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Evaluating the role of COPD in patients with heart failure using multiple electronic health data sources

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Declaration of originality

I, Claudia Gulea declare that the material presented in this thesis is my own work. Where information has been derived from other sources, I confirm that this has been appropriately recognised.

Claudia Gulea

Copyright declaration

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ABSTRACT

Heart failure (HF) and COPD frequently co-exist. Shared symptoms and risk factors make diagnosis and management difficult and current understanding of the relationship between the diseases is limited.

I used several electronic healthcare record (EHR) data sources, from the United States (US) and the United Kingdom (UK) to evaluate the impact of COPD on outcomes in patients with HF.

First, I aimed to demonstrate that comorbidity data from EHR can be used to derive meaningful clusters in patients with chronic HF, expecting COPD to be a main driver of this phenotyping endeavour. Second, I compared outcomes (hospitalisation, mortality, healthcare utilisation) in patients with COPD-HF, between left ventricular ejection fraction (LVEF) groups. Third, I pooled data from previously published studies to assess the overall effect of HF management (beta-blockers) on outcomes in COPD. In a fourth study I examined whether COPD was associated with in-hospital mortality and management of patients hospitalised for HF and assessed association with LVEF. Lastly, I investigated whether COPD affected readmission in a population of patients hospitalised for HF.

This work provides evidence to suggest that while COPD may not play a major role in determining a HF classification system based on comorbidities only, it affects clinical outcomes in the long-term, particularly for chronic HFpEF patients. Conversely, HF management such as beta-blockers does not appear to worsen outcomes in COPD patients. In the acute setting, coexisting COPD is independently associated with increased in-hospital mortality and decreased HF medication prescription and access to healthcare services amongst patients who survived their first HF admission. Readmission risk is higher amongst those with HF and COPD

compared with HF-alone, though the most frequent reason for returning to hospital is still due to a cardiovascular cause.

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Chapter 1 INTRODUCTION

This chapter provides an introduction on the relationship between heart failure (HF) and chronic obstructive pulmonary disease (COPD). This serves as background to the rationale and aims of this thesis, presented subsequently.

1.1 Background

There are approximately 26 million people living with HF globally[1] and this number is projected to increase due to general aging of populations and improvements in post myocardial infarction (MI) survival. Around 6.5 million people have HF in the United States (US) alone, and one third of the population have conditions predisposing to HF. The yearly cost of HF was estimated to be $30.7 billion in 2012 and it is projected to increase to $69.7 billion by 2030 [2]. In the UK there are approximately 900,000 patients with HF[3, 4], whose care accounts for 2% of the total National Health System (NHS) expenditure. Repeated hospitalisations and inadequate management of comorbidities are a significant driver of costs as well as a major cause of poor functional status [5]. Despite increases in utilisation of HF therapy, HF is associated with modest survival estimates of 50% and 10% at 5 and 10 years [6].

HF is defined as a progressive, multi-factorial clinical syndrome which most frequently manifests in the elderly. It affects various organ systems including the heart (failure to pump/eject blood from the heart), lung (dyspnoea) and the kidneys (salt and water retention). The most common symptoms of HF are breathlessness and fatigue on exertion, which are associated with exercise limitation and subsequently poor quality of life[1, 7]. The core feature of HF is an underlying structural and/or functional cardiac abnormality. Most commonly this refers to systolic and/or diastolic dysfunction of the left ventricle (LV) known as “left-sided HF”, which is the subject of investigation throughout this thesis. Isolated right ventricular failure, called “cor pulmonale”[8], occurring as a consequence of primary lung disease with pulmonary hypertension, is not considered throughout the remainder of this thesis, nor is rheumatic HF which is of infectious aetiology.

Diagnosis of HF is challenging and requires integration of information from patient history, physical examination, and clinical investigations[9]. While there is no single diagnostic test for HF, the European Society for Cardiology (ESC) requires objective evidence of cardiac dysfunction, based on echocardiographic or other imaging data, as well as assessment of natriuretic peptides[10].

1.2 Classification of heart failure

There are multiple classifications of HF which capture the distinct characteristics of the syndrome, and thus are used according to context and purpose. The New York Heart Association (NYHA)[10] functional classification system is used to describe the severity of symptoms and exercise intolerance but does not incorporate, nor necessarily correlate with severity of LV dysfunction (see **Table 1.1**).

TABLE 1.1: New York Heart Association functional classification of heart failure

Class I	No limitation of physical activity. Ordinary activity does not cause undue breathlessness, fatigue or palpitations
Class II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in undue breathlessness, fatigue or palpitations
Class III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity results in undue breathlessness, fatigue or palpitations
Class IV	Unable to carry on any physical activity without discomfort. Symptoms at rest can be present. If any physical activity is undertaken, discomfort is increased.

The American College of Cardiology Foundation/American Heart Association (ACCF/AHA)[11] classification refers to the degree of LV remodeling and extends to include patients at risk of HF but does not consider symptoms (see **Table 1.2).**

TABLE 1.2: American Heart Association stages of heart failure

A	At high risk for HF but without structural heart disease or symptoms of HF
B	Structural heart disease but without signs or symptoms of HF
C	Structural heart disease with prior or current symptoms of HF
D	Refractory HF requiring specialised interventions

There are two more pragmatic classifications of HF: the distinction between chronic and acute HF and the distinction based on left ventricular ejection fraction (LVEF).

Individuals who had been diagnosed with HF for a while are said to have "chronic HF". A patient who is treated for chronic HF and whose symptoms remain unchanged for one month is considered to have "stable chronic HF". If a patient with stable chronic HF deteriorates (i.e. may experience a sudden-onset of symptoms), they are described as having decompensated or acute HF[1].

1.2.1 Acute heart failure

The rapid onset of new or recurrent HF symptoms is defined as "acute heart failure", generally requires urgent evaluation and leads to emergency hospitalisation[10]. Acute HF is increasingly recognised as a distinct disorder[12] with unique aetiology, treatments, and outcomes. Mortality risk is higher after an acute admission for HF both in-hospital, and more than one year after discharge, compared with stable, chronic HF[13, 14]. The most common symptoms include congestion and peripheral oedema, which are treated with diuretics and vasodilators; however, specific treatments for prevention of in-hospital worsening of HF have not yet been devised.

Nevertheless, it has been shown that patient follow-up after discharge by a multidisciplinary team has an important role in improving patient prognosis[15].

1.2.2 Left ventricular ejection fraction

The main classification of HF is based on measurement of the LVEF. Patients are categorised as HF with reduced LVEF [considered as LVEF ≤ 40%] (HFrEF), or HF with preserved LVEF [considered as LVEF ≥ 50% (HFpEF)]. The 2016 ESC guidelines[10] included a third category: HF with midrange EF (HFmrEF) – to include patients with a LVEF ranging from 40% to 49%.

The diagnosis of HFpEF is more challenging than the diagnosis of HFrEF and there is no consensus on the exact definition[16]. Patients with HFpEF generally do not have a dilated LV, but often have an increase in LV wall thickness and/or increased left atrial size. Most have impaired LV filling capacity, known as diastolic dysfunction – which contributes to HF in these patients. However, the majority of patients with HFrEF (or systolic HF) also have diastolic dysfunction, and subtle abnormalities of systolic function have been shown in patients with HFpEF[10].

The main implication of the LVEF-based HF classification is treatment: whilst disease modifying treatments that reduce mortality exist for HFrEF, no benefit for these have been demonstrated in patients with HFpEF, among whom prognosis is often regarded as similarly poor.

1.2.3 Beyond left ventricular ejection fraction

It is increasingly recognised that no current established classification of HF captures the full complexity of HF. The most widely used classification is limited as it relies on a single factor -

LVEF - and while this is an important determinant, it is not always measured accurately, and measurement can vary across technology used[17]. Studies have shown variability between imaging modalities for LVEF assessment and even when echocardiography only is used, the inter-rater reliability is not consistent across echocardiographers[18].

Further, the cut-offs for LVEF measurement are arbitrary and vary across international bodies (the AHA guidelines categorise those with LVEF of 41-49% as borderline HFpEF, whereas according to the ESC, these patients fit the HFmrEF category) and none classify acute HF based on LVEF (perhaps due to the lack of correlation between outcomes and LVEF after acute admission[19]). LVEF can also change throughout a patients' life, which may lead to misclassification and failure to implement the appropriate treatment[20].

It is also important to consider that the LVEF paradigm for HF classification has been extensively used in clinical trials which were designed[21] with practical considerations in mind, such as cost, or achieving appropriate statistical power, rather than pathophysiological characteristics or patient complexity. This had a considerable influence in the way HF is conceptualised and how new treatments are being tested. Given the oversimplification of this syndrome, it is perhaps not surprising that no effective treatments have been developed for HFpEF, which is thought to have multiple sub phenotypes.

With the arrival of "big data", not limited to international registries and prospective studies, or electronic healthcare records, but also encompassing data collected from wearables or smartphones[22], it is now possible to use the wealth of information captured by multiple systems in order to rethink HF classification. There is now growing interest in identifying novel HF phenotypes[23-27] using data such as clinical and molecular variables, biomarkers, comorbidity data, risk and sociodemographic factors, which will hopefully aid not only in

understanding HF as a progressive syndrome but also identify subgroups responsive to specific therapies.

1.3 Aetiology of heart failure

The aetiology of HF is diverse and includes cardiovascular and non-cardiovascular factors. Usually, risk factors lead to cardiac injury and/or myocardial dysfunction, culminating in clinical symptoms and signs of HF. Thus, the most common causes of HF include ischemic heart disease (IHD), hypertension and inherited or acquired cardiomyopathy. Other risk factors include valve disease and exposure to cardiotoxic agents (alcohol, amphetamines, cancer treatment, radiation). Differences in aetiology across HFrEF and HFpEF phenotypes have been observed[10]. One of the most frequent causes of HFrEF is coronary artery disease (CAD) with antecedent MI (HFrEF), whereas the precise pathophysiology of HFpEF is still being debated. According to one hypothesis, comorbidities such as hypertension, obesity, iron deficiency and COPD interact to cause a systemic inflammatory state, resulting in decreased left ventricular compliance and thus lead to HFpEF[28].

1.4 Management of HFrEF

Neurohormonal antagonists are the mainstay of treatment HFrEF as they have been proven to decrease mortality and hospitalisation. Ideally, patients should receive “triple-therapy” which includes the following three guideline-recommended agents: first, angiotensin-converting-enzyme inhibitors (ACEis) are recommended in all patients with HFrEF, though for patients who are intolerant, angiotensin receptor blockers (ARBs) can also be used. ACEis work by increasing vasodilation, reducing blood pressure and block maladaptive neurohumoral activation that drives further LV remodelling [29].

