**Title:** 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

Running headline: COPD severity and HF outcomes

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**Key points**

**Question:** Who are the highest risk heart failure (HF) patients with COPD?

**Findings:** In this population-based study of over 50,000 patients with HF, COPD increased the risk of hospital admission and death by over a third. However, increased risk was specific to patients on the most intense COPD medication regimens; triple inhaler therapy, prescribed oral corticosteroids or oxygen therapy. Spirometry recording was limited in the community setting and was restricted to more severe patients with HF and COPD. For these patients the risk of mortality significantly increased alongside increasing airway limitation.

**Meaning:** Optimal care of patients with HF and COPD requires accurate diagnosis and targeting of severe COPD markers to prevent admissions and death.

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**Abstract**

**Importance:** In heart failure (HF), chronic obstructive pulmonary disease (COPD) increases the risk of poor outcomes, but the effect of COPD severity is unknown. This information is important for early intervention tailored to the highest risk groups.

**Objectives:** To determine the associations between COPD medication intensity or stage of airflow limitation and the risk of hospitalisation or death in patients with HF.

**Design:** A nested case-control study with risk-set sampling.

**Setting:** Population-based study using the Clinical Practice Research Datalink (CPRD) linked to Hospital Episode Statistics (HES) between 1st January 2002 and 1st January 2014 (analysed 2017/18).

**Participants:** Patients aged 40 years and over with new diagnosis of HF in their family practice clinical record.

**Exposures:** Inpatients with HF, those with COPD were compared to those without. International COPD (‘GOLD’) guidelines were used to stratify patients with COPD by seven ‘medication intensity’ levels and four ‘airflow limitation’ severity stages using automatically recorded prescriptions and routinely requested forced expiratory volume (FEV1) data.

**Outcomes:** First all-cause admission or all-cause death.

**Results:** There were 50,114 patients with new HF, median age 79 years and 46% women during the study time-period. In HF, COPD (14%; n=18,478) was significantly associated with increased mortality (adjusted Odds Ratio [aOR] 1.31;95% CI 1.26,1.34) and hospitalisation (1.33; 1.26,1.39). The three most severe medication intensity levels showed significantly increasing mortality associations from full inhaler therapy aOR 1.17 (1.06,1.29) to oral steroids aOR 1.69 (1.57,1.81) to oxygen therapy aOR 2.82 (2.42,3.28). The respective estimates for hospitalisation were aOR 1.17 (1.03,1.33), 1.75 (1.59,1.92) and 2.84 (1.22,3.63). Availability of spirometry data was limited but showed that adjusted mortality associations significantly increased with increasing airflow limitation: FEV1 ≥80%; 1.63 (1.42,1.87), FEV1 50-79%; 1.69 (1.56,1.83), FEV1 30-49%; 2.21 (2.01,2.42), FEV1<30%; 2.93 (2.49,3.43). The strength of associations between FEV1 and hospitalisation risk were similar among stages ranging from FEV1 ≥80%; aOR 1.48 (1.31,1.68) to FEV1<30%; aOR 1.73 (1.40,2.12).

**Conclusion:** In the UK HF community setting, increasing COPD severity was associated with increasing risk of mortality and hospitalisation. Prescribed COPD medication intensity and airflow limitation provide the basis for targeting high risk groups.

**Key words:** heart failure, chronic obstructive pulmonary disease, comorbidity, prognosis, death

**Abbreviations**

aOR adjusted Odds Ratio

BMI Body mass index

BP Blood pressure

CI Confidence Interval

COPD Chronic obstructive pulmonary disease

eGFR Estimated glomerular filtration rate

CPRD Clinical Practice Research Datalink

FEV1 Forced expiratory volume in one second

GOLD Global initiative for chronic obstructive lung disease

HF Heart Failure

**Introduction**

Heart failure (HF) and chronic obstructive pulmonary disease (COPD) are common diseases of ageing and leading causes of morbidity and mortality worldwide.(1) Old age, as well as shared risk factors and pathophysiology,(2) means that these two diseases are often experienced together, with each influencing the clinical course of the other.(3) Prevalence of COPD affects approximately a third of patients with HF(4) and studies have consistently shown COPD to be associated with higher mortality for patients with HF. These studies were mostly conducted in small HF cohorts in specialist care populations or following discharge from hospital, with some evidence suggesting that the risk of COPD associated death in HF might differ according to COPD severity.(5-10) However, there is limited evidence on the impact of COPD on hospitalisations(11) or on patients with HF in the community setting.(12) Whether any elevated risk of hospitalisation or death associated with COPD in community patients with HF differs according to clinical severity is unknown. This is important for identifying individuals with the greatest risk for treatment optimisation of both conditions.

In a national cohort of newly diagnosed patients with HF, we investigated whether the associations between COPD and subsequent risk of hospitalisation and death, were significantly stratified by two severity measures of COPD; intensity of prescribed medications and routinely measured airflow limitation.

