suggest this is limited to women or smokers[6] and depends on age of asthma-onset[7]. This is further complicated by a component of chronic irreversible airflow obstruction in some people with long standing asthma, associated with a reduced response to asthma therapy[8]. This may, in turn, affect treatment choices in this group of patients and increase vulnerability to adverse events, versus either disease occurring alone. Meta-analyses and observational studies have suggested the use of beta-agonists or inhaled corticosteroids in both COPD and asthma has been associated with HF-onset, HF-related hospitalisation and increase in cardiovascular events[9-11], which depend on disease severity and study setting, but nevertheless worsen prognosis[1 7].

Our main aim was to compare in-hospital mortality and post-discharge HF management (referrals to HF services, discharge medication) among patients admitted to hospital with

decompensated HF, with and without COPD or asthma in a sample of patients from the National Heart Failure Audit (NHFA) from England and Wales. We also investigated whether ejection fraction (EF) status affects outcomes in these patient groups.

Methods

We included patients older than 18 years of age admitted to hospital for HF between March 2012 to April 2018 whose data were submitted to the NHFA. We considered their first HF hospitalisation only (**Supplemental Methods, Supplemental Table 1**).

Exposures

COPD was defined as having a history of COPD - chronic bronchitis and/or emphysema, confirmed by spirometry or beta agonist/steroid inhaler use.

Asthma was defined as having a history of childhood asthma and atopy or having an asthma diagnosis confirmed by a respiratory physician.

No diagnostic test results were provided for COPD or asthma (**Supplemental Table 2**), and for the purposes of this work were based on being recorded as “yes” (present) or “no” (absent) in the audit data as defined above.

EF status was defined as HFrEF and HF with preserved EF (HFpEF), determined through echocardiography, MRI, nuclear scan, or angiogram. Those with an EF <40% were categorised HFrEF. Due to a lack of information regarding specific diagnostic tests required to make a HFpEF diagnosis, we determined HFpEF as patients not categorised as HFrEF[12].

Covariates were age, sex, New York Heart Association [NYHA] classification and place of care (cardiology ward vs. other place of care [i.e., general ward]) and comorbidities (atrial fibrillation [AF], ischemic heart disease [IHD], diabetes, valve disease, hypertension [**Supplementary Table 2**]).

Outcomes

Our primary outcome was in-hospital death during the index event (HF admission), defined as a dichotomised variable (died/alive at discharge), according to COPD or asthma status. Secondary analyses included post-discharge referral to HF services (cardiology, HF nurse, HF MDT [multidisciplinary team]) and prescriptions for HF medications at discharge in those with HFrEF.

Statistical analysis

Differences in baseline characteristics between patients with COPD-HF/Asthma-HF and HF alone are presented using percentages for categorial variables and medians and interquartile ranges [IQR] for continuous variables. We assessed differences between groups using chi-square and Kruskall-Wallis tests. We assessed differences in outcomes between patients with COPD-HF compared with HF alone and between asthma-HF compared with HF-alone using multilevel logistic regression with a random effect for hospital, to calculate odds ratios (OR) and 95% confidence intervals (CI) **(Supplemental Methods).** In the main analysis, we adjusted for confounders with less than 20% missing data: age, sex, comorbidities, place of care and NYHA status. The model building process is presented in **Supplementary Table 3**. Analyses of referrals were conducted similarly and excluded patients who died in-hospital. Associations between COPD or asthma and HF medication prescriptions at discharge (beta blockers, angiotensin-

converting-enzyme inhibitors [ACEis], angiotensin receptor blockers [ARBs] and mineralocorticoid receptor antagonists [MRAs]) excluded those with HFpEF.

Sensitivity analyses

Due to potential confounding, smoking and Body Mass Index (BMI) were multiply imputed using a multilevel approach (**Supplemental methods**). We also repeated the main analysis in a cohort of patients including only a "confirmed HF diagnosis" (ICD-10 HF diagnosis confirmed by imaging/BNP testing, or adjudicated by a clinician in the absence of echocardiography)[13].

Analyses were performed with R v4.0.3.

Results

Baseline characteristics are presented in **Table 1**. In total, 217,329 patients were admitted to hospital in England-Wales due to decompensated HF between 2012 and 2018, with data on COPD/asthma status available **(Supplemental Figure 1).** The median age was 81 years (IQR 72-87) and 53.7% were male. In-hospital death occurred in 12% of patients. COPD was diagnosed in 15% of patients and asthma in 6.6%. Most patients were characterised by either marked or severe breathlessness and half had a recorded HF management plan in place at discharge. Length of stay and deprivation ranking did not differ significantly between patients with COPD-HF, asthma-HF and HF alone. COPD-HF patients were mostly male, were less often admitted to cardiology and were more frequently diagnosed with IHD compared with those with HF alone; hypertension was slightly less common among COPD-HF patients, whereas diabetes was more common. The proportion of patients with HFpEF was marginally higher in the COPD-HF group, compared with the HF-only group. Asthma-HF patients were mostly female, with higher levels

of diabetes and hypertension compared to HF-only. Conversely, AF was less common in the asthma-HF compared with the HF-alone group; there were also more patients with HFpEF.

In-hospital death

The association between COPD and in-hospital death, is presented in **Figure 1, Table 2, and Supplementary Table 4.** Overall, COPD was independently associated with increased odds of in-hospital death ([adjusted]OR_{adj}, 95% CI: 1.10, 1.06-1.14). The relationship between COPD and in-hospital death differed according to EF: COPD was associated with an increase in mortality in patients with HFrEF (OR_{adj}: 1.15, 1.09 – 1.21), but not in those with HFpEF (OR_{adj}: 1.05, 0.99–1.10).

Conversely, asthma was associated with a decrease in the odds of in-hospital death compared with HF patients without asthma (OR_{adj}, 95%CI: 0.85, 0.79-0.88). The odds of death did not vary by EF status for patients with asthma-HF **(Figure 1, Table 2).**

Sensitivity analyses where smoking status and BMI were imputed due to missing data (**Supplementary Table 5**), and where patients with a confirmed HF diagnosis only were included (**Supplementary Table 6**), showed similar results to the main analysis.

Referrals to HF services

In the fully adjusted models, COPD was associated with decreased likelihood of outpatient referral to a cardiologist (OR_{adj}, 95%CI 0.79, 0.77-0.81) and to a HF-MDT (OR_{adj}, 95% CI 0.94, 0.91-0.97). Patients with COPD-HFrEF were less likely to be referred to a cardiologist than those with HFrEF without COPD (OR_{adj}: 0.85, 95% CI 0.81-0.88) while patients with COPD-HFpEF were

significantly less likely to be referred, compared to HFpEF without COPD (OR_{adj}, 95CI% 0.73, 0.70-0.76). COPD was associated with a decreased likelihood of documented HF-MDT referral only for patients with HFpEF (OR_{adj}, 95%CI, 0.90, 0.86-0.94).