Second, beta-blockers are recommended in stable, chronic patients and are complimentary to ACEis. They are the first line of treatment in those who suffered from a MI or those with asymptomatic LV dysfunction and work by reducing heart rate, which has been associated with a reduced the risk of sudden cardiac death. Beta-blockers should be initiated in stable patients at a low dose and up-titrated to a maximum tolerated dose.

Third, mineralocorticoid receptor antagonists (MRA) (spironolactone and eplerenone which block receptors that bind aldosterone) are recommended in patients with HFrEF and LVEF ≤35%, though caution needs to be exercised when used in those with impaired renal function and high potassium levels.

Based on recent data, angiotensin receptor blocker neprilysin inhibitors (ARNIs) are also beneficial in HF[10, 11]. Use of the combined ARNI sacubitril/valsartan is recommended to replace ACEis in patients who fit a specific criterion, similar to those who took part in the PARADIGM-HF trial[30], on the basis on which the compound gained marketing authorisation. Most recently, as of 2020, SGLT2 inhibitor dapagliflozin was approved for use in those with HFrEF in the European Union and the UK.

Finally, diuretics are recommended to reduce congestion, though their impact on mortality or hospitalisation rates has not been proven.

1.5 Management of HFpEF

To date, there are no treatments convincingly proven to improve survival or hospitalisation rates in patients with HFpEF, though in clinical trials and in routine practice, these individuals often receive similar treatments as their HFrEF counterparts for other indications, such as vasodilators for hypertension management or beta-blockers for atrial fibrillation. Diuretics have been shown

to improve congestion, though no HFrEF therapy, nor the newly devised sacubitril/valsartan have shown benefits in phase 3 clinical trials in HFpEF.

1.6 Comorbidities in heart failure

There is a high prevalence of comorbidities in patients with HF: between 40% to 80% of patients have two or more additional chronic diagnoses[31], [32]. The most common comorbidities are hypertension, IHD and cardiac arrythmias[33], and the total number of additional diagnoses is also increasing over time[4] (see **Figure 1.1**).

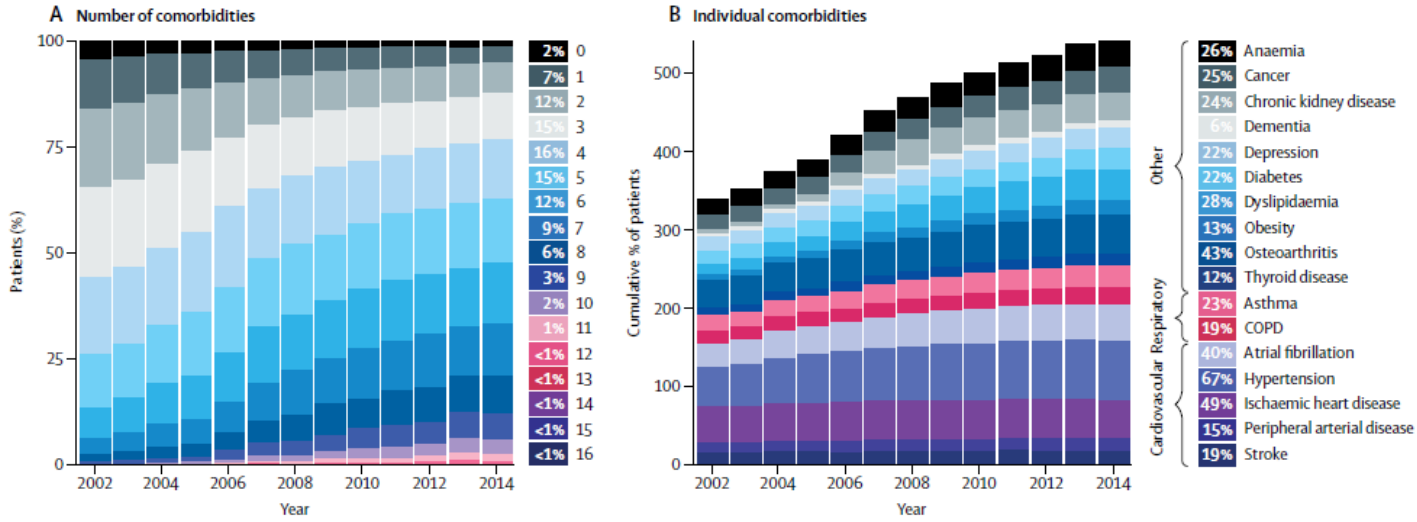

FIGURE 1.1: Comorbidities among patients diagnosed with incident heart failure, from 2002 to 2014

Figure reproduced from: reference[4] *Conrad, N., Judge, A., Tran, J., Mohseni, H., Hedgecott, D., Crespillo, A.P., Allison, M., Hemingway, H., Cleland, J.G., McMurray, J.J. and Rahimi, K., 2018. Temporal trends and patterns in heart failure incidence: a population-based study of 4 million individuals. The Lancet, 391(10120), pp.572-580.* https://doi.org/10.1016/S0140-6736(17)32520-5; reproduced under Creative Commons Attribution (CC BY 4.0).

The frequency of comorbidity is higher in patients with more severe HF[32, 34]. This puts forward the consideration that there may be either common aetiological factors in determining both HF and comorbidities (such as age, sex, cardiovascular risk factors) or that here may be a causal link with HF. The interaction between comorbidities themselves and comorbidities within the cardiovascular system may indeed determine the heterogenous manifestations of HF as a complex multi-organ syndrome[35], as shown previous studies, which found that chronic kidney disease, anaemia and diabetes were independently linked to any-cause mortality and hospitalisation in patients with HF[34].

Comorbidities complicate the management of HF, as they are associated with decreased likelihood of evidence-based therapy prescription and with worse side effects. They also negatively impact medication adherence and may exacerbate symptoms and other clinical outcomes [34, 36]. For instance, the use of renin–angiotensin system inhibitors may not be possible in patients with severe renal dysfunction, or conversely, drugs used in arthritis or cancer may cause worsening on HF[10].

Importantly, there is a trend towards increase of non-cardiovascular comorbidities as a substantial contribution to multimorbidity in patients with HF[4]. It has been shown that more than half of hospitalisations of patients with HF are due to non-cardiovascular causes[37] and while mortality due to cardiovascular reasons is decreasing, there is a surge in non-cardiovascular deaths[4]. This means the clinical management of patients with HF is increasingly more complex and affects the burden on healthcare systems and demand for multi-disciplinary input along cardiology services.

1.7 The particular case of COPD in heart failure

COPD is one of the most common non-cardiovascular comorbidities in those with HF. Globally, there are an estimated 300 million people living with COPD and approximately 3 million die of COPD each year, though these numbers are likely underestimated, due to widespread under-diagnosis. COPD is the main contributor to mortality attributed to chronic lower respiratory diseases and one of the leading causes of death in the US [38].

COPD represents a group of respiratory conditions and is defined as a "persistent airflow limitation which is progressive over time", characterised by a post-bronchodilator ratio of Forced Expiratory Volume in 1 second, percent predicted (FEV_1) / Forced Vital Capacity (FVC) of less than 0.7[39]. COPD is associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases[39]. Affected individuals experience acute episodes named acute exacerbations due to COPD (AECOPD) which range from mild symptoms normally treated in primary care, to respiratory failure requiring hospitalisation and mechanical ventilation. Similar to HF, COPD is more prevalent in older adults, and around 8% of those in their 70s have the condition.

There is no single diagnostic test for COPD, though current guidelines indicate it should be considered in individuals over 35 years old, who have dyspnoea, chronic cough or sputum production and/or a history of exposure to known risk factors – the most common is a smoking status of either current or ex-smoker. Spirometry is required to confirm the diagnosis of COPD in a suspected case.

Traditionally, the severity of COPD was denoted by the level of loss of lung function expressed as FEV_1% predicted. However, in 2011, the Global Initiative for Chronic Obstructive Lung

Disease (GOLD) introduced a revised algorithm which includes measures of symptom burden and exacerbation frequency[39] (see **Table 1.3**).

TABLE 1.3: Classification of COPD severity by GOLD

GOLD grade	Description
A	Low symptom burden (mMRC 0-1 or CAT <10) and FEV_1 ≥50% and/or 0-1 exacerbations per year
B	High symptom burden (mMRC ≥2 or CAT ≥10) and FEV_1≥50 and/or 0-1 exacerbations per year
C	Low symptom burden (mMRC 0-1 or CAT <10) and FEV_1 <50% and/or ≥2 exacerbations per year
D	High symptom burden (mMRC ≥2 or CAT ≥10) and FEV_1 <50% and/or ≥2 exacerbations per year

CAT= COPD assessment test; FEV_1= forced expiratory volume in 1 second; GOLD= Global Initiative for Chronic Obstructive Pulmonary Disease; mMRC= modified Medical Research Council dyspnea scale.

1.8 Heart failure and coexisting COPD

HF and COPD commonly co-exist as attested by shared risk factors and pathogenic mechanisms; however, each is an independent predictor of mortality, morbidity and healthcare use[40].

Between 10% and 40% of patients with HF also present with COPD[41]. Both conditions are strongly associated with socioeconomic deprivation and pose challenges in diagnosis and treatment[41, 42]. Evidence suggests COPD significantly decreases survival one year after hospitalisation for HF[42] and the number of hospital admissions in patients with HF and COPD is larger than in those with COPD alone[43].

It is estimated that roughly 90% of COPD cases are due to smoking, however, in studies reporting prevalence of COPD in HF patients, percentages of never smokers vary between 20 and 50%, raising suspicion of overdiagnosis[44].

1.8.1 Pathophysiological link between heart failure and COPD

HF is increasingly seen as a continuum, where risk or initiating factors such as myocardial injury initiate a chain of events which ultimately lead to end-stage heart disease. COPD is an implicating influence not only through smoking as a common risk factor, but also through additional determinants such as lung hyperinflation, hypoxaemia, pulmonary hypertension, oxidative stress, exacerbations, and low-grade systemic inflammation[45, 46]. It is believed that pro-inflammatory agents such as cigarette smoking, air pollution and occupational exposures stimulate systemic inflammation and oxidative stress, inducing events which underpin chronic disease such as COPD and HF[45, 47](see **Figure 1.2**). However, while increased levels of inflammation markers (cytokines) accelerate disease progression and exacerbation of each disease, the significance of each illness in the development of the other is still debated[48].

To date, no functional link has been established between specific genes and either COPD or HF phenotypes, indicating an area for future research, which could help establish a clearer understanding of the interaction of these two diseases.