**Methods**

**Study population**

We used the Clinical Practice Research Datalink (CPRD),(13) an internationally used database of anonymised records from a representative sample of the UK general population,(14) linked to the hospital episode statistics (HES) database of all admissions in the UK. CPRD includes detailed patient demographic and clinical information and linkage to HES is available for approximately 60% of the CPRD population. CPRD has ethical approval from the Health Research Council to supply and link anonymised data from consenting family practices. Individual patient consent is not required but patients can opt out if they wish. The Independent Scientific Advisory Committee provided permission for this study (Protocol 12\_162). Data is reported following the STROBE guidelines for case-control studies.

From the database, we included all patients aged ≥40 years, with a new HF diagnosis in their clinical record between 1st January 2002 and 1st March 2012, and who had at least three years of CPRD approved clinical data prior to their study entry. A clinically validated HF code set(15) as well as additional HF specific codes were used (**S1 Table**). Patients were followed up until the first of either their date of transfer out of practice, their index outcome-event, or the 1st January 2014 which was the study end (**S1 Figure**).

**Selection of cases and matched controls**

We conducted two separate nested case-control studies within the HF cohort for the outcomes of: (i) all-cause mortality and (ii) first all-cause first hospitalisation after HF diagnosis. A nested case-control design with risk-set sampling was used to account for patients with HF who develop COPD during follow-up and for the varying nature of COPD severity over time. Using this approach, all cases are included in the analyses and are matched on their HF diagnosis date (+/- 1 month) and duration of follow-up with up to four randomly sampled controls from the HF cohort still at risk of the event. Controls are eligible to be selected multiple times and later as a case, and exposure measurement is prior to the match date. This closely resembles the programming statements approach to Cox-regression with time varying covariates and produces unbiased estimates of hazard ratios.(16,17) For the HF cohort (N=50,114), cases were defined by all-cause mortality during follow-up and for the sub-cohort with linked HES data (n=30,061), cases were defined by a first hospitalisation after, but not including the HF diagnosis date. Date of death was based on clinical codes in CPRD using a CPRD algorithm.

**Measurement of COPD severity**

In patients with HF, COPD was identified by a clinical code and at least one COPD related medication as recommended by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines(18) prior to the match date (See **S2 Table** for COPD codes). A standard coding classification for COPD based on previous validation(19) and expert clinical review was used and non-specified bronchitis codes were excluded.

*Medication intensity levels*

GOLD guidelines introduce an algorithm for the initiation and escalation for medication prescribing in COPD using a ‘stepped up’ approach based on severity. This approach combines airflow limitation stage with history of symptoms and exacerbations to define 4 severity groups (A to D). Whilst the definition of COPD severity for prescribing has changed in the latest GOLD guidelines(18) the algorithms for medication prescribing are consistent. We used the GOLD guidelines to devise ordered medication intensity levels (**Table 1**). Exclusive levels ranged from the ‘least severe’ that included short acting anticholinergics or beta2-antagonists only, to mono (GOLD group A), dual (GOLD group B or C) or triple (GOLD group D) therapy using a combination of long-acting anticholinergics, beta2-antagonists and inhaled corticosteroids. GOLD groups B and C were combined due to their substantial overlap in the guidelines. We also added two ‘most severe’ levels which included oral corticosteroids and oxygen therapy, which are most commonly used following acute exacerbations or in patients with most severe disease. Each medication intensity level was defined by at least one of the specified medications prescribed in the four-month time-window before the match date to identify all patients on such long term medications.

*COPD airflow limitation stages*

GOLD guidelines recommend the use of forced expiratory volume in one second (FEV1) to measure the severity of airflow limitation in COPD.(18) COPD patients with routinely recorded spirometry were stratified by four severity stages recommended by GOLD; (i) ‘Mild’: FEV1 ≥80% predicted, (ii) ‘Moderate’: 50% ≤ FEV1 <80% predicted, (iii) ‘Severe’: 30% ≤FEV1 <50% predicted and (iv) ‘Very severe’: FEV1 <30% predicted. The most recent FEV1 prior to the match date was used within a maximum three-year time-window. The median FEV1 measurement time was 295 [137 to 524] days prior to mortality matching and 247[103 to 280] days prior to admission matching.

**Measurement of confounders**

For potential confounders(20) **(S3** **Table**) the most recent measure before the match date was used. Medication measures were defined by at least one prescription in a four-month time-window prior to the match date.

**Statistical analysis**

Statistical analyses were performed for the two outcomes separately. First, patient and clinical characteristics were compared between cases and matched controls. To build the multivariable models, quadratic terms were added for non-linear continuous variables and first order interactions were tested between COPD and main confounders. Multiple imputation was performed for the missing confounder data (<15%, **S4 Table**) using matching variables and full-conditional specification in StataMP 14 to produce ten imputed datasets which were combined using Rubin’s rules.(21)

Next, unadjusted and adjusted conditional logistic regression was used to compare patients with HF and COPD, to patients with HF but without COPD, for the outcome event. The COPD group was then stratified into sub-groups by (i) measures of recent medication treatment intensity and (ii) measures of airflow limitation. The sub-groups with COPD were then compared to the reference group, patients with HF but without COPD. All estimates are presented as adjusted odds ratios (aOR) with 95% confidence intervals. Significant difference among groups with COPD by medication treatment intensity or airflow limitation were indicated where confidence intervals for estimates did not overlap.(22)

*Sensitivity analyses*

Sensitivity analyses were performed to investigate COPD association with outcomes stratified by a) those with and without a spirometry recording and b) those with a HF index date prior to or post 1st April 2006. This date is two years following the introduction of incentives to improve use of echocardiogram and spirometry diagnostics in the Quality Outcomes Framework in the UK.