Overall, referral odds did not differ in patients with asthma-HF compared to those with HF-alone. There was a significant increase in the odds of referral to a cardiologist for those with asthma-HFrEF (OR_{adj}, 95%CI 1.08, 1.03-1.14) and a decreased likelihood of referral for patients with asthma-HFpEF (OR_{adj} 95CI, 0.93, 0.88-0.98), compared to HFrEF, HFpEF-alone, respectively. Referrals to HF nurse or HF MDT were not different between those with HF alone or HF and asthma **(Figure 2).**

HF medication prescription at discharge

Patients with COPD-HF had lower prescription proportions of ACEIs/ARBs, beta-blockers and double (ACEi/ARB+beta-blocker) and triple-therapy (ACEi/ARB+beta-blocker+MRA) compared to those with HF-only. ACEIs/ARBs, MRAs and triple-therapy were prescribed more frequently in the asthma-HF group compared with the HF-alone group; however beta-blockers or double-therapy were less often prescribed for asthma-HF vs. HF-alone **(Figure 3).**

In patients with HFrEF, COPD and asthma were associated with decreased likelihood of beta-blocker prescription at discharge (OR_{adj} 0.66, 95%CI 0.59-0.67, OR_{adj}: 0.57, 95%CI 0.54-0.60). COPD was associated with lower chance or ACEi/ARB prescription, but did not affect MRA prescriptions, while asthma was associated with increased odds of ACEi/ARB and MRA **(Table 3).**

Discussion

This is the first study to provide a large assessment of contemporary HF practice, generalisable to the population of England-Wales, evaluating the effect of COPD and asthma on clinical and management outcomes. We found that patients with COPD-HF were more likely to die during their HF admission, compared to patients with HF-only; those with asthma-HF had a reduced probability of in-hospital death, compared to patients with HF-alone. Referrals to HF services also differed: COPD was associated with a 21% reduction in post-discharge cardiology referral whilst a diagnosis of asthma did not affect this outcome.

Airways diseases, particularly COPD is associated with adverse events in patients with HF[1-3 14-16], however diagnostic misclassification is under-estimated and studies of the independent effect of asthma are lacking. We report several findings which add to previous literature.

The finding that COPD is associated with in-hospital mortality confirms reports from previous European data which considered longer term follow-ups[17 18]. A greater severity of cardiovascular disease amongst those with COPD-HF may have contributed to the increase in mortality, as indicated by the higher proportions of patients in NYHA classes III and IV, compared with those with HF alone. Further explanations could include admission to non-cardiology wards for COPD-HF patients, which has been linked with poorer outcomes in acute HF[19].

A COPD diagnosis was associated with increased in-hospital death in those with HFrEF, but not in those with HFpEF, which is surprising, given that COPD is suggested to be more severe in the latter group[20]. In contrast with our report, previous studies found that risk of death is increased in those with COPD-HFpEF compared to COPD-HFrEF[21 22], however these may be confounded by a lack of validity of EF status (inferred by ICD codes rather than echocardiography) or

spirometry to confirm COPD status, consideration of long-term rather than short term effects on mortality, or by including chronic rather than hospitalised HF. Our result therefore may be explained by poor uptake of disease-modifying treatments available for HFrEF in those with COPD[17], which has been previously reported and could be more pronounced in a cohort of patients newly admitted for HF.

After adjusting for age, sex and other baseline characteristics including comorbidities, and further adjustments for smoking status and BMI, differences between those with and without COPD, respectively asthma, did not materially change the association between the two lung diseases with in-hospital mortality. This suggests an independent contribution of COPD to increased mortality in patients hospitalised with HF, significant beyond the potential confounders considered in this analysis.

While previous reports suggest asthma is associated with increased risk of developing cardiovascular disease[6], no prior study has reported on the association between asthma and death during acute HF hospitalisation. We found that, on average, asthma was independently associated with a 24% reduction in risk of death in patients with HF. The mechanisms underlying this epidemiological association are unclear. Several factors may explain our result. Asthma management is reliant on anti-inflammatory agents such as inhaled corticosteroids (ICS), which have been linked to cardioprotective effects[23 24] including lower all-cause mortality and lower risk of myocardial infarction ([MI], a precursor to HF). Potential long-term ICS use in our asthma-HF cohort could have diminished patients' baseline mortality risk.

The nature of inflammation is different in COPD compared with asthma, and influences response to medication. One hypothesis which may underlie the diverging findings on the

effect of the two lung diseases on outcomes in patients with HF thus relates to differences in management and their subsequent differential cardiovascular risk. Bronchodilator medications, which are central to the symptomatic treatment of COPD, have been associated with increased cardiovascular risk[9]. While combination treatments such as ICS/LABA may have a good cardiovascular safety profile in asthma, this differs in COPD[8 16]. RCTs have not demonstrated mortality benefits with ICS in individuals with COPD, although some observational studies suggest the opposite. The largest trial[25] examining all-cause mortality in 16,000 patients with COPD and risk of cardiovascular disease showed the treatments evaluated (long-acting beta-agonists and/or inhaled corticosteroids) were well tolerated by patients, however the effect on patients with existing HF remains under debate.

Since both lung diseases were diagnosed prior to HF admission, it would be plausible to assume that any effects of long-term pulmonary medication could influence the chance of death in our cohort. Thus, the heightened risk of in-hospital mortality observed in the COPD-HF group, but not in asthma-HF could be related to more frequent use of bronchodilators and a poorer safety profile of ICS in COPD compared to asthma. Alternatively, COPD-specific characteristics such as such as progressive lung function decline may have influenced in-hospital mortality in those admitted for HF.

However, due to large amounts of missing data on respiratory disease medication prescription in our cohort (**Supplemental Table 7**), we could not verify these assumptions in our dataset. Future studies incorporating accurate information on bronchodilator use in patients with concomitant HF and respiratory disease should be conducted.

The association between COPD/asthma and referral to follow-up cardiology services has not been studied before in hospitalised HF patients. Overall, patients with COPD-HF were less likely to be referred to a cardiology service after hospital discharge, compared with those who had HF-alone. This indicates that a COPD diagnosis may be an obstacle preventing access to HF specialist care. According to NICE, all patients with a HF diagnosis need to be seen by a HF specialist within two weeks of discharge, but data suggest these timelines are not met[26]. The compounded effect of a COPD diagnosis has the potential to further impair the long-term prognosis of these comorbid patients. Further, more than 60% of patients with COPD and HF were admitted to a general ward rather than a specialised cardiology ward, which may also explain the low likelihood of cardiology referrals in this group.

Our study also indicated EF status mediated the relationship with referrals, as individuals with COPD-HFpEF were less likely to have an appointment compared with their COPD-HFrEF counterparts. This is particularly worrying as HF, irrespective of EF, is best monitored and managed within specialist HF teams.

Asthma did not adversely influence referrals to HF services, but we identified an increased likelihood of referral to cardiology in asthma-HFpEF as compared with asthma-HFrEF. One possible explanation is greater uncertainty in clinical management of patients with HFpEF, leading to increased referral, though this needs to be assessed in future studies. Clarifying these clinical management pathways offers a potential to improve HF prognosis by ensuring access to care is timely and tailored to individual patients' risk, pathology, and health.

Patients with COPD-HFrEF were 34% less likely to receive a beta-blocker prescription at discharge, compared with patients with HFrEF alone, despite recent data supporting use of these agents in COPD[27 28]. Similar to data on patients post-MI[29], it is worrying that COPD was also associated with decreased likelihood of guideline recommended ACEi/ARB prescription in those with HF, as there is no contraindication for those with pulmonary disease. Efforts need to be made to ensure appropriate therapeutic management of these patients.

Those with asthma-HFrEF had 43% less chance of being prescribed a beta-blocker compared with patients with HF-alone. Current guidelines recommend that asthma patients with chronic HFrEF should not receive disease-modifying beta-blocker treatment due to possible bronchoconstriction, despite evidence to suggest that cardioselective beta-blockade may be used with careful up-titration and monitoring[30 31], where benefits may outweigh risks in individual patients. Based on the low uptake across the whole spectrum of HF medications in patients with additional lung disease (**Figure 3**), we expect these patients would have worse prognosis compared to their more adequately treated counterparts.