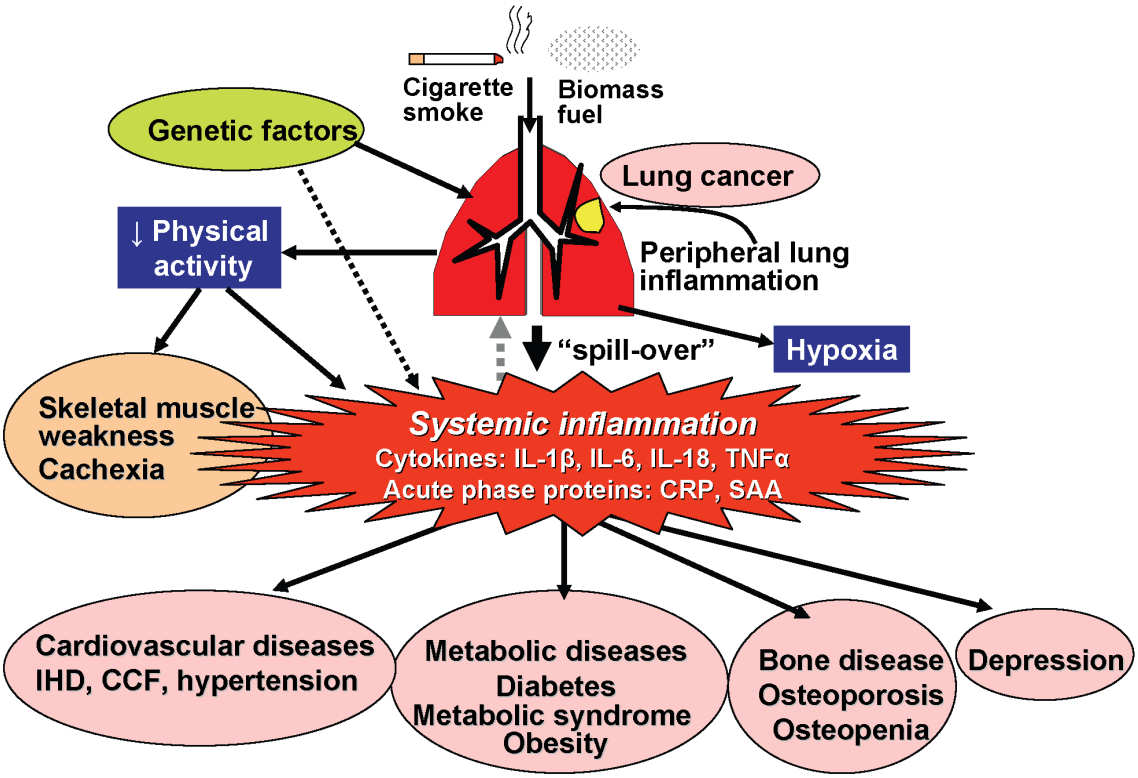

FIGURE 1.2: Inflammatory pathways involved in the cardio-pulmonary systems

COPD is characterised by peripheral lung inflammation and increased circulating cytokines. This low-grade inflammation may underlie the link with increased cardiovascular risk. Source: reference*[49], Barnes, P.J., 2010. Chronic obstructive pulmonary disease: effects beyond the lungs. PLoS medicine, 7(3),* reproduced under Creative Commons Attribution License (CC BY)).

1.8.2 Diagnostic and management challenges of comorbid heart failure and COPD

Patients with HF or COPD experience a multitude of symptoms, several of which are not specific or unique to either condition. Diagnostic tests commonly used may be misleading in the comorbid patient. For instance, those with HF display both obstructive and restrictive ventilatory

defects, which may amplify, or mask airflow limitation characteristic of COPD. Though obligatory for confirmation of COPD diagnosis, performing spirometry in those with HF is problematic due to presence of interstitial and alveolar oedema which cause compression and obstruction of the airways. Thus, even though the concurrence between HF and COPD is recognised, misdiagnosis and over-diagnosis of COPD is very likely and common, if lung function testing is done on non-euvolemic patients. In such cases, pulmonary congestion due to HF, or obesity may result in incorrect labelling as COPD. With diuresis, FEV_1 often returns to normal, thus, spirometry is recommended in stable HF patients[50]. Challenges remain though as HF patients are typically elderly and experience a natural decline in lung function – which may again lead to overdiagnosis of COPD. Similarly, COPD can affect the quality of HF diagnostic tests. Air trapping due to pulmonary disease may impede echocardiography and result in low image quality, impacting on diagnosis accuracy.

Beta-blockers, ACEi/ARBs and MRAs reduce hospitalisations and mortality in HFrEF, while there are no disease-modifying treatments for COPD. The main management option for those with the pulmonary disease consists of long-acting inhaled bronchodilators (anticholinergic or beta-agonist), corticosteroids, or combination therapy[51-54]. The latter is normally reserved for those whose symptoms and exacerbations are not optimally controlled by bronchodilators only. Therefore, the opposite pharmacological effects of beta-blockers and beta-agonists may play into clinicians' reserve to prescribe beta-agonists for individuals with HF or beta-blockers for those with COPD[55]. This can result in potential undertreatment of each disease and can in turn impair outcomes for the comorbid patient.

1.8.3 Beta-blockers and COPD

Evidence suggests that patients with COPD are less likely to receive the guideline recommended treatment for their cardiac condition. Beta-blockers, one of the most widely used types of medications used in management of HFrEF, are often not prescribed due to clinicians' fear of bronchoconstriction in patients with COPD [56]. Recent clinical trial data on beta-blocker use in patients with COPD have consistently indicated there are no significant adverse effects related to lung function [57] and observational studies have suggested mortality benefits[45]. One of few trials investigating beta-blockers in COPD patients[58] reported more hospitalisations due to COPD exacerbations in patients treated with metoprolol compared to placebo and reported worsening of overall pulmonary symptoms. This suggests there is a need to assess a wider range of both respiratory outcomes and different beta-blockers, to draw conclusions on the benefits of this overall therapeutic class of agents in HF-COPD patients.

1.8.4 Beta-agonists and heart failure

Bronchodilators are the main treatment for COPD. There is increasing evidence from observational studies suggesting associations with adverse cardiovascular events such as incident HF and increased mortality, as well as hospitalisation in those with existing HF or LVSD[56, 59-61]. However, some studies have found no differences in long-term mortality of HF patients on beta-agonists compared to those not receiving beta-agonists[62]. The largest trial[63] 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.

1.9 Rationale and overall aim

HF remains a challenging syndrome, debilitating for patients and difficult to treat for physicians. Whilst the last 40 years have brought disease modifying treatments for HFrEF, ensuring that patients are receiving up-titrated doses and are adherent to guideline recommended medications remains a challenge. Furthermore, a large proportion of acute HF and those with preserved LVEF remain at risk of increased hospitalisation and mortality due to lack of approved therapies.

The role of cardiovascular and non-cardiovascular comorbidities is increasingly being recognised as playing a major role in the prognosis of patients with HF. Guidelines now recommend targeted treatment for each additional disease: when facing the complex HF patient, clinicians are encouraged to switch from the "what to treat first" philosophy to a treatment pathway adjusting for the presence of multiple comorbidities at the same time.

COPD is one of the most prevalent co-occurring diseases in HF and, arguably, one of the most important. This is due to a shared pathological mechanism and symptoms resulting in both diseases having the potential to exacerbate each other and to affect management pathways, notwithstanding diagnosis difficulty when both are present. There is an added layer of complexity when studying HF-COPD comorbidity: HF is a heterogenous syndrome and the number of different combinations of comorbidities and characteristics poses a high-dimensionality problem which further complicates treatment.

Therefore, defining the temporal relationship of COPD to HF, and then exploring its specific role within the context of multimorbidity in HF patients would offer a more rounded picture of these intercalated issues. Those with HF with incident versus prevalent COPD may have different characteristics and prognosis, as shown in other indications with high levels of additional chronic

disease[64]. This thesis aims at evaluating COPD as a prevalent comorbidity to HF rather than as an incident one, and thus COPD is always identified as a comorbidity diagnosed prior to HF in all studies presented subsequently.

There is an increasingly acute need to identify how the complex relationship between the two conditions is handled in routine clinical care, with a view to improve treatment provision. Due to heterogeneity of HF, patients experience different clinical manifestations and severity of symptoms and therefore are being treated in different ways across healthcare providers [65]. In addition, healthcare systems may have different approaches to both conditions worldwide. Therefore, it is equally important to assess the relationship between HF and COPD from a global perspective.

My research used big clinical datasets, which offer advantages such as very large sample sizes and the ability to detect even small, statistically significant effect sizes, which could relate to important clinical outcomes.

The overall objective of this thesis was to assess the role of COPD in shaping outcomes and clinical management of patients with HF and to describe these using UK and US electronic health data sources. The findings presented here will address some of the gaps in our understanding of the relationship between HF and COPD and, I hope, will help identify opportunities to improve the management of the individuals living with these co-occurring illnesses.

Based on the background presented in the previous section, the five specific aims which form the basis of this thesis are outlined below. The first three aims focus on chronic HF and the last three on acute (hospitalised) HF.

1.10 Specific aims

Aim 1 – Comorbidities in HF

Multiple HF phenotypes exist, among which the most established is determined by LVEF status. First, I wanted to determine whether I could identify novel, clinically meaningful HF phenotypes, based on comorbidity data routinely available from electronic health care records and thus easily accessible to clinicians and researchers. Second, I aimed to evaluate the association between comorbidity clusters and long-term clinical outcomes (such as admission to hospital, mortality) and healthcare utilisation, as this may provide novel understanding into prognosis and could offer opportunities to better optimise and personalise care for HF patients. Further, patients with HF are highly heterogenous, however, only a fraction of this group are currently being considered for clinical trials evaluating new therapeutic targets. This highly specific, "RCT-suitable" subgroup may not represent the typical, multimorbid patient, therefore, I wanted to stimulate discussion around comorbidity and how it can be used to aid inclusion into future trials. Since COPD is a major additional chronic diagnosis in HF (and has been shown to have an important role in clustering studies in other cardiovascular diseases, for example, in IHD), I expected it would play a major role in determining the make-up of the comorbidity clusters in HF.

Aim 2 - Differences in outcomes in COPD-HF patients between LVEF phenotypes

The premise of this aim was based on the finding that COPD did not play a major role in determining the comorbidity clusters (as detailed in Aim 1), compared to other chronic diseases.