**Results**

*Study population*

There were 50,114 patients with incident HF, median age 79 years and 46% women. Deaths occurred in 26,729 (53%) over a median follow-up of 2.6 years [IQR 0.8-5.0]. Of the linked hospitalisation sample (n=30,061), 24,339 (81%) had a first hospitalisation during a median follow-up of 82 [IQR 12-435] days. Cases for both outcomes were older, with more comorbidities but fewer cardiovascular medications and a lower BMI, cholesterol, haemoglobin and blood pressure (**Table 2**). For mortality, 4,630 (17%) cases had COPD compared to 13,848 (13%) controls and for first hospitalisation, 3,230 (13%) cases had COPD versus 8,673 (10%) controls. Beta blockers were prescribed for 55% of the total sample (**Table 2**) and this was lower in the groups with COPD and more severe airflow limitation (16-30%) (**S5 Table**). Most patients with HF and COPD were prescribed inhaler medications (57%) but 13% and 18% had not been prescribed any COPD-related medications in the 4 months prior to their match dates for mortality and hospitalisation respectively (**Table 3**). A quarter of patients with HF and COPD were prescribed oral steroids and 3% were prescribed oxygen therapy and both were more likely in the cases than controls for both outcomes. A spirometry recording was only available for 8,515 (46%) of patients with COPD in a three-year time-window prior to the mortality match date and 4,652 (39%) prior to the hospitalisation match date. Of the patients with HF and COPD, those with a spirometry measure were more likely to be older, male, deprived, with a lower BMI, cholesterol and haemoglobin than those without (**S6 Table**). They were also most likely to have moderate to severe airflow limitation (70%) and less likely to have mild airflow limitation (15%). Very severe airflow limitation was present in 10% (**Table 3**).

*COPD in HF and outcomes*

Presence of HF and COPD was significantly associated with all-cause mortality (adjusted odds ratio [aOR] 1.31;95% CI 1.26,1.36) and with first hospitalisation (1.33;1.26,1.39) (**Table 4**). These associations were not affected by beta blockers (*p*-value for interaction > 0.05) but mortality risk was significantly higher in females (1.41;1.30,1.53) than males (1.26;1.18,1.34) (*p*-value for interaction 0.007) (**S7 Table**). When the group with COPD was stratified by the presence or absence of spirometry data and compared to HF patients without COPD (reference group), patients without spirometry data had decreased mortality; aOR 0.87(0.82,0.92) and reduced risk of admission. Within the group with COPD, patients with spirometry recording had significantly increased mortality (aOR 2.22;2.06,2.39) and hospitalisation (1.28;1.17,1.40) compared to those without spirometry recording **(S8 Table**).

*COPD medication intensity in HF and mortality*

The adjusted associations between COPD and mortality differed significantly by levels of COPD medication intensity. Patients with no COPD medications in the 4 months before outcome, or on oral corticosteroids or oxygen therapy had the strongest risk associations with mortality; aOR 1.23(1.11,1.37), 1.69(1.57,1.81) and 2.82(2.42,3.28) respectively. No significant association with mortality was found for those on mono or dual therapy (GOLD groups A to C), however a significant risk increase was observed for those on triple therapy (GOLD group D); aOR 1.17(1.06,1.29) (Table 4)

*COPD medication intensity in HF and hospitalisation*

The adjusted associations between COPD and hospitalisation also significantly increased from those on triple therapy; aOR 1.17(1.03,1.33) to oral corticosteroids, 1.75(1.59,1.92) to oxygen therapy, 2.84(1.22,3.63). Compared to patients with HF but without COPD, there was no significant association with hospitalisation for patients with COPD who were not prescribed COPD medications in the 4 months prior to admission or who were prescribed dual therapy, whereas those prescribed short term inhalers only or monotherapy had increased risk; aOR 1.28(1.10,1.47) and 1.26(1.12,1.42) respectively.

*COPD stratified by airflow limitation in HF and mortality*

When patients with HF and COPD were stratified by GOLD stages according to airflow limitation measured by FEV1 and compared to the HF reference group without COPD, there was a significant difference in estimates amongst the severity stages. Patients with severe (30% ≤FEV1 <50%) and very severe COPD (FEV1 <30%) had the highest risk association with mortality (aOR 2.21; 2.01,2.42 and 2.93; 2.49,3.43 respectively). Patients with mild and moderate COPD (GOLD stages 1 and 2) were also associated with an increased risk of mortality (1.63;1.41,1.87 and 1.69;1.56,1.83 respectively).