Considering these results, management needs to be optimized in patients with COPD or asthma and concurrent HF. The arrival of new treatments such as sodium-glucose co-transporter 2 inhibitors (SGLT2-i) have widened treatment choice in HFrEF, and there is now evidence supporting their use in individuals with COPD[32]. Given beta-blockers are avoided in asthma, these new treatments should urgently be assessed in this population, as data are currently lacking.

Strengths and limitations

The main strength of this study is the large sample size and representativeness of a hospitalised population with HF from England and Wales. We did not have however have information on duration and severity of asthma or COPD, nor lung function test results and thus we could not verify accuracy of these diagnoses, which are often subject to misclassification, especially in the elderly[33]. Data on bronchodilator use was largely missing for our cohort (**Supplemental Table 7**), limiting assessment of both diagnostic accuracy of the respiratory diseases, and association with outcomes evaluated in this study. We also could not differentiate between childhood asthma or late-onset asthma which may have different implications [34].

HFpEF was determined as a HF diagnosis without systolic dysfunction, which has been used in previous NHFA reports. Nevertheless, there is no consensus gold standard HFpEF diagnosis[12] and it remains difficult to validate. Further work in this area is needed, particularly in accurately distinguishing between HFpEF and COPD, which have similar clinical presentation.

There was a considerable proportion of missing data on bronchodilators/inhaled corticosteroids in the dataset which prevented assessment of whether the impact of COPD and asthma on outcomes is mediated, in part, by their treatment. Future studies incorporating accurate information on bronchodilator use in patients with concomitant HF and respiratory disease should be conducted.

Smoking status was also characterised by a large percentage of missing data, however an analysis using multiple imputation indicated that even after adjusting for this confounder in the imputed dataset, the association between both COPD and asthma on in-hospital mortality remained unchanged. **(Supplementary Table 5).**

We only focused on decompensated HF and the picture may change when investigating long-term mortality, recurrent admissions, or other aspects of treatment such as medication adherence.

While the referral likelihood estimates provide a first glimpse into the association between COPD/asthma and potential healthcare service provision for HF patients in England-Wales, we did not have access to data on concrete healthcare utilisation amongst our cohort.

Due to lack of data, we could not establish whether cause of death varied amongst the groups and whether the increased mortality associated with COPD was underlined by higher rates of respiratory versus cardiac or other disease.

Conclusion

This analysis adds to the growing body of evidence that COPD and asthma affect outcomes in patients with acute HF. Our data suggest that while COPD is a main contributor to in-hospital mortality and is associated with decreased referral to cardiology services amongst HF patients, asthma does not negatively impact these outcomes. Both lung diseases are however responsible for significant decreases in the prescription of HF treatments at discharge, particularly beta-blockers. These findings highlight a need for better integration of cardiopulmonary services with an aim to tailor healthcare provision for these patients.

Competing interests

CG, CK and RZ have nothing to declare. Prof. Quint's research group has received funds from AZ, GSK, The Health Foundation, MRC, British Lung Foundation, IQVIA, Chiesi, and Asthma UK outside

the submitted work; grants and personal fees from GlaxoSmithKline, Boehringer Ingelheim, AstraZeneca, Bayer, Insmed outside the submitted work.

Data availability

The data that support the findings of this study have been provided by the Healthcare Quality Improvement Partnership from the National Heart Failure Audit Programme, but restrictions apply to the availability of these data and so are not publicly available.

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Author contributions

Conceptualization & Methodology: CG, JKQ, CK. Original draft: CG. Editing and final approval: CG, JKQ, RZ, CK; Data curation & Formal data analysis: CG; Data acquisition: JKQ.

Ethics approval

This study involved analysis of pre-existing, de-identified data, thus it was exempt from Institutional Review Board approval.

Patient and public involvement

Patients were not involved in the design and conduct of the study.

Figure legends

Figure 1 - Association between COPD, asthma and in-hospital death, adjusted for age, sex, valve disease; IHD, hypertension, diabetes, AF, NYHA, place of care and EF status; odds ratio with 95% confidence intervals.

Figure 2. Association between COPD, asthma and referrals to HF services, adjusted for age, sex, valve disease; IHD, hypertension, diabetes, AF, NYHA, place of care and EF status.

Figure 3. HF-medication prescription rates at discharge, according to comorbid respiratory disease status

Table 1. Baseline characteristics according to COPD and asthma status, in patients hospitalised for HF in England-Wales.

	HF alone (N=170297)	COPD + HF (N=32695)	Asthma + HF (N=14400)	Overall (N=217,392)
Age, median [IQR]	81 [72, 88]	79 [72, 85]	79 [69, 86]	81 [72, 87]
Missing	67 (0.1%)	22 (0.1%)	10 (0.1%)	199 (0.1%)
Male	91837 (53.9%)	19072 (58.3%)	5936 (41.2%)	116845 (53.7%)
Missing	74 (0.1%)	44 (0.1%)	21 (0.1%)	239 (0.1%)
Place of admission				
Cardiology	76428 (44.9%)	12361 (37.8%)	6147 (42.7%)	94936 (43.7%)
Other	93358 (54.8%)	20246 (61.9%)	8218 (57.1%)	21822 (56.0%)
Missing	511 (0.3%)	88 (0.3%)	35 (0.2 %)	634 (0.3%)
Died in-hospital	20316 (11.9%)	4181 (12.8%)	1337 (9.3%)	25834 (11.9%)
Device therapy				
None	147485 (86.6%)	28962 (88.6%)	12818 (89.0%)	189265 (87.1%)
CRT-D	3047 (1.8%)	496 (1.5%)	189 (1.3%)	3732 (1.7%)
CRT-P	1681 (1%)	296 (0.9%)	142 (1%)	2119 (1.0%)
ICD	3001 (1.8%)	511 (1.6%)	211 (1.5%)	0 (0%)
Missing	15083 (8.9%)	2430 (7.4%)	1040 (7.2%)	18553 (8.5%)
Comorbidities				
Valve disease	38213 (22.4%)	7005 (21.4%)	2906 (20.2%)	48124 (22.1%)
Missing	3426 (2.0%)	822 (2.5%)	335 (2.3%)	4583 (2.1%)
IHD	65992 (38.8%)	14198 (43.4%)	5175 (35.9%)	85365 (39.3%)
Missing	3667 (2.2%)	811 (2.5%)	335 (2.3%)	4813 (2.2%)
Hypertension	91477 (53.7%)	16838 (51.5%)	8208 (57%)	116523 (53.6%)
Missing	1326 (0.8%)	381 (1.2%)	125 (0.9%)	1832 (0.8%)
Diabetes	50194 (29.5%)	10348 (31.7%)	4772 (33.1%)	65314 (30%)
Missing	459 (0.3%)	142 (0.4%)	54 (0.4%)	655 (0.3%)
AF	72235 (42.4%)	13728 (42%)	5508 (38.2%)	91471 (42.1%)
Breathlessness (NYHA)				
No limitation of physical activity	12273 (7.2%)	1254 (3.8%)	768 (5.3%)	14295 (6.6%)
Slight Limitation of ordinary physical activity	24541 (14.4%)	3951 (12.1%)	1993 (13.8%)	30485 (14.%)
Marked Limitation of ordinary physical activity	68179 (40%)	13671 (41.8%)	6011 (41.7%)	87861 (40.4%)
Symptoms at rest or minimal activity	54652 (32.1%)	12191 (37.3%)	4809 (33.4%)	71652 (33%)
Missing	10652 (6.3%)	1628 (5.0%)	819 (5.7%)	13099 (6.0%)
Echocardiography performed	137955 (81%)	26165 (80%)	11342 (78.8%)	175462 (80.7%)
Ejection fraction status				
HFrEF	92619 (54.4%)	16408 (50.2%)	7334 (50.9%)	116361 (53.5%)