However, COPD was present in more than half of patients in two (metabolic-vascular and ischemic) of the five identified clusters. These clusters corresponded to the worst clinical prognosis amongst all, were characterised by high levels of additional illnesses and had higher levels of therapeutic management. I therefore wanted to further characterise a cohort of patients with HF and COPD, with the aim to shed light on the natural course of these two diseases. One of the gaps in the literature was the nature of the association between LVEF status and outcomes in those with coexisting disease. LVEF determines treatment of those with HF, as disease-modifying treatments exist for HFrEF, but not for HFpEF, and COPD may additionally alter treatment pathways which subsequently also impact on prognosis. I thus set out to investigate whether differences in clinical outcomes, healthcare use and management exist between patients with COPD-HF with preserved and reduced LVEF.

Aim 3 – Beta-blocker effects in patients with COPD

Previous studies have shown that COPD impacts HF management, particularly beta-blocker use which is low in those with obstructive lung disease due to fears of bronchoconstriction. I aimed to provide a comprehensive assessment on the effect of beta-blockers on a wide-ranging list of outcomes, going beyond respiratory outcomes. I included mortality, admission to hospital, FEV_1 and quality of life. In addition, I sought to assess whether a best-in-class beta-blocker agent can be identified for use in individuals with COPD, based on lung function effects. I conducted a systematic literature review and used meta-analysis to analyse all available data on patients with COPD with an indication for a beta-blocker, in order to cast a wide net on the typology of patients included. The rationale for this lies in the existence of multiple aetiologies for HF (such

as hypertension or MI for which beta-blockers may be prescribed) and thus I ensured all patients diagnosed with precursors to HF are captured in the synthesis of data.

Aim 4 - COPD and in-hospital mortality and management of patients hospitalised with HF

HF is a chronic disease, though patients may experience acute decompensations, leading to hospital admissions, resulting in acute HF. Since the management and prognosis of patients experiencing these episodes are markedly different compared to long-term chronic HF, I intended to evaluate the effect of COPD on hospital-specific outcomes and management.

In the first study, I compared in-hospital mortality, odds of referral to HF post-discharge services as well as guideline-recommended treatment in patients with HF with and without COPD. Due to possibility of misclassification of COPD with asthma (particularly in patients with HF where symptoms are non-specific, are overlapping and may be hard to attribute to either pulmonary or cardiac cause), I also evaluated the effect of asthma on patients with HF, as to contextualise findings across a range of possible obstructive lung disease phenotypes. Further, both asthma and COPD patients are being treated with similar compounds (inhaled corticosteroids and beta-agonists – which have been linked with increased but differential cardiovascular risk, depending on type of lung disease). However, HF management impacts those with COPD and asthma differently as beta-blockers are not recommended in severe asthma but are frequently used in COPD. Therefore, the inclusion of the asthma group allowed for a more granular analysis of risk of in-hospital death in patients with obstructive lung disease amongst patients principally diagnosed with HF and helped strengthen the clinical implications of the study.

Aim 5 - COPD and readmission outcomes in patients hospitalised with HF

For the last aim of my thesis and the second study on acute HF, I aimed to offer a greater understanding on the link between COPD and readmission in patients hospitalised for HF. I described a sample of patients with HF and COPD from a nationally representative readmissions database from the US and investigated whether patients with COPD were at heightened risk of 30-day readmission risk, compared to those with HF alone.

Since a high proportion of hospitalisation in HF are of non-cardiovascular cause, I additionally investigated cause-specific admission, detailing reasons for returning to hospital. Further, I assessed whether those with HF and COPD are at a disadvantage in terms of in-hospital mortality compared with those with HF alone.

Figure 1.3 below provides a schematic of the structure of this thesis.

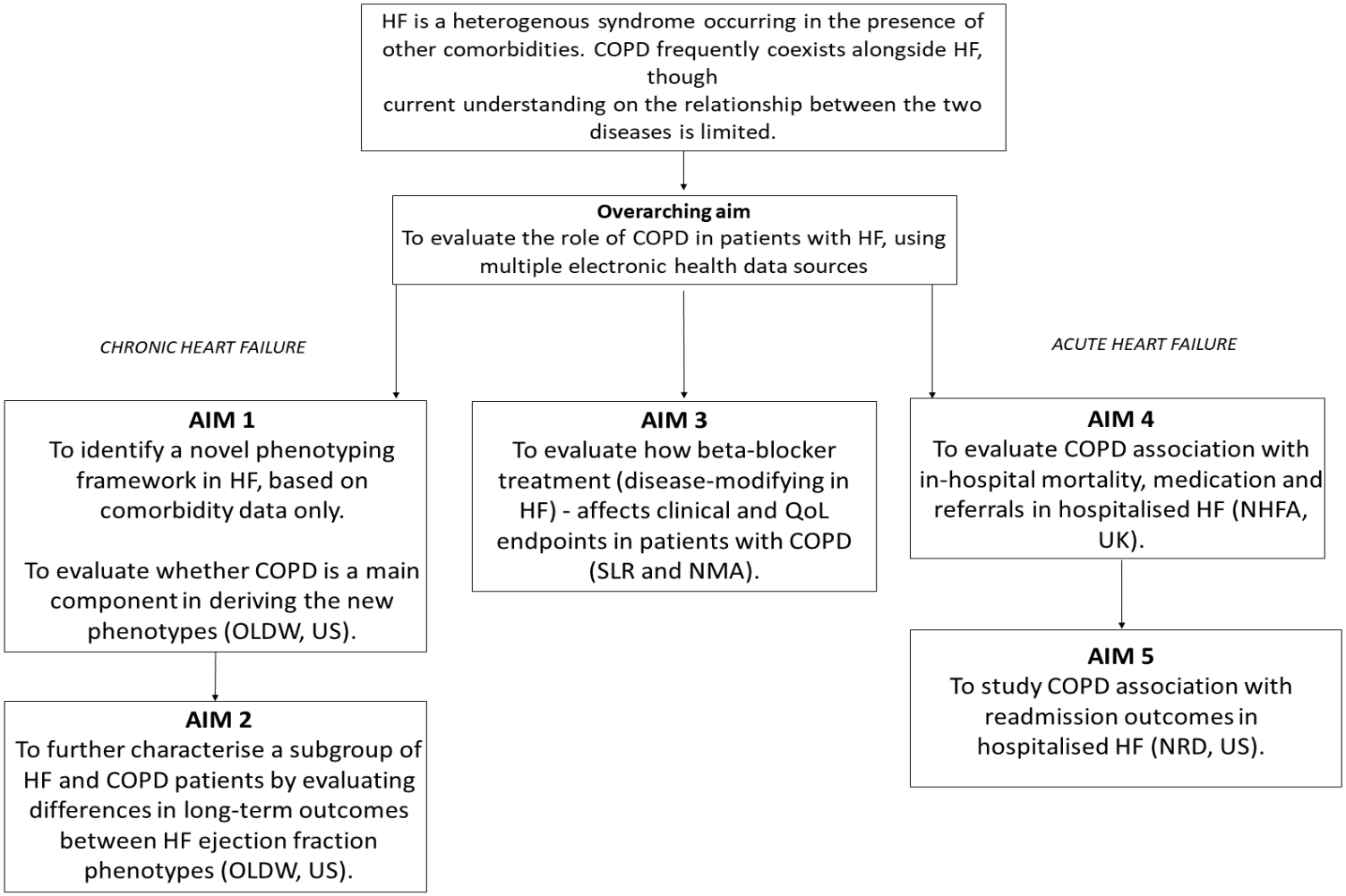

FIGURE 1.3: Schematic of thesis

NMA= network meta-analysis; NHFA= National Heart Failure Audit; NRD= National Readmissions Database; OLDW= OptumLabs DataWarehouse; QoL= quality of life; SLR= systematic literature review; US= United States.

Chapter 2 DATA SOURCES

Description of electronic health records

This chapter describes the data sources used in this thesis and provides an overview of their main strengths and limitations. I used data from both the US and UK – two countries with profoundly different healthcare systems - therefore the main differences in organisation of care and subsequent health data available across these two regions are also outlined.

Finally, I briefly summarise the factors that play into the reliable identification of HF and COPD patients across data sources.

Detailed variable definitions are provided in each data-analysis chapter.

2.1 Overview

Modern healthcare systems across the globe increasingly record patient medical and treatment history using electronic healthcare record (EHR) systems. These include administrative databases, hospital records, patient registries or primary care databases. Information such as when patients visited the doctor, what symptoms were reported and what treatment was prescribed, as well as demographic variables such as age, sex and socio-economic status may be stored. In some cases, linkages between different sets of data are provided. Primary care databases may be linked to secondary care databases, capturing patient journey from General Practitioner (GP) visit to specialist care provided in hospitals, which enhance the type and amount of available health information.

Originally designed as administrative tools rather than research-ready, scientists are ever more engaged in transforming these enormous amounts of data into insights aimed to improve patient outcomes. These sources of information vastly increase opportunities for epidemiological research, are recognised sources of "big data" and have become crucial in studying patterns of disease, treatments and quality and efficiency of healthcare. The main advantage of EHRs is that they describe populations of patients who are treated in uncontrolled settings, thus allowing investigations of population and patient-level outcomes (including treatment uptake and pharmacovigilance, disease surveillance and preventative care).

However, big EHR data does not come without limitations. High quality in routinely collected datasets may be difficult to achieve due to a multitude of reasons including[66]:

- Variation in the amount of data that is entered into the system at clinician, health and/or regional system level.

- Accuracy of data entered, which is liable to recall and reporting bias.
- Missingness of information.

The sheer availability of data within the EHR system does not mean that it can be used to answer any research question, largely because data are not collected for a specific research purpose and data may be missing relative to either observed or unobserved patient characteristics. While some databases implement data quality protocols (such as the Clinical Practice Research Datalink [CPRD] in the UK), these are related to measures used in routine care rather than research requirements.

2.2 Electronic Health Records in the United States

Digitalisation of medical care records in the US has been expanding since the 1990s. However, in 2009, when the Health Information Technology for Economic and Clinical Health Act (HITECH) was introduced by the Obama administration marked the expansion of EHRs, sustained by dedicated government funding. This enabled incentive payments for care providers when using EHRs to achieve improvements in delivery of care. The act mandated the basic elements needed to be recorded to support a "meaningful use" of EHR data. These included storing variables such as patient demographics, vital signs (height, weight, blood pressure), problem and medication lists, smoking status and lab tests[67].

In 2008, only 9% of hospitals in the US had EHR and in 2017, the percentage rose to 96% of hospitals and 86% of physicians[68].

A significant goal of the HITECH was to achieve interoperability between all sectors of care, so that patient data could be linked and shared between providers regardless of software used. This

has been more challenging to achieve, as in 2015, only 12% of doctors were able to share clinical data with other clinicians involved in patients' care who used systems different to their own.

One implicating factor may be the US health care system organisation, which relies on a mix of public and for-profit private insurers.