*COPD stratified by FEV1 in HF and hospitalisation*

All groups with COPD stratified by airflow limitation were significantly associated with increased risk of hospitalisation (**Table 5**). The most severe group (GOLD stage 4) had the highest risk (aOR 1.73;1.40,2.12), but there was no significant difference in risk among groups.

**Discussion**

This is the largest population-based study to investigate the association between COPD and outcomes in an incident cohort of over 50,000 patients with HF. Uniquely, in the HF community setting, we have shown that the increased risk of death and hospitalisation associated with COPD, significantly differs by medication intensity and the severity of airflow limitation. COPD was not associated with any increased risk of death when patients were managed by inhaler therapies, until prescribing ‘intensity’ reached triple inhaler therapy and risk of both outcomes were significantly higher in those prescribed oral corticosteroids and oxygen therapy. Spirometry assessment may be underutilised in the community but indicated a more severe HF and COPD group, with worse outcomes for those with the most severe airflow limitation. These findings provide key evidence for risk stratifying patients with HF and COPD in the community, where most patients are routinely managed.

Our findings have four key clinical implications. First, to improve HF prognosis, the importance of accurately identifying and effectively managing comorbidities is increasingly recognised.(23) Our findings show that 1 in 7 patients with HF in the community also have COPD, which carries a 30% increase in risk of death and hospitalisation compared to patients with HF but without COPD. Prevalence of COPD in the community was similar to other clinical database studies(5,8) but was much lower than in HF studies using formal spirometry screening, which indicates a potential prevalence of up to 40%.(6,7,10) This means the number of patients with HF and COPD in the community is likely to be a lot higher than was recorded,(24,25) with a potentially even greater impact on outcomes. The prescribing of beta blockers was particularly low for COPD patients but was comparable to other studies.(7,8) however, adjustment did not explain the association between COPD and risk of mortality or hospitalisation.

Spirometry recording is not recorded for up to a third of patients with COPD in the community,(26) and was missing for half of patients with HF and COPD during the study time period. We found that, in those without a spirometry recording, the COPD association with mortality was protective and with hospitalisation was reduced. Given that the common symptom of breathlessness potentially drives spirometry assessment, it is likely that the COPD group without spirometry includes those with milder severity COPD as well as less severe HF compared to the reference group. An alternative consideration is the potential misclassification of COPD in this group in the absence of pulmonary function assessment, particularly at lower grades of severity. The diagnosis of COPD in patients with HF is complicated by non-specific shared symptoms such as breathlessness and spirometry is required for accurate diagnosis,(27) which can be particularly challenging in the community setting. Whilst we used specific clinical COPD diagnostic codes which have demonstrated high precision in CPRD,(19) this study highlights an urgent need to improve routine assessment of lung function for all patients with HF and COPD in the community.

Second, our findings show that COPD associated risk differed significantly according to medication intensity in patients with HF and so provide a potential indicator of disease progression. Patients with HF and COPD who were on inhaler therapies (GOLD groups A-C) had comparable mortality risk to patients with HF but without COPD. Similarly, hospitalisation risk was not increased for those prescribed dual therapy (GOLD group B-C), but was increased for patients with COPD prescribed short term inhalers only or monotherapy which may reflect newer onset, unstable COPD in these groups. Whilst the inhaler groups were overall at lower risk than those on oral corticosteroids and oxygen, there was poor differentiation in risk among inhaler groups for both outcomes. This finding is corroborated by previous evidence showing poor discrimination of GOLD severity classifications for mortality.(28) Newer GOLD guidelines focus on symptoms based severity assessment which create new challenges in patients with HF who share breathlessness and functional limitation as predominate symptoms. Consequently, this may lead to overtreatment with pulmonary inhaler therapies in patients with HF and COPD.

A third of patients with COPD were prescribed oral steroids or oxygen therapy and had up to a three-fold increase in risk of death or hospitalisation. In COPD, corticosteroids have been associated with increased mortality risk which may relate to their adverse effect on other comorbidities such as diabetes,(29) weakened respiratory muscle strength after prolonged therapy, or retention of sodium and water,(30) all of which might lead to exacerbations of HF. Alternatively, short term prescribing of oral steroids or oxygen therapy are usually a result of acute COPD exacerbations which are also a predictor of mortality(31) and are a likely pseudo-marker of more severe COPD disease. Of interest was the higher risk of mortality for patients with COPD prescribed no related medications in the four months prior to death, which might indicate end-stage HF severity when de-prescribing may occur.

Third, comparing patients with HF and COPD to those without COPD, the risk of mortality increased with more severe airflow limitation from GOLD stages 1 to 4. Other hospital studies have found no association between COPD in HF with mortality for mild(6,7) or moderate(10) airflow limitation or for overall COPD.(6,10) These studies used formal spirometry screening in patients with HF to identify and assess COPD severity and so included a much higher proportion of patients with mild severity COPD. In our community cohort of patients with COPD and spirometry data, just under half were in the most severe two stages which might partly explain these differences, combined with the higher power of a large sample. The lack of risk stratification using FEV1 for the hospitalisation outcome is perhaps not surprising given that most first admissions may have been driven by the new HF diagnosis, but further research in a prevalent HF cohort would determine the prognostic value of FEV1 for admissions.