	HF alone (N=170297)	COPD + HF (N=32695)	Asthma + HF (N=14400)	Overall (N=217,392)
HFpEF	77678 (45.6%)	16287 (49.8%)	7066 (49.1%)	101031 (46.5%)
HF management plan				
Pre-discharge management plan in place	11760 (6.9%)	2152 (6.6%)	1002 (7.0%)	14914 (6.9%)
Management plan has been discussed with the patient	10572 (6.2%)	1894 (5.8%)	954 (6.6%)	13420 (6.2%)
Management plan has been communicated to the primary care team	19880 (11.7%)	3963 (12.1%)	1780 (12.4%)	25623 (11.8%)
All of the above	83507 (49%)	15496 (47.4%)	7140 (49.6%)	106143 (48.8%)
No plan	18021 (10.6%)	3937 (12.0%)	1546 (10.7%)	23504 (10.8%)
Missing	26557 (15.6%)	5253 (16.1%)	1978 (13.7%)	33788 (15.5%)
Referral to HF MDT	53898 (31.6%)	9719 (29.7%)	4455 (30.9%)	68072 (31.3%)
Missing	29946 (17.6%)	5722 (17.5%)	2216 (15.4%)	37884 (17.4%)
Referral to cardiology follow up	70925 (41.6%)	11875 (36.3%)	6241 (43.3%)	89041 (41%)
Missing	13827 (8.1%)	2882 (8.8%)	984 (6.8%)	17693 (8.1%)
Referral to HF nurse follow-up	76170 (44.7%)	13728 (42.0%)	6249 (43.4%)	96147 (44.2%)
Missing	13442 (7.9%)	2658 (8.1%)	952 (6.6%)	17052 (7.8%)
LOS				
Median [IQR]	8 [3, 15]	8 [4, 16]	7 [3, 14]	8 [4, 15]
IMD Wales (quartile)	**N=8205**	**N=1889**	**N=776**	**N= N=10870**
1st (most deprived)	2126 (25.9%)	371 (19.6%)	188 (24.2%)	2685 (24.7%)
2nd	2058 (25.1%) 396	(21.0%) 190	(24.5%) 83	2644 (24.3%)
3rd	1977 (24.1%)	459 (24.3%)	196 (25.3%)	2632 (24.2%)
4th (least deprived)	1824 (22.2%)	607 (32.1%)	185 (23.8%)	2616 (24.1%)
Missing*	-	-	-	-
IMD England (quartile)	**N=159540**	**N=30352**	**N=13433**	**N=203325**
1st (most deprived)	35836 (22.5%)	9338 (30.8%)	3449 (25.7%)	48623 (23.9%)
2nd	38347 (24.0%)	7762 (25.6%)	3403 (25.3%)	49512 (24.4%)
3rd	40131 (25.2%)	6848 (22.6%)	3166 (23.6%)	50145 (24.7%)
4th (least deprived)	41387 (25.9%)	5615 (18.5%)	3072 (22.9%)	50074 (24.6%)
Missing	3839 (2.4%)	789 (2.6%)	343 (2.6%)	4971 (2.4%)

AF= atrial fibrillation; COPD= chronic obstructive pulmonary disease; CRT-P= cardiac resynchronisation therapy pacemaker; CRT-D= cardiac resynchronisation therapy defibrillator, HF= heart failure; HFrEF= heart failure with reduced ejection fraction; *HFpEF= heart failure with preserved ejection fraction; ICD= implantable cardioverter defibrillator; IHD= ischemic heart; disease; IMD= indices of multiple deprivation; LOS= length of stay; MDT= multi-disciplinary team; NYHA = New York Heart Association; * not shown due to small numbers.

Table 2 – Association between COPD, asthma and outcomes in patients hospitalised for HF in England-Wales

	Fully adjusted[a] interaction model COPD*EF OR (95% CI)		Fully adjusted[b] interaction model Asthma*EF OR (95% CI)	
Outcome	COPD * HFrEF	COPD* HFpEF	Asthma * HFrEF	Asthma * HFpEF
In-hospital death (N= 194,156[c])	Interaction *P*-value = 0.01		Interaction *P*-value = 0.842	
Fixed-effects	1.15 (1.09 – 1.21, p=0.294*10^{-10})	1.05 (0.99 – 1.10, p=0.081)	-	-
Random effects (hospitals, n=216)				
Variance	*0.201*		-	
LR test P-value[d]	*P=0.22*10^{-16}*		-	-
Referral to cardiology follow-up (N= 166,658[c])	Interaction *P*-value= 0.288*10^{-7}		Interaction *P*-value=0.0001	
Fixed effects	0.85 (0.81, 0.88, p=0.2*10^{-16})	0.73 (0.70, 0.76, p=0.2*10^{-16})	1.08 (1.03-1.14, p=0.2*10^{-16})	0.93 (0.88- 0.98, p=0.003)
Random effects (hospitals, n=216)				
Variance	*0.512*		*0.512*	
LR test p-value[d]	*0.22*10^{-16}*		*P=0.22*10^{-16}*	
Referral to HF MDT (N=149,098[c])	Interaction *P*-value = 0.017		Interaction *P*-value=0.095	
Fixed effects	0.97 (0.93, 1.02, p=0.263)	0.90 (0.86, 0.94, p=0.265*10^{-5})	-	-
Random effects (hospitals, n=216)				
Variance	*2.139*		-	-
LR test p-value[d]	*0.22*10^{-16}*		-	-
Referral to HF nurse (N= 166,723[c])	Interaction *P*-value = 0.249		Interaction *P*-value = 0.450	

COPD= chronic obstructive pulmonary disease; HF= heart failure; HFrEF= heart failure with reduced ejection fraction; HFpEF= heart failure with preserved ejection fraction; LR= likelihood ratio; MDT= multidisciplinary team; OR= odds ratio; CI= confidence interval

[a] Adjusted for age, sex, diabetes, hypertension, ischemic heart disease, atrial fibrillation, asthma, place of care and New York Heart Association status

[b] Adjusted for age, sex, diabetes, hypertension, ischemic heart disease, atrial fibrillation, COPD, place of care and New York Heart Association status

[c] Excludes patients with missing data on covariates included in model

[d] Likelihood ratio test comparing fixed to random effects for hospital model fit, significant indicates random effects model performed better than fixed effects model

Table 3. Association between COPD, asthma and HF medication prescription at discharge, in patients with HFrEF

Medication prescription at discharge	COPD unadjusted OR (95%CI)	COPD fully adjusted[a] OR (95%CI)	Asthma unadjusted OR (95%CI)	Asthma fully adjusted[b] OR (95%CI)
Beta-blockers (N= 86449[a,b])				
Fixed effects	0.61 (0.58, 0.64, p=$0.22*10^{-16}$)	0.66 (0.64, 0.68, P=$0.22*10^{-16}$)	0.63 (0.59, 0.67, p=$0.22*10^{-16}$)	0.57 (0.54 0.60, p=$0.22*10^{-16}$)
Random effects				
Variance	*0.553*	*0.578*	*0.549*	*0.578*
LR test p-value	$0.22*10^{-16}$	$0.22*10^{-16}$	$0.22*10^{-16}$	$0.22*10^{-16}$
ACEis/ARBs (N=96080 [a,b])				
Fixed effects	0.87 (0.84, 0.90, p=$0.139*10^{-13}$)	0.91 (0.87-0.95, p=$0.256*10^{-6}$)	1.13 (1.07, 1.19, p=$0.16*10^{-6}$)	1.07 (1.01, 1.13, p=0.0143)
Random effects				
Variance	*0.149*	*0.130*	*0.148*	*0.130*
LR test p-value	$0.22*10^{-16}$	$0.22*10^{-16}$	$0.22*10^{-16}$	$0.22*10^{-16}$
MRA (N=96080 [a,b])				
Fixed effects	0.97 (0.94, 1.01, p=0.114)	1.02 (0.98, 1.06, p=0.268)	1.08 (1.04, 1.13, p=0.00043)	1.07 (1.02, 1.12, p= 0.0084)
Random effects				
Variance	*0.232*	*0.195*	*0.226*	*0.195*
LR test p-value	$0.22*10^{-16}$	$0.22*10^{-16}$	$0.22*10^{-16}$	$0.22*10^{-16}$