In the absence of universal healthcare, there are five types of insurance available:

- Medicaid (government programme for people with limited income)
- Medicare (national insurance programme for people aged 65 or over)
- Insurance provided by employer (insurance paid for by businesses to employees)
- Insurance provided for military staff and dependants (funded by the Department of Military Health Systems; though conditions not related to military service are not covered)
- Direct purchase insurance

In 2018, over half of the US population was insured through their employer (55.2%), 20.5% was on Medicaid, 17.6% on Medicare, 13.4 % purchased their individual plans, 8.9% were uninsured and 5% had military insurance[69].

The systems outline above operate independently and sometimes interact with each other (for example, Medicare only covers some of the healthcare needs of those insured through it, and the remaining costs must be covered by individuals either through a supplemental insurance plan or out-of-pocket). In addition, private insurance plans vary in their coverage and benefits provided. According to type and level of insurance, access to primary, secondary and tertiary care is highly variable amongst US residents: uninsured individuals don't have access to primary care, while the insured may choose to access specialist care directly[70]. Continuity of care is thus hindered

as there is no formal “link” between primary and secondary care, in the absence of a unified or unifying system.

This affects whether EHR data in the US can be used for public and population-level health research, which has requirements of generalisability at national or regional level, going beyond the types of data needed for individual patient care assessment normally retained in individual electronic systems. To provide data relevant for populations, EHRs additionally must have standardised measures for ascertaining disease and they need to adhere to standardised reporting protocols. Currently, there is no unified protocol of data collection across the hundreds of systems in place across the country, which have their own clinical terminologies and functional capabilities. This makes make it difficult to create a format for sharing and linking data which limits interoperability[71].

2.2.1 National Readmissions Database

2.2.1.1 Ethics approval

The National Readmissions Database (NRD) was used for the data analysis presented in Chapter 7. Ethics approval was not needed as it contains de-identified patient data. Approval for data access was obtained from the Healthcare Cost and Utilization Project (HCUP) for this study presented in Chapter 7 (see Appendix A, Figure A1).

2.2.1.2 Dataset description

The NRD is part of a family of publicly available, all-payer databases developed by the Agency for Healthcare Research and Quality (AHRQ) for the HCUP [72]. It enables reporting on national readmissions rates to support public health professionals and clinicians in decision

making, with a view to reduce hospital readmission rates while improving quality of life for patients and containing costs.

The NRD started collecting data during calendar year 2012 and can be purchased through the HCUP Central Distributor. It is created from the State Inpatient Databases from 28 states that are geographically distributed and represent 59.7% of the total US resident population and 58.7% of all US hospitalisations[73].

The NRD includes all discharge records of patients treated in all hospitals provided by the HCUP Partners (community/specialty/Federal/public hospitals and academic medical centers) but excludes rehabilitation and long-term acute care facilities.

The NRD contains data from approximately 15 million discharges per year. Each record in the database represents one discharge from an inpatient stay. If a patient returns to hospital multiple times, a separate record is added for each stay and an anonymised patient identifier is used to track the patient across the dataset and across hospitals.

2.2.1.3 Variable description

There are more than 100 data elements in the NRD, such as as age, sex, income and education level, type of insurance, urban/rural location of patient, reasons for hospital admission and returning to hospital for care, hospital costs for discharges and in hospital procedures, length of stay, comorbidities. Data is provided within within four files (**Table 2.1**):

TABLE 2.1: NRD data files

Type	Data
Core	Patient sociodemographic information, diagnoses codes associated with discharge record, readmission specific data
Severity	Comorbidity data and other aids in assessing the severity of a diagnosis, calculated by the NRD such as "risk of mortality")
Diagnosis and procedure groups	Additional diagnoses or procedure information derived by the NRD
Hospital level	Hospital characteristics

Reason for admission is based on the International Classification of Diseases Clinical Modification coding systems (ICD-9CM or ICD-10CM, year 2015 is the cut-off data for switching to the latest iteration of the ICD system) and each discharge record contains up to 25 diagnoses associated with the hospital stay. Additionally, the Clinical Classifications Software (CCS) system is used, which is a diagnosis and procedure categorisation system based on the ICD-9CM. All 14,000 ICD-9CM diagnoses codes and 3,900 procedure codes are collapsed into smaller numbers of clinically relevant categories, for ease of statistical analysis. CCS consists of two classification systems, single and multi-level. For the purpose of this thesis, I used the single-level system which aggregates conditions into 285 mutually exclusive categories. Therefore, the main CCS category to identify hospitalisation related to HF for the purpose of this thesis was category 108 "Congestive heart failure" (see **Table 2.2**).

TABLE 2.2: CCS and ICD diagnosis coding system equivalence

Condition	ICD-9CM diagnoses	CCS Category
Congestive heart failure	428 – 428.9	108

In the NRD, comorbidities are identified using the AHRQ comorbidity measures. This system identifies comorbid diseases which are not related to the principal diagnosis associated with an admission and have been ascertained before the hospital stay.

The key advantages of using the NRD include: a large sample size, generalisable to the US population, allowing investigation of readmissions for a wide variety of conditions.

An important limitation of the NRD database is that it is an annual file - it does not provide a patient tracking identifier which would allow to track patients across the years (if data available to researcher spans multiple years), nor is it possible to identify whether subsequent admissions are related. Therefore, patients admitted within one year but discharged within the following year are not captured. For this reason, one year of discharge data does not allow investigating readmissions which are more than 90 days apart. While patients can be tracked across hospitals, data is only captured within a state (thus readmissions within neighbouring states are not recorded).

2.2.2 OptumLabs DataWarehouse

2.2.2.1 Ethics approval

The OptumLabs® Data Warehouse (OLDW) was used to source the data for Chapters 3 and 4. Since it uses de-identified data, no ethical approval was required. A Detailed Research Application (DRA) was completed and approved from OLDW for data access (DRA #10279) which outlined the main objectives of the research.

2.2.2.2 Dataset description

OptumLabs was founded in 2013 as a partnership between Mayo Clinic and Optum, a commercial data, infrastructure services and care organisation with its core linked data asset OLDW [74]. Data are integrated across care settings (primary, secondary) and longitudinally linked at patient level[75]. Data are de-identified in accordance with the Health Insurance Portability and Accountability Act (encryption methods and a second level of deidentification are used to prevent identification of personal information).

OLDW covers people who are insured through their employer (or through their family's employer); those who purchase coverage individually and individuals insured through Medicare Advantage (a type of insurance that provides Medicare benefits through government approved private insurers and supplemental benefits compared with Medicare plans, such as additional prescription coverage). However, premiums and other offerings may vary according to insurer.

Data in OLDW is held in a secure location and researchers' access is ensured through secure environments guarded by firewalls and robust security controls, specific to each study.

For the purpose of this thesis, I used administrative claims to identify two base cohorts, which were linked to the EHR, Socio Economic Status (SES), mortality data and health risk behaviour linkages to provide additional data either for descriptive or outcome analyses. (see **Figure 2.1**).

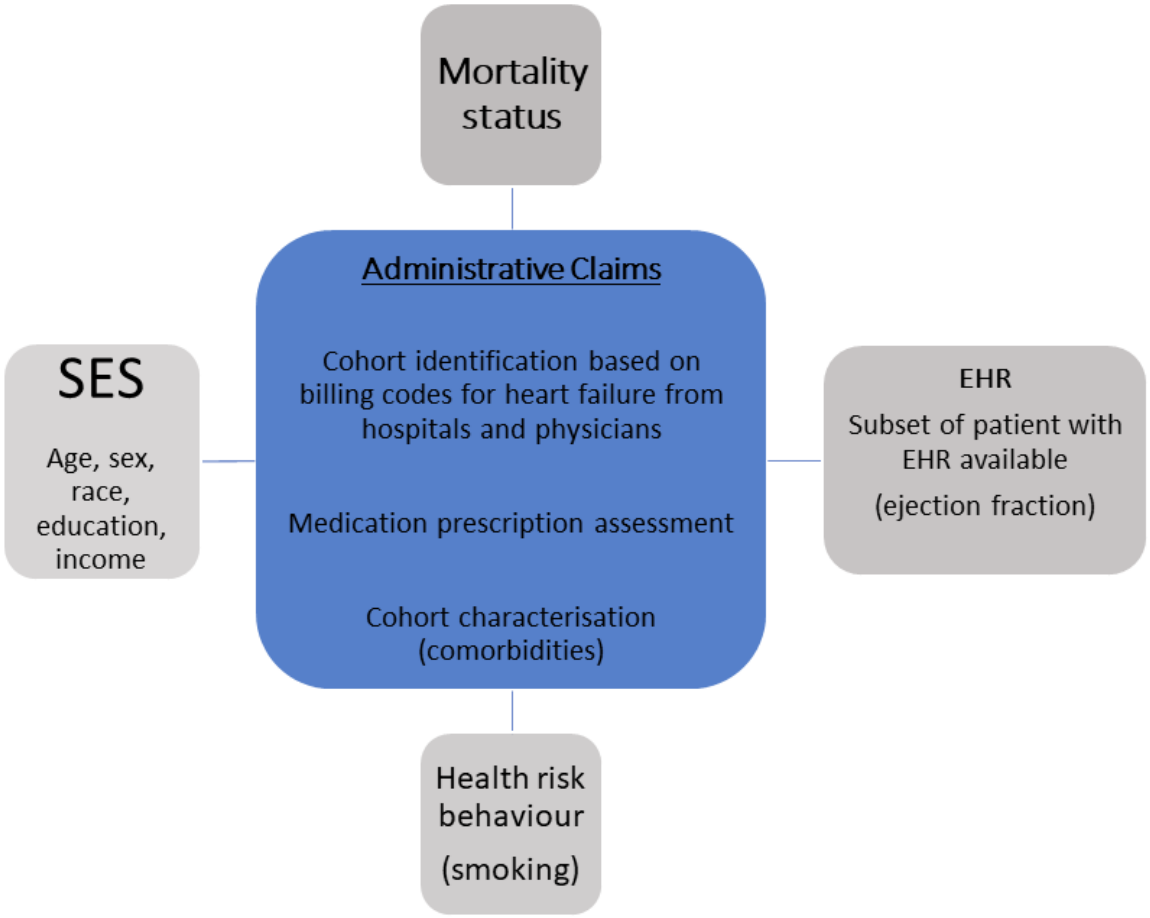

FIGURE 2.1: OLDW data elements used in cohort identification (Chapters 3 and 4)

2.2.2.3 Variable description

Administrative claims

Administrative claims consist of in and outpatient medical facilities medical, pharmacy and enrolment records. These data are mainly used for billing purposes (as is the case for all administrative health databases across the US), thus, only elements needed for financial reimbursement are recorded.