Of note was the higher risk of both outcomes in the mildest airflow limitation group than in the overall group with COPD. This indicates that use of spirometry assessment in the community setting was itself, associated with a higher risk group. On further examination, the COPD patients with spirometry data had a worse risk profile than those without, meaning that risk factors as well as COPD severity may drive some of the clinical decisions to request spirometry. Whilst the COPD associations were adjusted for these risk factors, the worse risk profile in the spirometry group is also likely to indicate worse HF severity.

Fourth, COPD in women with HF was associated with a 15% higher risk of death than in men. Other studies have previously reported higher mortality rates in women than men, despite comparable lung function and even lower levels of smoking.(32) Similarly, whilst mortality rates are falling for men with COPD, they are rising in women.(33) Reasons for higher mortality in women range from genetics and physiology, to delayed diagnosis, to sub-optimal treatment responses(34) which are accelerated post-menopausal age.(35) Our findings add new evidence that gender differences also occur in patients with HF and indicates an important group for treatment optimisation.

**Strengths and limitations**

Our study is the largest to date to investigate COPD in the general HF population. The UK national database of routinely recorded medication and clinical data meant that we could devise and test guideline driven COPD severity groups using readily accessible information and adjust for a wide range of patient, medication and clinical factors. Whilst the CPRD is a clinically validated and globally used epidemiological database,(14) routinely collected data can be subject to measurement error. We based the HF cohort on validated clinical codes which have high precision,(36) but these data did not include ejection fraction to determine the HF phenotype and may still include some misclassification of HF. Further investigation in a HF cohort with brain natriuretic peptide or echocardiographic data would be important.(37) Validated COPD clinical codes and related medications improved the precision of diagnosis,(19) but this does not negate undiagnosed COPD in the community setting. However, any such misclassification due to under-ascertainment of COPD is likely to bias the associations towards the null value.

FEV1 can be influenced by HF status(38) that can mimic obstruction(24) resulting in approximately a quarter of patients with HF but without COPD having reduced FEV1,(10,39) leading to measurement error of COPD severity. Furthermore, where there is an imbalance in the reduction of FEV1 and forced vital capacity as a consequence of pulmonary congestion, a spurious obstructive pattern can occur, resulting in misdiagnosis of COPD. It is therefore, particularly important in HF to consider hyperventilation using body plethysmography as an alternative approach to COPD diagnosis and assessment.(40) Lack of ejection fraction data meant that we could not investigate the study findings in different HF phenotypes or take account of HF severity in the COPD associations. So, whilst we could show the direction and pattern of COPD associations stratified by measures of COPD severity in a real-world community setting, we were not able to fully disentangle COPD severity from HF severity. Further validation of the study findings in a prospective community HF cohort with pulmonary and cardiac function testing is required.

**Conclusions**

Our study has shown that routine measures of COPD severity in the community population with HF offer potentially important prognostic tools for risk stratification. Optimal treatment for HF and COPD becomes challenging when they occur together as evident by our study findings. The results generate the hypothesis that some of the adverse outcomes in the HF population with COPD could be improved by targeting better diagnosis of both, optimising drug treatment for both, and identifying the most severe patients for early aggressive treatment or close monitoring.

**Conflicts of Interest:** none declared.

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**Data**

CL had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. This study is based in part on data from the Clinical Practice Research Datalink obtained under licence from the UK Medicines and Healthcare products Regulatory Agency. However, the interpretation and conclusions contained in this report are those of the author/s alone. Data access is through permissions from CPRD only.

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| Table 1 COPD medication severity classifications | | | | | |
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| Medication intensity levelsa | | **Descriptionb** | **GOLD severity groups** | |
| No medications | | No COPD medications |  | |
| Short term inhalers only | | Any short-acting anticholinergic or beta2-agonist but no other COPD medications |  | |
| Monotherapy | | One long-acting bronchodilator (anticholinergic or beta2-agonist) +/- short-acting inhalers but no other COPD medications | A | |
| Dual therapy | | An inhaled corticosteroid AND one long-acting bronchodilator (beta2-agonist OR anticholinergic) +/- short-acting inhalers but no other COPD medications OR both long-acting bronchodilators\* (beta2-agonist and anticholinergic) +/- short-acting inhalers but no other COPD medications | B & C | |
| Triple therapy | | An inhaled corticosteroid AND both long-acting bronchodilators\* (beta2-agonist and anticholinergic) +/- short-acting inhalers but no other COPD medications | D | |
| Non-inhaled steroids | | Non-inhaled steroids can include any other COPD medications but not oxygen therapy |  | |
| Oxygen | | Oxygen therapy can include any other COPD medications |  | |
| COPD; Chronic Obstructive Pulmonary Disease, GOLD; Global Initiative for Obstructive Lung Disease  a Medicationintensity levels for this study were devised using GOLD pharmacological treatment escalation guidelines.(19) These guidelines combine airflow limitation stage with symptom and exacerbation history to group patients from A to D (A: Less symptoms, low risk; B: More symptoms, low risk; C: Less symptoms, high risk; D: More symptoms, high risk) with corresponding prescription regimens. The first and last two intensity levels were added to the GOLD groupings by the study investigators to define least and most severe prescribing groups to cover the full range of prescribing for patients with COPD. Medications were defined by at least one prescription in the 4-months prior to the match date. Severity levels were mutually exclusive  b Methylxanthines may replace one of the long-acting bronchodilators  . | | | | | |