Abbreviations
COPD= chronic obstructive pulmonary disease; OR= odd ratio; CI= confidence intervals; LR= likelihood ratio
[a]Adjusted for age, sex, diabetes, hypertension, ischemic heart disease, atrial fibrillation, asthma, place of care and New York Heart Association status
[b]Adjusted for age, sex, diabetes, hypertension, ischemic heart disease, atrial fibrillation, COPD, place of care and New York Heart Association status
Likelihood ratio test comparing fixed to random effects for hospital model fit, significant indicates random effects model performed better than fixed effects model

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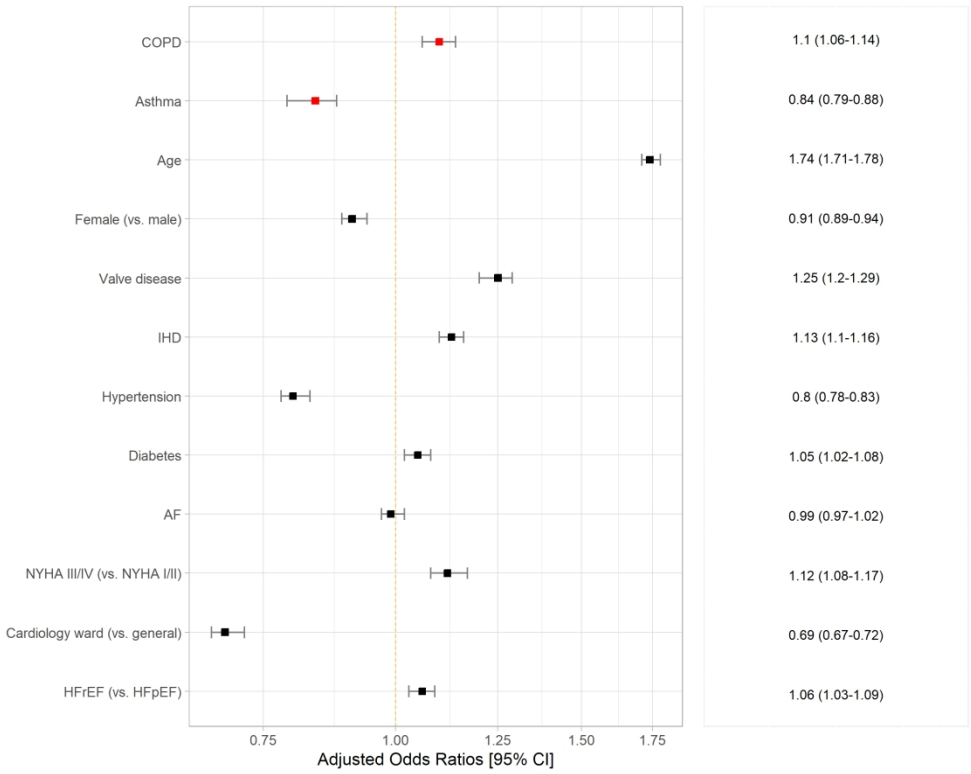


Figure 1 - Association between COPD, asthma and in-hospital death, adjusted for age, sex, valve disease; IHD, hypertension, diabetes, AF, NYHA, place of care and EF status; odds ratio with 95% confidence intervals.

581x452mm (118 x 118 DPI)

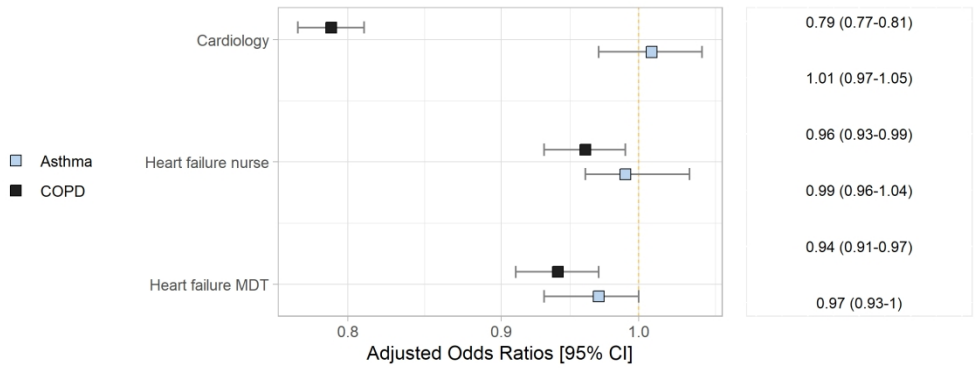


Figure 2. Association between COPD, asthma and referrals to HF services, adjusted for age, sex, valve disease; IHD, hypertension, diabetes, AF, NYHA, place of care and EF status.

516x193mm (118 x 118 DPI)

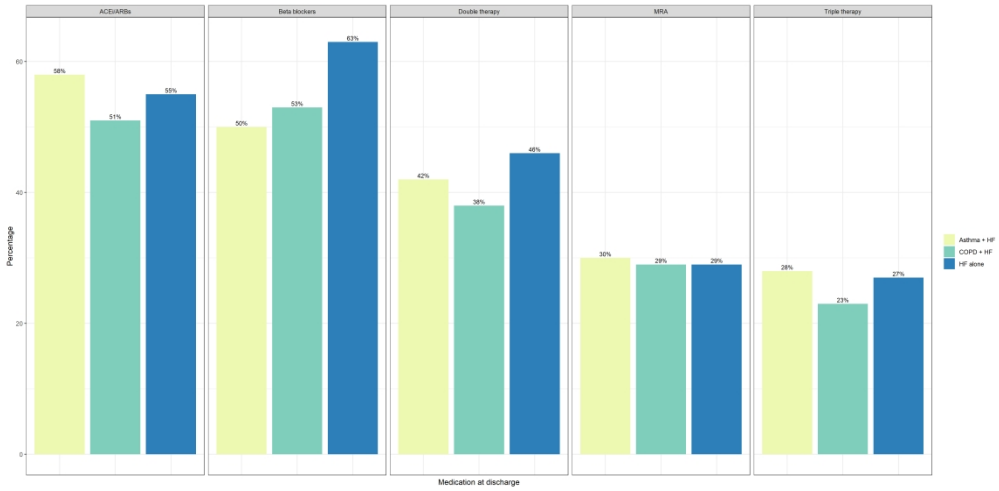


Figure 3. HF-medication prescription rates at discharge, according to comorbid respiratory disease status

1291x645mm (118 x 118 DPI)

Supplemental Material

Supplemental Methods

Data source

The NHFA was established in 2007 for hospitals in England-Wales to assess the quality of care and outcomes of hospitalised patients with a HF diagnosis in the first position at death or discharge, identified using ICD-10 codes (**Supplementary Table 1**). Admissions coded in the audit are compared to HF episodes in the Hospital Episode Statistics (HES) in England and the Patient Episode Database of Wales (PEDW) to determine the case ascertainment rate. The number of participating NHS trusts fluctuated from 145 in 2012–13 (97%) to 136 (82%) in 2017/2018. This corresponds to an increase from capturing 60% of national HF admissions in 2012, to 76% at the end of April 2018. Data are entered into the audit by hospital staff, using case ascertainment forms and data are categorised as mandatory (main indicators such as HF treatments, comorbidities, echocardiography) or non-mandatory (i.e., smoking status, pulmonary oedema, ethnicity). Since non-mandatory data elements are not expected to be included, there are considerable proportions of missing data across these variables (**Supplemental Table 2**). Some mandatory variables also have significant amounts of missing data (e.g., more than 70% missing data on BNP measurements, weight, height). The breadth of variables collected varied throughout the history of the audit, to reflect changes in HF guidelines and quality standards, which evolved over time. For example, haemoglobin and serum creatinine were collected routinely only after 2012[1].