Medical claims include: multiple diagnoses (recorded with the ICD-9CM codes until 2015; with ICD-10-CM after); procedures (recorded with ICD procedure codes, Current Procedural Terminology (CPT) or Healthcare Common Procedure Coding system (HCPCS) codes; sites of service; speciality of provider; patient and insurance plan paid amounts. Treatments occurring during an inpatient episode are recorded using the HCPCS/CPT codes.

Pharmacy claims contain claims for filled medications prescriptions and include drug name, dosage, days of supply, patient and health plan paid amounts.

Electronic healthcare records

Supplementing administrative data with detailed clinical information by linkage with an EHR database, which contains data elements such as laboratory data (i.e., left ventricular ejection fraction, spirometry) or behavioural data (i.e., smoking or alcohol use). Diagnoses are recorded using either ICD-9, ICD-10, or SNOMED, though they are mostly reliant on ICD coding. Around one third of patients with administrative claims have EHR data available[75].

Mortality status

There are four sources of mortality in the OLDW:

- Sourced from the Social Security Administration's (SSA) Death Master File.
- Indicated by a discharge status of "expired".
- Indicated by an ICD-9 or ICD-10 code.
- Indicated by clinical data.

There is an important limitation to the mortality data in OLDW. While three of the mortality information sources have remained unchanged, due to implementation of restrictions in publicly sharing information from the SSA, the availability of this source has changed since 2011 and thus data are incomplete after that. Additionally, cause of death is not available.

Socioeconomic status

Data elements contained include race/ethnicity, occupation, household income category and education – supplied by a national supplier of consumer marketing data and thus collected for purposes other than research. The percentage of missing data across these variables is variable.

Health risk behaviour data

This database contains information on height, weight, Body Mass Index, smoking status, and alcohol use. These data are not available for Medicare advantage enrollees.

Advantages of the OLDW database include that it contains longitudinal health data representing a diverse mixture of ages, ethnicities and geographics regions across the US, comparing favourably with the insured population of the country. A granular characterisation of patient

population is available through the continual integration of EHR data. However, it is limited in its' ability to offer information on uninsured individuals or those who change insurance plans.

2.3 Electronic Health Records in the United Kingdom

Unlike the US, both the provision of healthcare and EHR are different in the UK. The National Health System (NHS) is the universal, public provider of health which all residents are entitled to and which is funded through taxation and National Insurance contributions. It was established in 1948 and it offers comprehensive care (from "cradle-to-grave"), free at the point of delivery.

Primary and secondary care are integrated and the first point of contact when accessing services is generally a GP, who makes referrals to more specialised care, though this can also happen directly. Importantly, GP records provide information about both primary and secondary care interactions which makes the system well suited for facilitating research of longitudinal health data.

One of the main sources of EHR data in the UK is the CPRD [76], which collects data from GPs and captures around 7% of the UK population. Approximately 60 % of all CPRD records are linked with Hospital Episode Statistics (HES) which contains details on hospitalisations outcomes across NHS hospitals in England. CPRD is also linked with the Office of National Statistics (ONS) which provides information on the place and cause of death.

2.3.1 National Heart Failure Audit

2.3.1.1 Ethics approval

This data source was used for the analysis presented in Chapter 6 of this thesis. Ethical approval was not required, in accordance with the UK Research and Innovation Medical Research Council

tool (http://www.hra-decisiontools.org.uk/ethics/, Appendix A, Figure A2). A Data Access Request Form was approved by the Healthcare Quality Improvement Partnership (HQIP) (#HQIP329).

2.3.1.2 Dataset description

In addition to CPRD, HES and ONS, health data in the UK is also collected through national audit programmes. The National Clinical Audit and Patient Outcomes Programme (NCAPOP) is managed by the Healthcare Quality Improvement Partnership HQIP, on behalf of the NHS and contains more than 30 national audits related to a range of illnesses[77].

The National Heart Failure Audit (NHFA)[78] is a national clinical audit of care which was established in 2007 and aims to collect data on all patients admitted to hospital with a primary diagnosis of HF in England and Wales. Its purpose is to assess the quality of care and outcomes of patients with HF, from admission to discharge and to measure hospital performance and implementation of management guidelines for HF, from the National Institute and Clinical Excellence (NICE)[79] and the European Society of Cardiology (ESC) Heart Failure Guidelines[1]. The audit is managed by the National Institute of Cardiovascular Outcomes (NICOR), which collects and manages the data from hospitals. Participation in the audit is mandated by the Department of Health's NHS Standard Contracts (since 2012) and by the NHS Wales National Clinical Audit.

2.3.1.3 Variable description

The NHFA contains information on patient demographics, in-hospital investigations (cardiovascular medication administered at admission, diagnostic and biomarker tests),

comorbidities (such as asthma, COPD, hypertension, ischemic heart disease, diabetes, valve disease) as well as discharge plans and follow-up treatment and tests (medication at discharge, follow-up plans such as referrals to specialty services, serum creatinine, brain natriuretic peptide test [BNP], N-terminal pro-N-type BNP [NT-proBNP]). Data are entered into a secure electronic collection system by healthcare professionals.

The participation in the NHFA has increased since its inception in 2007[80] when seven hospitals (reporting on 691 admissions) contributed to data collection in a pilot scheme, to the inclusion of 68,266 visits for the 2017-2018 report[16].

Admissions coded in the audit are compared to HF episodes in the HES in England and the Patient Episode Database of Wales (PEDW) to determine the case ascertainment rate. In HES, HF is determined by the presence of the following ICD-10 codes for a discharge or death (**Table 2.4**):

TABLE 2.3: ICD-10 codes used to identify HF in NHFA and HES

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
HES= Hospital episode statistics; HF= heart failure; NHFA= National Heart Failure Audit.

The aggregate HES data are then compared to audit data to compute a case ascertainment percentage. This is currently at 83%, indicating that a majority of hospitalised HF admissions in England and Wales are being captured by the audit[81].

Therefore, the main advantages of the NHFA audit are its size and generalisability to the England and Wales populations. The audit is however an administrative database rather than one designed for research, therefore there are some limitations, such as issues with data accuracy. While there are systems in place to mitigate erroneous data entry, such as validity checks (i.e., range and logic checking, rejection of invalid fields), nonetheless, errors can still be made during data entry in a busy clinical environment. Changes in data collection systems or format of variables across time has affected completeness of data (i.e., collection of % left ventricular ejection fraction is planned from 2021 onwards, however this variable is not available in previous releases).

The NHFA only captures admissions with a primary diagnosis of HF, thus excluding those who may have been diagnosed in a primary care or non-acute, community setting. However, the NHFA includes in-depth clinical variables such as echocardiography results which provided further diagnosis validation, compared to other databases which rely on diagnosis codes only.

The NHFA also includes information on deprivation though the Index of Multiple Deprivation (IMD) which identify areas of multiple deprivation at the neighborhood area. The dimensions which are used to calculate the IMD include assessment of income, employment, education and health. Separate indices have been constructed for each of the UK countries and they are not directly comparable due to differences in method and geographical areas used to calculate them.

2.3.2 Index for Multiple Deprivation

The IMD is the official measure of relative deprivation at the neighborhood level (or lower-layer super output area [LSOA]) in England. There are approximately 32,000 LSOAS in England, all ranked according to their levels of deprivation compared to that of other areas, though there is no definitive threshold above which an area is considered "deprived"[82]. The Welsh Index of Multiple Deprivation (WIMD) is used to rank approximately 2.000 LSOAS in Wales.

The IMD and WIMD were used to describe relative deprivation in the study presented in Chapter 6, separately for England and Wales.

2.4 Identifying heart failure and COPD in Electronic Healthcare Records

Making a diagnosis of HF entails multiple components, starting with conducting a clinical assessment of symptoms (such as breathlessness, signs of congestion), measurement of biomarkers such as NT-proBNP and finally, performing echocardiography to assess the functional status of the heart. The diagnosis of HFpEF is challenging and in some cases may require a stress test or confirmation of invasively measured elevated left ventricular filling pressure[10]. COPD is diagnosed based on spirometry ($FEV_1/FVC<70\%$), a history of smoking (being a current or ex-smoker) and age over 35 years old[39].

A pre-requisite of using EHR to investigate HF and COPD is the good validity of case identification. Unlike clinical trials or prospective studies where diagnostic ascertainment is made using specialist investigations and in-depth clinical assessment such as the ones outlined above, EHR databases rely on coding systems to store diagnoses. Therefore, the use of reliable and validated processes to correctly identify patients is crucial, especially in the context of a

heterogenous syndrome as HF. Even so, upon deciding on a strategy, there is usually a trade-off between aiming for high sensitivity (using a large number of codes to identify as many cases as possible) but risking inclusion of false positives, (i.e., cases which are incorrectly labeled as HF or COPD) and high specificity (by restricting the codes to include only highly specific ones). Additionally, choice of case identification algorithm may be dependent on multiple factors, such as diagnostic system used, whether data is collected within separate EHR systems, or regional differences in coding and clinical practice.

Patient data used in this thesis was sourced from multiple EHR sources from two different countries, however, the underlying diagnosis system across all sources was the ICD system (with the exception of the NHFA where diagnoses were also verified by echocardiography or clinical assessment). Strategies to identify patients with HF based on ICD codes have been previously validated with positive predictive values ranging from 81% to 100% across Europe and North America[83-85]. Similarly, identifying patients with COPD based on the ICD diagnostic system has been validated, with accuracy of 85%, which is acceptable for epidemiological research[80, 86].

Therefore, for studies presented in Chapters 4, 5, 6 and 7, ICD-9 and ICD-10 codes were used to identify HF. COPD was identified using ICD codes, in the studies presented in Chapters 4, 5, and 7. The NFHA which was used to source data for the analysis presented in Chapter 6 contained a variable to identify COPD, collected from patient clinical history and entered in the database by healthcare staff. While this variable was based on spirometry and clinical judgment, diagnostic tests were not available, and the information was recorded as either “yes” - indicating presence of COPD or “no” – indicating absence of COPD. All cohorts were derived by identifying patients with incident HF first and then assessing prevalent COPD. This was done to limit the

potential diagnosis misclassification due to overlap in clinical symptoms and difficulty of interpretation of diagnostic tests (i.e., spirometry) when both COPD and HF are present[45]. Additionally, this scenario allows for speculation of the prognostic implications of having COPD before development of HF[35].

Chapter 3 COMORBIDITIES IN HEART FAILURE

The next five chapters present the results of the analyses which constitute the research project and correspond to the specific aims outlined Chapter 1, Introduction. The first two rely on data sourced from OptumLabs Data Warehouse®.

This chapter describes the first set of analyses which had the aim of identifying comorbidity clusters in patients with HF using routinely collected data.