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| Table 2 Patient characteristics by outcomes | | |  |  | | |
|  | **Mortality sample** | | | **Hospitalisation subsample** | | |
| **Patient characteristics** | All  (n=133,645) | Cases (n=26,729) | Controls (n=106,916) | All  (n=110,789) | Cases  (n=24,339) | Controls  (n=86,450) |
| Age, years; median [IQR] | 79[IQR 71-85] | 83[76-88] | 78[70-84] | 78[IQR 70-84] | 79[72-85] | 78[70-84] |
| Women; No. (%) | 61,732(46.2) | 12,974(48.5) | 48,758(45.6) | 53,804(48.6) | 11,388(46.8) | 42,416(49.1) |
| IMD quintile; No. (%) |  |  |  |  |  |  |
| 1 | 15,908(20.0) | 3,064(18.7) | 12,884(20.4) | 22,559(20.4) | 4,668(19.2) | 17,891(20.7) |
| 2 | 18,089(22.8) | 3,708(22.6) | 14,381(22.8) | 26,609(24.0) | 5,614(23.1) | 20,995(24.3) |
| 3 | 16,666(21.0 | 3,570(21.8) | 13,096(20.8) | 23,009 (20.8) | 5,153(21.2) | 17,856(20.6) |
| 4 | 16,451(20.7) | 3,427(20.9) | 13,024(20.7) | 22,575(20.4) | 5,068(20.8) | 17,507(20.3) |
| 5 | 12,269(15.5) | 2,613(16.0) | 9,656(15.3) | 16,037(14.5) | 3,836(15.8) | 12,201(14.1) |
| BMI (Kg/m2); median [IQR] | 26.9[23.5-31.0] | 25.4[22.1-29.3] | 27.3[24.0-31.3] | 27.2[23.9-31.2] | 26.6[23.4-30.4] | 27.2[24.1-3123] |
| Cholesterol (mg/dL); mean (SD) | 174±46.4 | 170.1±46.4 | 177.9±46.4 | 181.7±46.4 | 180.2±46.4 | 182.9±46.4 |
| Hb (g/dL); mean (SD) | 13.0±1.9 | 12.3±2.0 | 13.1±1.8 | 13.3±1.7 | 12.9±1.9 | 13.4±1.6 |
| Systolic BP (mmHg); mean (SD) | 131.4±20.5 | 126.9±22.3 | 132.5±19.9 | 135.6±20.2 | 134.1±21.5 | 136.0±19.8 |
| Diastolic BP (mmHg); mean (SD) | 73.3±11.4 | 71.1±12 | 73.9±11.1 | 75.7±11.2 | 74.7±12.0 | 75.9±11.0 |
| Diuretics; No. (%) | 103,283(77.3) | 21,574(80.7) | 81,709(76.4) | 79,860(72.1) | 17,023(69.9) | 62,837(72.7) |
| Beta blocker; No. (%) | 74,221(55.5) | 12,171(45.5) | 62,050(58.0) | 44,467(40.1) | 8,893(36.5) | 35,574(41.2) |
| ACEi; No. (%) | 74,373(55.7) | 12,207(45.7) | 62,166(58.1) | 63,907(57.7) | 12,477(51.3) | 51,430(59.5) |
| ARB; No. (%) | 22,753(17.0) | 3,170(11.9) | 19,583(18.3) | 19,324(17.4) | 3,722(15.3) | 15,602(18.1) |
| ACEi or ARB; No. (%) | 94,547(70.7) | 15,079(56.4) | 79,468(74.3) | 80,420(72.6) | 15,645(64.3) | 64,755(74.9) |
| Aspirin; No. (%) | 99,180(74.2) | 20,151(75.4) | 79,029(73.9) | 74,639(67.4) | 16,657(68.4) | 57,982(67.1) |
| AA; No. (%) | 23,863(17.9) | 5,610(21.0) | 18,253(17.1) | 13,272(12.0) | 3,230(13.3) | 10,042(11.6) |
| COPD; No. (%) | 18,478(13.8) | 4,630(17.3) | 13,848(13.0) | 11,903(10.7) | 3,230(13.3) | 8,673(10.0) |
| Diabetes; No. (%) | 31,962(23.9) | 6,714(25.1) | 25,248(23.6) | 21,291(19.2) | 5,577(22.9) | 15,714(18.2) |
| Renal disease (eGFR <60 mm/min/m2); No. (%) | 66,301(55.4) | 15,827(66.2) | 50,474(52.7) | 49,768(51.3) | 12,053(56.5) | 37,714(49.8) |
| Atrial fibrillation; No. (%) | 48,968(36.6) | 10,108(37.8) | 38,860(36.4) | 35,298(31.9) | 8,365(34.4) | 26,933(31.2) |
| Hypertension; No. (%) | 77,453(58.0) | 15,403(57.6) | 62,055(58.0) | 62,502(56.4) | 13,895(57.1) | 48,607(56.2) |
| Ischaemic heart disease; No. (%) | 58711(49.1) | 11,150(41.7) | 43,159(40.4) | 37,782(34.1) | 9,283(38.1) | 28,499(33.0) |
| Myocardial infarction; No. (%) | 35,998(26.9) | 7,509(28.1) | 28,489(26.7) | 23,670(21.4) | 6,171(25.4) | 17,499(20.2) |
| Smoking status; No. (%) |  |  |  |  |  |  |
| Current | 14,941(11.2) | 3,125(11.7) | 11,816 (11.1) | 12,184(11.0) | 3,057(12.6) | 9,127 (10.6) |
| Not current | 61,874(46.3) | 12,541(46.9) | 49,333 (46.1) | 53,150(48.0) | 11,236(46.2) | 41,914 (48.5) |
| Past smoker | 56,830(42.5) | 11,063(41.4) | 45,767(42.8) | 45,455(41.0) | 10,046(41.3) | 35,409(41.0) |
| Alcohol status; No. (%) |  |  |  |  |  |  |
| Current | 92,456(69.2) | 17,661(66.1) | 74,795(70.0) | 81,695(73.7) | 17,489(71.9) | 64,206(74.3) |
| Not current | 34,648(25.9) | 7,651(28.6) | 26,997(25.3) | 24,741(22.3) | 5,801(23.8) | 18,940(21.9) |
| Past drinker | 6,541(4.9) | 1,417(5.3) | 5,124(4.8) | 4,353(3.9) | 1,049(4.3) | 3,304(3.8) |
| IMD, index multiple deprivation (1=least deprived, 5=most deprived); BMI, body mass index; Hb, haemoglobin; BP, blood pressure; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; AA, aldosterone antagonist (spironolactone or eplerenone**);** COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate | | | | | | |

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| Table 3 COPD severity measures in those with HF and COPD | | | | | | |
|  | **Mortality sample** | | | **Hospitalisation subsample** | | | |
| COPD severity | HF with COPD  ( N=18,478) | COPD Cases  (n=4,630) | COPD Controls (n=13,848) | HF with COPD  ( N=11,903) | COPD Cases  (n=3,230) | COPD Controls  (n=8,673) | |
| Medication intensity levels; No. (%)a | | | | | | | |
| No medications | 2,359(12.8) | 561 (12.2) | 1,798(13.0) | 2,093(17.6) | 498(15.4) | 1,595(18.4) | |
| Short term inhalers only | 1,624(8.8) | 380 (8.2) | 1244(9.0) | 1,192(10.0) | 301(9.3) | 891(10.3) | |
| Monotherapy | 2,417(13.1) | 542 (11.7) | 1875(13.5) | 1,725(14.5) | 446(13.8) | 1,279(14.8) | |
| Dual therapy | 3,329(18.0) | 664 (14.3) | 2665(19.2) | 2,305(19.4) | 539(16.7) | 1,766(20.4) | |
| Triple therapy | 3,140(17.0) | 699 (15.0) | 2441(17.6) | 1,588(13.3) | 393(12.2) | 1,195(13.8) | |
| Any inhalers only | 10,510(56.9) | 2,285(49.4) | 8,225(59.4) | 6,801(57.2) | 1,679(52.0) | 5,131(59.2) | |
| Oral steroids but no oxygen | 2,817(23.7) | 1,415(30.6) | 3329(24.0) | 2,673(22.5) | 895(27.7) | 1,778(20.5) | |
| Oxygen therapy | 343(2.9) | 369(8.0) | 496(3.6) | 337(2.8) | 158(4.9) | 169(2.0) | |
| Spirometry | N=8,515  (53.9% missing) | Cases  (n= 2,859) | Controls (n=5,656) | N=4,652  (60.9% missing) | Cases  N=1,453 | Controls  N=3,199 | |
| FEV1(percent predicted)b median [IQR] | 54.1 [IQR 39.7-70.0] | 51.9 [37.7-68.5] | 55.2 [40.6-70.6] | 54.1 [IQR 39.7-70.0] | 53.0 [IQR 38.5-70.6] | 53.0 [IQR 38.4-69.0] | |
| COPD GOLD airflow limitation stagec |  |  |  |  |  |  | |
| 1: FEV1 ≥80% normal (mild) | 1,284(15.1) | 396(13.9) | 888(15.7) | 721(15.5) | 237(16.3) | 484(15.1) | |
| 2: FEV1 50-79% normal (moderate) | 3,721(43.7) | 1140(39.9) | 2581(45.6) | 1,896(40.8) | 585(40.3) | 1,311(41.0) | |
| 3: FEV1 30-49% normal (severe) | 2,679(31.5) | 989(34.6) | 1690(29.9) | 1,512(32.5) | 464(31.9) | 1,048(32.8) | |
| 4: FEV1 <30% normal (very severe) | 831(9.8) | 334(11.7) | 497(8.8) | 523(11.2) | 167(11.5) | 356(11.2) | |
| COPD, chronic obstructive pulmonary disease; HF, heart failure; GOLD; Global Initiative for Obstructive Lung Disease; FEV1, forced expiratory volume in 1 second  a Mono, dual or triple therapy; respectively one, two or three of: long acting beta2-antagonist, long acting cholinergic, Methylxanthines, inhaled steroid either individually or in combination inhalers  b Most recently recorded FEV1 (pp) before the match date was used to measure airflow limitation within a maximum of a 3-yr time window..  c COPD GOLD severity stages according to airflow limitation | | | | | | | |