Statistical analysis

The analysis for the main outcome was implemented in a stepwise manner. First, an unconditional model including, COPD was considered. In a second step we added asthma. Third, we added an interaction term between COPD and asthma, to assess whether both diagnoses had a significant contribution to the model. In lack of statistical significance these patients were not considered in further analyses. We then evaluated effect modification by EF status (HFrEF/HFpEF) by including separately an interaction term between COPD and EF, then asthma and EF.

Handling of missing data

Sensitivity analysis – missing data imputation

While the proportions of missing data (see above) were considerable, we deemed necessary to investigate further two important factors: “smoking status” and “Body Mass Index (BMI)”. In particular, we were interested in assessing whether COPD has an independent association with death in patients with HF, when controlling for smoking status, or whether the relationship is influenced by this factor.

We assumed data on smoking and BMI to be missing at random in our cohort, as the distribution in observed cases was similar to other UK cohorts of patients with HF[2 3]. We then used a multi-level approach[4] which takes into consideration the hierarchical data structure, clustered at hospital level. A Gibbs sampling procedure was used to generate 20 imputed data sets after a burn-in of 1000 iterations.

Table 1. Inclusion criteria for National Heart Failure Audit

ICD-10 code	Diagnosis
I11.0	Hypertensive heart disease with (congestive) heart failure
I25.5	Ischaemic cardiomyopathy
I42.0	Dilated cardiomyopathy
I42.9	Cardiomyopathy, unspecified
I50.0	Congestive heart failure
I50.1	Left ventricular failure
I50.9	Heart failure, unspecified
ICD= International Statistical Classification of Diseases and Related Health Problems	

Table 2. Comorbidity definitions, according to NHFA dataset[1], variables recorded from patient history

COPD	History of COPD - chronic bronchitis, emphysema or their cooccurrence. Must be indicated by pulmonary function testing evidence .ie FEV1<75% predicted value or use of beta agonist/steroid inhalers.
Asthma	History of childhood asthma and atopy, or asthma confirmed by respiratory physician for adult onset.
Diabetes	Diagnosis of diabetes prior to admission. This includes a confirmed diagnosis of diabetes and/or the use of an oral hypoglycaemic agent or insulin, and/or a fasting blood glucose >6.7, and/or a random blood glucose >11.
Hypertension	Recorded Blood Pressure >140/90 on at least two occasions prior to admission, or already receiving treatment (drug, dietary or lifestyle) for hypertension
Ischemic heart disease	History of myocardial infarction, angina, ECG evidence of MI, CABG or angiogram documenting coronary artery disease.
Cerebrovascular accident	A past neurological deficit of cerebrovascular cause, including episodes that persist beyond 24 hours and transient ischaemic attacks lasting less than 24 hours.
Atrial fibrillation	An ECG was performed showing atrial fibrillation.
Valve disease	History of clinically diagnosed valve disease, moderate or severe stenosis or regurgitation on imaging, or an operative valve replacement/repair

[1] Available: https://www.nicor.org.uk/national-cardiac-audit-programme/datasets/

Table 3. Model building - association between COPD, asthma (including interaction with ejection fraction group) and in-hospital death in patients hospitalised for heart failure.

Predictors	Model 1	Model 2	Model 3	Model 4	Model 5a	Model 5b	Model 6
Fixed effects [coefficient estimate, SE]							
COPD	0.064 [0.017, p<0.001]	0.0706 [0.0174, p<0.001]	0.060 [0.018, p<0.001]	-0.0445 [0.0256, p=0.081]	0.064 [0.017, p<0.001]	-0.029 [0.0242, p=0232]	0.0468 [0.026, p=0.081]
Asthma	-	-0.263 [0.0255, p<0.001]	-0.287 [0.029, p<0.001]	-0.302 [0.040, p<0.001]	-0.2719 [0.034, p<0.001]	-0.266 [0.0255, p<0.001]	-0.179 [0.028, p<0.001]
COPD*Asthma	-	-	**0.098 [0.0573, p=0.087]**	0.149 [0.076, p=0.051]	-	-	-
EF	-	-	-	-0.208 [0.015, p<0.001]	-0.173 [0.014, p<0.001]	-0.207 [0.0149, p<0.001]	0.0410 [0.017, p<0.05]
COPD *EF	-	-	-	**0.205 [0.036, p<0.001]**	**-**	**0.195 [0.034, p<0.001]**	**0.096 [0.037, p<0.05]**
Asthma*EF	-	-	-	**0.018 [0.058, p=0.753]**	**0.013 [0.05, p=0.797]**	-	-
COPD*Asthma*EF	-	-	-	**-0.093 [0.112, p=0.402]**	-	-	-
Age	-	-	-	-	-	-	0.553 [0.0101, p<0.001]
Female (vs. male)	-	-	-	-	-	-	-0.0922 [0.0150, p<0.001]

Valve disease	-	-	-	-	-	-	0.219 [0.0169, p<0.001]
IHD	-	-	-	-	-	-	0.1204 [0.015, p<0.001]
Hypertension	-	-	-	-	-	-	-0.220 [0.0148, p<0.001]
Diabetes	-	-	-	-	-	-	0.0489 [0.0164, p<0.01]
AF	-	-	-	-	-	-	-0.0056 [0.0147, p=0.703]
NYHA	-	-	-	-	-	-	0.116 [0.018, p<0.001]
Place of care (cardiology vs not cardiology)	-	-	-	-	-	-	-0.363 [0.0168, p<0.001]
Random effects (hospitals, n=219)							
Variance	0.205	0.208	0.208	0.201	0.201	0.201	0.159
SD	0.453	0.456	0.456	0.448	0.449	0.449	0.399
AIC	160533.4	158837.1	158836.2	158652.0	158681.2	158649.7	133038.5

Abbreviations
AIC= Akaike information criterion; AF= atrial fibrillation; COPD= chronic obstructive pulmonary disease; CI=confidence intervals; EF= ejection fraction; NYHA= New York Heart Association; IHD= ischemic heart disease; SD= standard deviation; SE= standard error

Results from a 2-level unconditional model that included COPD as fixed-effect and hospital as random effect suggested COPD was associated with an increase in the estimate for in-hospital mortality. The addition of asthma to this model indicated it had an inverse relationship with likelihood of death. A test for the interaction between COPD and asthma was not significant, thus, it was not considered in subsequent analyses. Further, we wanted to assess whether the effects of COPD, respectively asthma on in-hospital death are different with respect to EF status group therefore, we added a three-way interaction between COPD, asthma and EF to the model. We detected a significant interaction between COPD and EF only, suggesting the effect of COPD only, not asthma would

be differential according to the EF status. In the final model, we estimated the association between COPD and mortality in HFrEF and in HFpEF and adjusted for baseline covariates.