Part of this analysis has been published in BMC Medicine in 2020 (Appendix G, Paper 1).

3.1 Introduction

The main classification of HF is based on left ventricular ejection fraction (LVEF) [1, 87]. The key implication of this is management: while treatments that reduce mortality exist for HFrEF, no benefit has been demonstrated for patients with HFpEF, among whom prognosis is often regarded as similarly poor. Despite this, recent evidence suggests the LVEF framework does not relay the complexity of HF, as it is characterized by cardiovascular but also non-cardiovascular burden, which contribute and are implicated in pathophysiology and prognosis[88-93].

Previous studies have attempted to include comorbidity information and to identify new phenotypes in HF, but most were limited by stringent inclusion criteria (i.e. included hospitalised patients only[94, 95]; used registry data[96]; preferentially including HFpEF[24, 27, 97], or HFrEF[23]; used RCT data [23, 25, 26, 98], only or included patients from geographical areas[96], excluding Western HF patients. While detailed clinical variables related to cardiac structure and function were commonly available in such analyses[27], allowing for in-depth characterisation, these data are frequently not available in population-based studies. This limits replication and the possibility of validation across larger cohorts from routinely collected administrative data sources, and small sample sizes on which potential subgroups are identified brings into question their generalisability to patients cared for in routine clinical settings.

As comorbidities are frequent in HF and affect outcomes of patients through their functions as either risk factors or in direct causation, I set out to better describe this population, using data from a large, routinely collected data asset.

3.2 Study aims

I had the following aims:

(1) To capture and describe comorbidity clusters in patients with HF, using a model-based approach.

(2) COPD is one of the most common comorbidities in HF. Previous data has suggested it is a main driver in comorbidity-based classification of ischemic heart disease (IHD) [99], which is one of the most common precursors of HF. Therefore, I wanted to determine whether COPD is a main discriminating factor in this clustering analysis.

(3) To evaluate whether there are differences in clinical outcomes (hospitalisation and mortality), management of disease (HF guideline-recommended pharmacological prescriptions) and healthcare resource used between the identified clusters.

3.3 Methods

3.3.1 Data source

The study used data from the OptumLabs Data Warehouse (OLDW) [74], which contains longitudinal health information on over 100 million commercial enrollees representing a diverse mixture of ages, ethnicities and geographies across the US, including all 50 states. The administrative claims data in OLDW includes medical, pharmacy claims and laboratory results for commercial and Medicare Advantage with part D prescription drug coverage patients. More details are available in Chapter 2, Data sources.

3.3.2 Population

Incident HF was defined as having at least one episode of acute HF that resulted in hospital admission within the study period or at least two outpatient claims on different dates within the study period (1st of January 2009 to 1st of January 2018) according to any ICD-9 or ICD-10 HF codes in any position on the claim (see **Table 3.1**). Only individuals over 18 years old were included (see **Figure 3.1**).

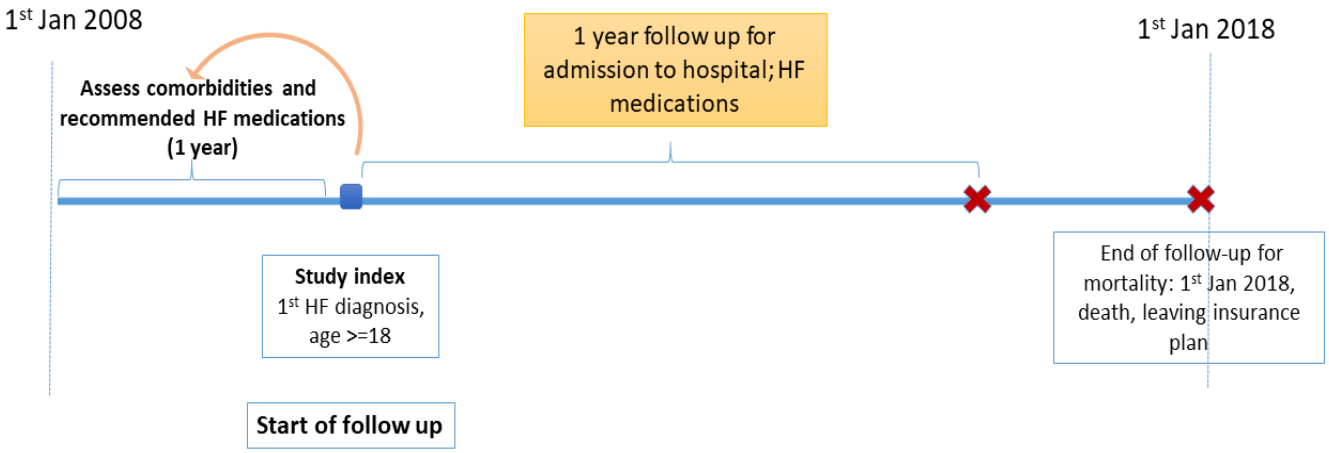

FIGURE 3.1: Study Design

To ensure identification of incident, rather than prevalent HF, patients were required to have at least 12 months of continuous medical coverage with no claim for a HF diagnosis (see **Table 3.1**) before inclusion, and 12 months follow-up thereafter.

TABLE 3.1: List of ICD-9 and ICD-10 codes used to identify heart failure patients

ICD-9 code	**Diagnosis**
42830	Diastolic heart failure
42831	Acute diastolic heart failure
42832	Chronic diastolic heart failure
42833	Acute on chronic systolic heart failure
42820	Systolic heart failure, unspecified
42821	Acute systolic heart failure
42822	Chronic systolic heart failure
42823	Acute on chronic systolic heart failure
42840	Combined systolic and diastolic heart failure, unspecified
42841	Acute combined systolic and diastolic heart failure
42842	Chronic combined systolic and diastolic heart failure
42843	Acute on chronic combined systolic and diastolic heart failure
4289	Heart failure, unspecified
4280	Congestive heart failure, unspecified
4281	Left heart failure
ICD-10 code	**Diagnosis**
I5020	Unspecified systolic (congestive) heart failure
I5021	Acute systolic (congestive) heart failure
I5022	Chronic systolic (congestive) heart failure
I5023	Acute on chronic systolic (congestive) heart failure
I503	Diastolic (congestive) heart failure
I5030	Unspecified diastolic (congestive) heart failure
I5031	Acute diastolic (congestive) heart failure
I5032	Chronic diastolic (congestive) heart failure
I5033	Acute on chronic diastolic (congestive) heart failure
I5040	Unspecified combined systolic (congestive) and diastolic (congestive) heart failure
I5041	Acute combined systolic (congestive) and diastolic (congestive) heart failure
I5042	Chronic combined systolic (congestive) and diastolic (congestive) heart failure

ICD-9 code	Diagnosis
I5043	Acute on chronic combined systolic (congestive) and diastolic (congestive) heart failure
I5084	End stage heart failure
I5089	Other heart failure
I500	Heart failure, unspecified
I501	Left ventricular failure
I11	Hypertensive heart disease with congestive heart failure

The earliest claim was used as the index HF diagnosis date when patients were identified using outpatient claims alone; alternatively, it was the date of admission to hospital for those identified using hospitalisation records. Patients with rheumatic HF (ICD-9 code 39891, ICD-10 code I09.81) were excluded due to cause of HF being rheumatic fever, which is infectious and not related to other causes of HF, considered throughout this thesis.

Comorbidities included: atrial fibrillation [AF], coronary artery disease [CAD], peripheral artery disease [PAD], cerebrovascular accident [CVA], hypertension, diabetes mellitus, obesity, depression, alcohol misuse disorder, dementia, cancer, peptic ulcer, liver disease, renal failure, anaemia and COPD. These were identified using ICD-9 and ICD-10 codes recorded any time before the diagnosis of HF (obesity and anaemia were assessed in the previous 12 only as they may be temporary). All codes available in Appendix B, Table B1.

Pharmacy prescription claims were identified for: cardioselective and non-cardioselective beta-blockers, angiotensin-converting-enzyme inhibitors [ACEi] or angiotensin receptor blockers [ARBs], mineralocorticoid receptor antagonists [MRA], thiazide, potassium sparing and loop diuretics (see Appendix B, Table B2). Given that hypertension and CAD are two of the most common causes of HF, it is expected that some patients identified with incident HF (due to these

conditions) would have already been prescribed some of the medications of interest (e.g., ACEis and beta-blockers). On the assumption that some of these patients would not receive new prescriptions immediately after a diagnosis of HF, but de facto, use the medications already, I identified all relevant pharmacological treatments at HF diagnosis, as well as in the baseline period (12 months before HF).

3.3.3 Outcomes

The main outcome of the study was all-cause hospitalisation, defined as the first admission to hospital with a minimum of an overnight stay, happening within one year of, but not including the date of initial HF diagnosis. Hospitalisation was identified using a combination of variables available in the claims data, including unique patient ID, admission and discharge dates, American Medical Association site code for revenue (21, 51, 55, 56, 61, Appendix B, Table B3) and primary provider tax ID (defined as non-null codes to indicate a valid tax code). I excluded all hospitalisations to rehabilitation (long-term) stays and there were no admissions related to nursery stays.

Secondary outcomes were:

- HF-specific hospitalisation (using the same definition as above but including HF ICD-9/ICD-10 codes in the primary diagnosis field for each admission, see **Table 3.1**).
- All-cause mortality.
- Healthcare resource use (codes available in Appendix B, Table B3):
    - Long-term care defined as a claim not meeting criteria for inpatient stay, with an AMA revenue code of 31, 32, 33, 34 or 54.

- Emergency department defined as a claim not meeting criteria for inpatient or long-term care and meeting one of two conditions: a revenue code or CPT (Appendix B, Table B3) code indicating emergency department visit or an AMA site code for emergency department appearing on the same date as an ER claim line shown by a revenue code.
- Outpatient visit (in hospital) defined as a claim not meeting criteria for above visits, with an AMA side code indicating outpatient site visit (22, 24, 62, 65)
- Office visit defined as a claim not meeting criteria for above visits with an AMA site code indicating outpatient hospital site visit (11, 26, 53, 71, 72).

- Medical and pharmacy costs (calculated in US dollars, $).

3.3.4 Statistical analysis

3.3.4.1 Latent class analysis

I used R package "poLCA" [100] to perform latent class analysis (LCA) to identify clusters of comorbidities in patients with HF. LCA is a model-based clustering technique that classifies individuals into subgroups based on multiple characteristics in a cohort (in this case comorbidities). Comorbidity variables used to derive the clusters were: AF, anaemia, CAD, cancer, COPD, CVA, diabetes mellitus, depression, liver disease, obesity, peripheral artery disease (PAD) and renal failure. Hypertension, alcohol misuse disorder, dementia and peptic ulcer were not used in the main LCA model as they were unlikely to discriminate subpopulations of patients (due to homogeneity in the former [95.2%] and small prevalence in the latter three characteristics (2.9%, 7.8%, respectively 5%). I also considered that by excluding unnecessary

variables, classification performance can be improved. Age, sex and sociodemographic variables were not used in the LCA, but I adjusted for these in subsequent analyses.