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| Table 4 COPD associations with and all-cause mortality in HF patients; stratified by drug and spirometry measures | | | | |
|  | **Mortality** | | **Hospitalisation** | |
|  | Unadjusted OR (95% CI) | AdjustedOR (95% CI)c | Unadjusted OR  (95% CI) | AdjustedOR  (95% CI)c |
| HF with no COPD (reference group) | 1.0 | 1.0 | 1.0 | 1.0 |
| COPD | 1.41 (1.36-1.46) | 1.31(1.26,1.36) | 1.41 (1.36-1.46) | 1.33(1.26,1.39) |
| COPD group stratified by medication intensity levelsa |  |  |  |  |
| HF with no COPD (reference group) | 1.0 | 1.0 | 1.0 | 1.0 |
| COPD with no medications | 1.31(1.19,1.44) | 1.23(1.11,1.37) | 1.17(1.06,1.30) | 1.16(0.04,1.30) |
| COPD with short term inhalers only | 1.28(1.14,1.44) | 1.10(1.11,1.25) | 1.25(1.10,1.43) | 1.28(1.10,1.47) |
| COPD with monotherapy | 1.22(1.11,1.34) | 1.09(0.98,1. 21) | 1.28(1.14,1.43) | 1.26(1.12,1. 42) |
| COPD with dual therapy | 1.05(0.96,1.14) | 0.99(0.90,1.09) | 1.13(1.02,1.24) | 1.09(0.98,1.21) |
| COPD with triple therapy | 1.21(1.11,1.31) | 1.17(1.06,1.29) | 1.21(1.07,1.35) | 1.17(1.03,1.33) |
| COPD with non-inhaled steroids but no oxygen therapy | 1.79(1.68,1.91) | 1.69(1.57,1.81) | 1.79(1.65,1.94) | 1.75(1.59,1.92) |
| COPD with oxygen therapy | 3.14(2.74,3.60) | 2.82(2.42,3.28) | 3.40(2.73,4.23) | 2.84(1.22,3.63) |
| COPD with any Inhalers only | 1.17(1.11-1.23) | 1.08(1.02-1.14) | 1.17(1.11-1.23) | 1.20(1.12-1.28) |
| COPD group stratified by airflow limitation (GOLD Stages)b | |  |  |  |
| HF with no COPD (reference group) | 1.0 | 1.0 | 1.0 | 1.0 |
| COPD GOLD stage 1 (FEV1 ≥80% normal) | 1.88(1.66,2.12) | 1.63(1.42,1.87) | 1.67(1.43,1.95) | 1.59(1.33,1.90) |
| COPD GOLD stage 2 (FEV1 50-79% normal) | 1.87(1.74,2.01) | 1.69(1.56,1.83) | 1.57(1.43,1.74) | 1.50(1.34,1.67) |
| COPD GOLD stage 3 (FEV1 30-49% normal) | 2.47(2.27,2.68) | 2.21(2.01,2.42) | 1.58(1.41,1.77) | 1.48(1.31,1.68) |
| COPD GOLD stage 4 (FEV1 <30% normal) | 2.84(2.47,3.27) | 2.93(2.49,3.43) | 1.64(1.366,1.97) | 1.73(1.40,2.12) |
| COPD, chronic obstructive pulmonary disease; HF, heart failure; OR, odds ratio; CI confidence interval. GOLD; Global Initiative for Obstructive Lung Disease; FEV1, forced expiratory volume in 1 second.  a Drug measures were defined by at least one prescription in a 4-month time window prior to the match date. Intensity levels are mutually exclusive. Mono, dual or triple therapy are respectively, one, two or three of a long acting beta2-antagonist, long acting cholinergic, Methylxanthines or inhaled steroid (individually or in combination inhalers) but no non-inhaled steroids or oxygen therapy.  b The most recently recorded FEV1 prior to the match date was used to within a maximum of a 3-yr time window  c Adjusted models included age, gender, body mass index (BMI), cholesterol, estimated glomerular filtration rate (eGFR), eGFR2, Haemoglobin (Hb), Hb2, systolic blood pressure (SBP), SBP2, diuretics, beta-blocker, angiotensin-converting enzyme inhibitor; angiotensin receptor blocker; aldosterone antagonist (spironolactone or eplerenone), Aspirin, atrial fibrillation, hypertension, ischemic heart disease, myocardial infarction, diabetes, smoking, alcohol and previous hospitalisation in 12-months (Hospitalisation models only). | | | | |