Table 4. Association between COPD, asthma and in-hospital death

Predictors	**COPD only (95% CI)**	**COPD + asthma**	**Fully adjusted model**	**Model with COPD and EF interaction, fully adjusted OR (95% CI)**
Fixed effects (95% CI)				P-value for interaction =0.01
COPD	**1.07 (1.03 – 1.10)**	**1.07 (1.04-1.11)**	**1.10 (1.06 – 1.14)**	1.04 (0.99-1.10)
Asthma	-	**0.77 (0.73 – 0.80)**	**0.84 (0.79, 0.88)**	0.83 (0.79-0.88)
COPD (Yes vs. No): HFpEF	-	-	-	**1.05 (0.99 – 1.10)**
COPD (Yes vs. No): HFrEF	-	-	-	**1.15 (1.09 – 1.21)**
Age	-		1.74 (1.71 -1.78)	1.74 (1.71-1.77)
Female (vs. male)	-		0.91 (0.89-0.94)	0.91 (0.89-0.94)
Valve disease	-		1.25 (1.20-1.29)	1.25 (1.20-1.29)
IHD	-		1.12 (1.10-1.16)	1.13 (1.10-1.16)
Hypertension	-		0.8 (0.78-0.83)	0.80 (0.78-0.83)
Diabetes	-		1.05 (1.02-1.08)	1.05 (1.02-1.08)
AF	-		0.99 (0.97-1.02)	0.99 (0.96-1.02)
NYHA (III/IV vs. I/II)	-		1.12 (1.08-1.17)	1.12 (1.08-1.17)
Place of care (cardiology vs. not cardiology ward)	-		0.69 (0.67-0.72)	0.69 (0.67-0.71)
Random effects (Variance)				
LR test p-value	P<0.001	P<0.001	P<0.001	P<0.001
Likelihood ratio test comparing fixed to random effects for hospital model fit, significant indicates random effects model performed better than fixed effects model Abbreviations				

AF= atrial fibrillation; COPD= chronic obstructive pulmonary disease; CI=confidence intervals; EF= ejection fraction; LR= Likelihood ratio test; NYHA= New York Heart Association; IHD= ischemic heart disease; SD= standard deviation.

Table 5. Association between COPD and in-hospital mortality in patients hospitalised with heart failure. Results from 20 models using imputed smoking status and BMI (estimates combined using Rubin's rule).

	Fully adjusted model, OR (95% CI)
Fixed effects (95% CI)	
COPD	1.12 (1.07 – 1.17)
Asthma	0.84 (0.80 – 0.90)
Age	1.67 (1.62 – 1.71)
Female (vs. male)	0.89 (0.86 – 0.92)
Valve disease	1.22 (1.18 – 1.26)
IHD	1.13 (1.10 – 1.17)
Hypertension	0.82 (0.89 – 0.85)
Diabetes	1.12 (1.08 – 1.15)
AF	1.01 (0.98 – 1.04)
NYHA (III/IV vs. I/II)	1.15 (1.10 – 1.20)
Place of care (cardiology vs. no cardiology ward)	0.70 (0.69 – 0.73)
EF	1.03 (0.99 – 1.06)
Smoking status (ref: Current smoker)	
Ex-smoker	0.90 (0.77 – 1.06)
Never	1 (0.84 – 1.19)
BMI (ref: normal weight)	
Underweight	1.31 (1.21 – 1.43)
Overweight	0.86 (0.81 – 0.91)
Obese	0.77 (0.73 – 0.81)
Random effects (Variance)	
LR test p-value	P<0.001

Abbreviations
AF= atrial fibrillation; BMI= Body Mass index; CI= confidence intervals; COPD= chronic obstructive pulmonary disease; EF= ejection fraction; IHD= ischemic heart disease; NYHA= New York Heart Association; OR= Odds ratio; ref= reference

Table 6. Association between COPD and in-hospital mortality in patients hospitalised with a confirmed diagnosis of HF.

	Fully adjusted model, OR (95% CI)
Fixed effects (95% CI)	
COPD	1.11 (1.07 - 1.16)
Asthma	0.84 (0.79 - 0.89)
Age	1.04 (1.04 - 1.05)
Female (vs. male)	0.91 (0.88 - 0.94)
Valve disease	1.26 (1.22 - 1.30)
IHD	1.15 (1.11 - 1.18)
Hypertension	0.81 (0.79 - 0.84)
Diabetes	1.06 (1.03 - 1.10)
AF	0.98 (0.95 - 1.01)
NYHA (III/IV vs. I/II)	1.13 (1.08 - 1.18)
Place of care (cardiology vs. no cardiology ward)	0.69 (0.66 - 0.71)
EF	1.04 (1.01 - 1.08)
Random effects (Variance)	0.166
LR test p-value	p<0.001
Abbreviations AF= atrial fibrillation; BMI= Body Mass index; CI= confidence intervals; COPD= chronic obstructive pulmonary disease; EF= ejection fraction; IHD= ischemic heart disease; LR= Likelihood ratio test; NYHA= New York Heart Association; OR= Odds ratio; ref= reference	

Table 7. Variables with considerable missingness in the National Heart Failure Audit 2012-2018

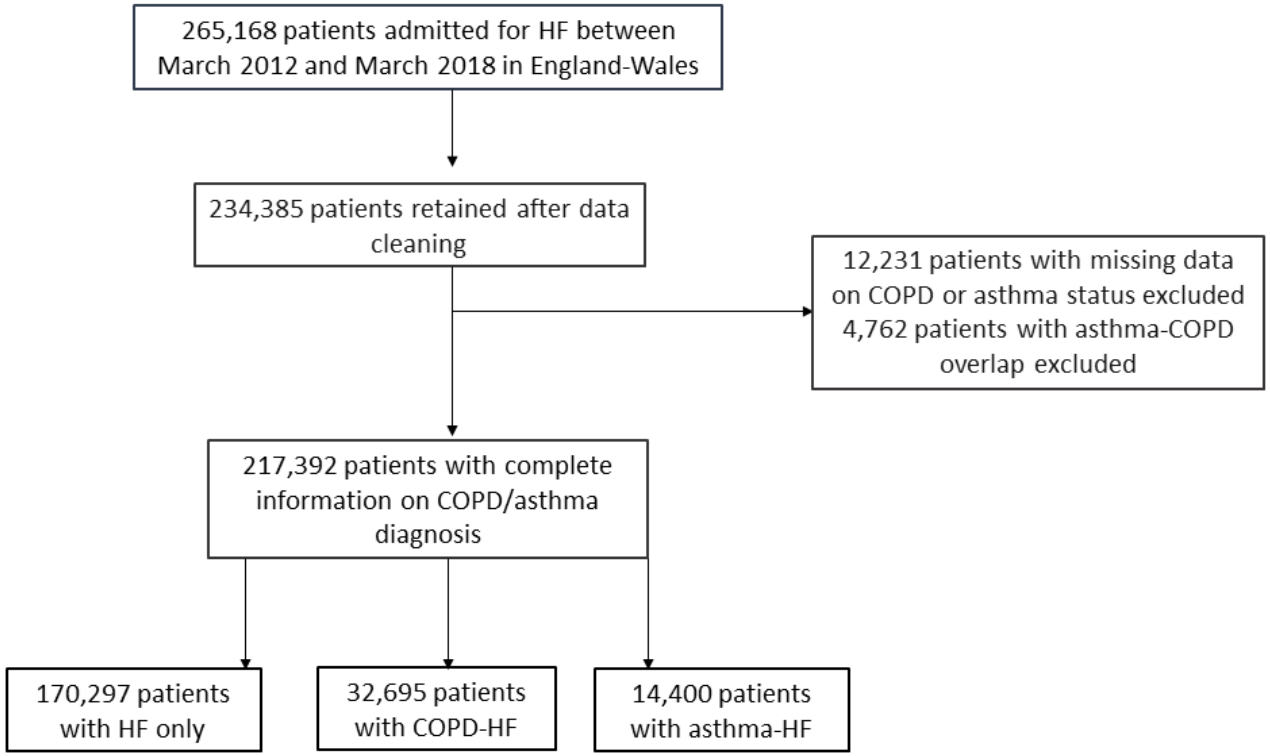
	HF alone (N=170297)	COPD + HF (N=32695)	Asthma + HF (N=14400)	Overall (N=217392)
Cerebrovascular accident	2882 (1.7%)	582 (1.8%)	244 (1.7%)	3708 (1.7%)
Missing	145636 (85.5%)	28115 (86.0%)	12279 (85.3%)	186030 (85.6%)
Alcohol units/week				
Median [Q1, Q3]	0 [0, 1.00]	0 [0, 2.00]	0 [0, 0]	0 [0, 1.00]
Missing	159233 (93.5%)	30570 (93.5%)	13314 (92.5%)	203117 (93.4%)
Smoking status				
Current smoker	1869 (1.1%)	911 (2.8%)	143 (1.0%)	2923 (1.3%)
Ex-smoker	8371 (4.9%)	2505 (7.7%)	715 (5.0%)	11591 (5.3%)
Never-smoker	8823 (5.2%)	673 (2.1%)	896 (6.2%)	10392 (4.8%)
Missing	151234 (88.8%)	28606 (87.5%)	12646 (87.8%)	192486 (88.5%)
Chest X-ray (pulmonary oedema)	3954 (2.3%)	692 (2.1%)	334 (2.3%)	4980 (2.3%)
Missing	157253 (92.3%)	30528 (93.4%)	13311 (92.4%)	201092 (92.5%)
Medications at admission				
ACEi	6316 (3.7%)	1116 (3.4%)	513 (3.6%)	7945 (3.7%)
Contraindicated	592 (0.3%)	140 (0.4%)	59 (0.4%)	791 (0.4%)
Missing	152642 (89.6%)	29598 (90.5%)	12903 (89.6%)	195143 (89.8%)
ARB	2392 (1.4%)	453 (1.4%)	305 (2.1%)	3150 (1.4%)
Not applicable	2570 (1.5%)	513 (1.6%)	240 (1.7%)	3323 (1.5%)
Stopped	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Contraindicated	338 (0.2%)	88 (0.3%)	32 (0.2%)	458 (0.2%)
Missing	151870 (89.2%)	29463 (90.1%)	12781 (88.8%)	194114 (89.3%)
Beta-blocker	9516 (5.6%)	1446 (4.4%)	598 (4.2%)	11560 (5.3%)
Not applicable	762 (0.4%)	144 (0.4%)	88 (0.6%)	994 (0.5%)
Contraindicated	153 (0.1%)	136 (0.4%)	74 (0.5%)	363 (0.2%)
Missing	151820 (89.2%)	29481 (90.2%)	12831 (89.1%)	194132 (89.3%)
Loop diuretic	5519 (3.2%)	1202 (3.7%)	490 (3.4%)	7211 (3.3%)

Missing	160255 (94.1%)	30820 (94.3%)	13532 (94.0%)	204607 (94.1%)
Thiazide or Metolazone	925 (0.5%)	140 (0.4%)	81 (0.6%)	1146 (0.5%)
Stopped*	-	-	-	-
Missing	152559 (89.6%)	29604 (90.5%)	12891 (89.5%)	195054 (89.7%)
MRA	2356 (1.4%)	502 (1.5%)	221 (1.5%)	3079 (1.4%)
Not applicable	225 (0.1%)	45 (0.1%)	27 (0.2%)	297 (0.1%)
Contraindicated	36 (0.0%)	*	*	42 (0.0%)
Missing	152494 (89.5%)	29570 (90.4%)	12885 (89.5%)	194949 (89.7%)
Digoxin	1700 (1.0%)	399 (1.2%)	168 (1.2%)	2267 (1.0%)
Missing	152631 (89.6%)	29622 (90.6%)	12874 (89.4%)	195127 (89.8%)
CCB	2847 (1.7%)	479 (1.5%)	280 (1.9%)	3606 (1.7%)
Missing	155279 (91.2%)	30261 (92.6%)	13150 (91.3%)	198690 (91.4%)
Bronchodilators	919 (0.5%)	1390 (4.3%)	750 (5.2%)	3059 (1.4%)
Missing	155316 (91.2%)	30248 (92.5%)	13136 (91.2%)	198700 (91.4%)
Ivabradine	186 (0.1%)	64 (0.2%)	31 (0.2%)	281 (0.1%)
Missing	153320 (90%)	29666 (90.7%)	12845 (89.2%)	195831 (90.1%)
BMI				
Median [Q1, Q3]	26.5 [22.9, 31.1]	27.1 [22.8, 32.2]	28.0 [23.6, 33.7]	26.7 [22.9, 31.4]
Missing	125287 (73.6%)	23693 (72.5%)	10274 (71.3%)	159254 (73.3%)
BNP				
Median [Q1, Q3]	428 [1.00, 1100]	350 [1.00, 985]	353 [1.00, 871]	412 [1.00, 1070]
Missing	153043 (89.9%)	29385 (89.9%)	12978 (90.1%)	195406 (89.9%)
NT_proBNP				
Median [Q1, Q3]	2790 [404, 7530]	2490 [349, 6820]	2440 [426, 6330]	2700 [393, 7320]
Missing	153022 (89.9%)	29161 (89.2%)	12818 (89.0%)	195001 (89.7%)

*not shown due to small numbers policy

ACEi= angiotensin-converting-enzyme inhibitors; ARB= angiotensin receptor blockers; BMI= Body mass index; BNP= brain natriuretic peptide; NT_proBNP= N-terminal (NT)-pro hormone BNP; MRA=mineralocorticoid receptor antagonist

Figure 1. Study flow
HF= heart failure; COPD=chronic obstructive pulmonary disease



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2. Conrad N, Judge A, Tran J, et al. Temporal trends and patterns in heart failure incidence: a population-based study of 4 million individuals. *The Lancet* 2018;391(10120):572-80. doi: 10.1016/s0140-6736(17)32520-5
3. Lawson CA, Mamas MA, Jones PW, et al. Association of Medication Intensity and Stages of Airflow Limitation With the Risk of Hospitalization or Death in Patients With Heart Failure and Chronic Obstructive Pulmonary Disease. *JAMA Netw Open* 2018;1(8):e185489. doi: 10.1001/jamanetworkopen.2018.5489 [published Online First: 2019/01/16]
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STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2,3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5,6
Objectives	3	State specific objectives, including any pre-specified hypotheses	5,6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6, 7, Supplement
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6, 7, Supplement
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7, 8, Supplement
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6, 7, Supplement*
Bias	9	Describe any efforts to address potential sources of bias	7, 8, 9, Supplement
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8, 9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8,9, Supplement
		(*b*) Describe any methods used to examine subgroups and interactions	8,9, Supplement
		(*c*) Explain how missing data were addressed	9, Supplement
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	6

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	9, Supplement
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6, Supplement flow chart
		(b) Give reasons for non-participation at each stage	Supplement flow chart
		(c) Consider use of a flow diagram	Supplement flow chart
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9, 10
		(b) Indicate number of participants with missing data for each variable of interest	20-22, Supplement
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	10-12
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	23, Supplement
		(*b*) Report category boundaries when continuous variables were categorized	9, 20-22
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10, Supplement
Discussion			
Key results	18	Summarise key results with reference to study objectives	12-16
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	18
Generalisability	21	Discuss the generalisability (external validity) of the study results	18
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	19

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.