Maximum-likelihood estimation was used to identify clusters for a range of 2 to 9 groups. Cluster membership was based on parametric estimates of grouping individuals (compared different models and best solution based on statistics and clinical interpretability). This approach is more robust over other distance-based clustering techniques as it permits a mathematical evaluation of how well a model represents the data.

The metrics used to determine the best cluster solution were based on the following criteria:

- Information criteria such as the Bayesian Information Criterion (BIC), sample adjusted BIC and Akaike Information Criterion (AIC) and log-likelihood where lower values indicate superior fit. While the fit indices continue to improve beyond the six-class solution, the incremental improvement in fit was not large enough to account for the increase in complexity of interpretation (see **Figure 3.2**).

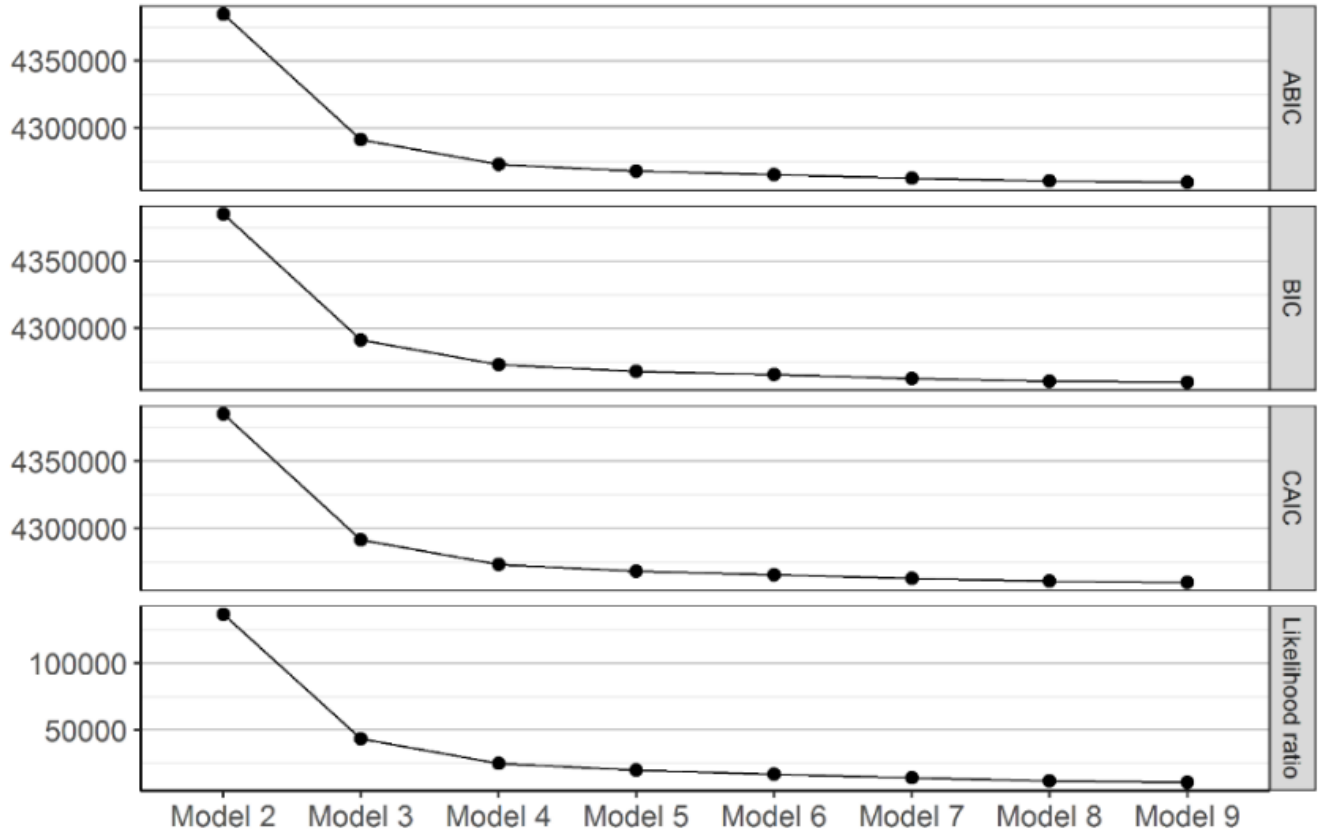

FIGURE 3.2: Fit indices for the 2 to 9 class solution models derived using latent class analysis.

- No small classes: the rule of thumb is that there is no cluster size below 5% of the overall study population (generally, this may represent a "left-over" class – of patients that cannot be assigned with confidence to any other class). In the present case, choosing a six-class model would result in one class consisting of 3.9% of the total cohort.
- Clinical interpretability – the five-class solution distinguished clinically relevant clusters, some of which have equivalence in previous HF studies (i.e., the metabolic cluster in Tromp et al. (2018)[96] or the common cluster in Lee et al (2014)[95] (see **Figure 3.3).**

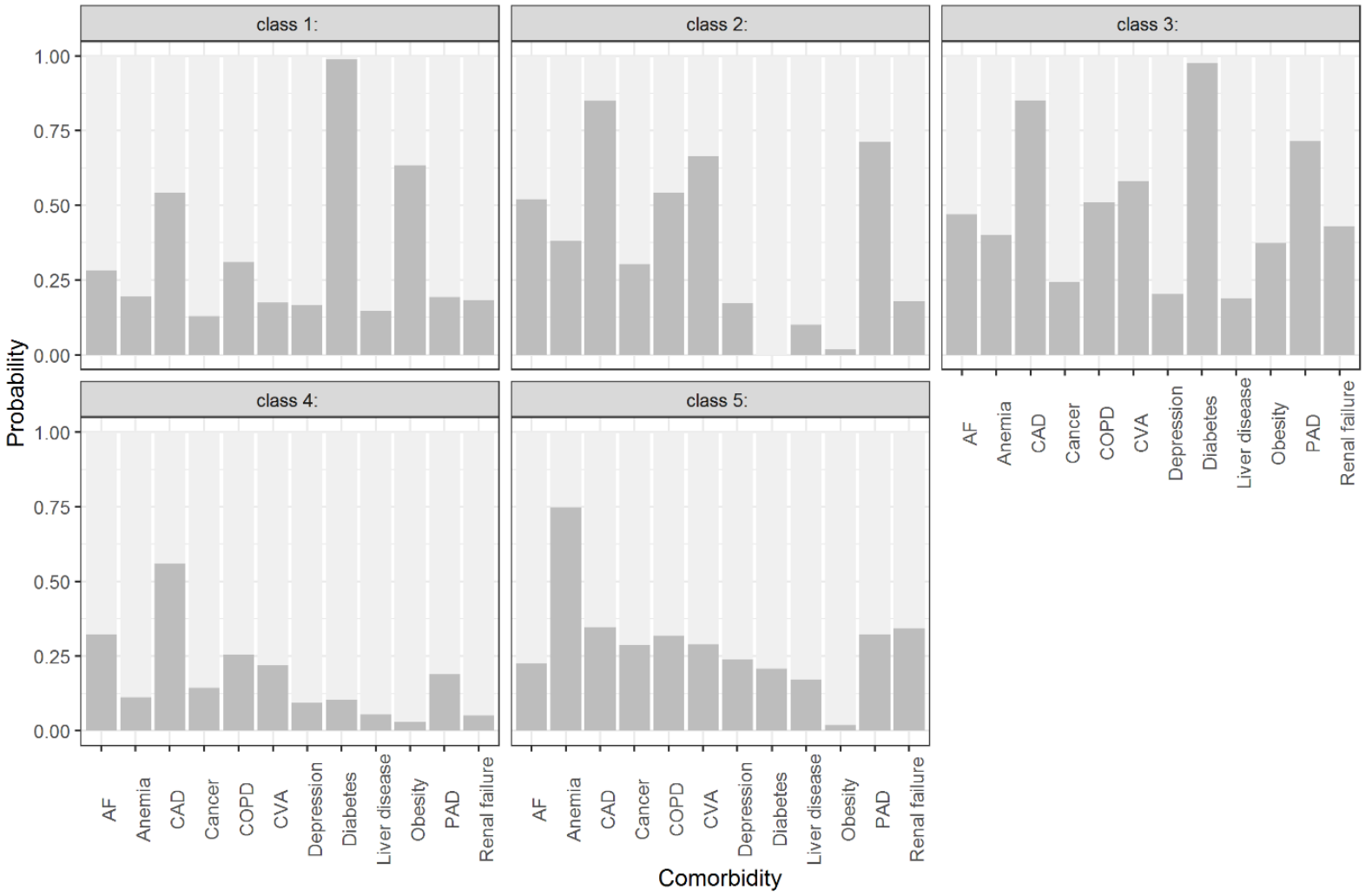

FIGURE 3.3: Partial probabilities of class membership for all variables used in deriving the clusters, per class.

Each model was estimated with 100 replications. There were no cases with missing data. After establishing the optimal number of classes, partial probabilities of being assigned to each class were calculated per patient. Thus, the identified classes represented probabilistic groups of patients with similar combinations of comorbidities. Final class selection was done according to patients' highest probability of being assigned to a class (**Table 3.2**).

TABLE 3.2: Median (IQR) probability of group membership for the 5-class solution

Cluster	Median (IQR)
Low-burden	0.84 (0.67, 0.93)
Metabolic-vascular	0.85 (0.67, 0.95)
Ischemic	0.81 (0.64, 0.92)
Anaemia	0.58 (0.47, 0.7)
Metabolic	0.70 (0.55, 0.90)

IQR= interquartile range

To assess whether adding "hypertension" data to the latent class model would increase model fit, I ran a five-class LCA with this variable included. The BIC penalises on the number of parameters in the model therefore it was used to compare the "hypertension" model with the main model. As expected, adding "hypertension" to the set of comorbidities used to derive the clusters did not improve model fit as the BIC for this model was higher compared to the main model (**Table 3.3**).

TABLE 3.3: Fit between main latent class model and latent class model with variable "hypertension" added.

	Main LCA model	Hypertension LCA model
BIC	4268117	4374723
sBIC	4267914	4374504
LCA= latent class analysis; BIC= Bayesian Information Criterion; sBIC= sample adjusted BIC		

The differences in baseline characteristics between comorbidity clusters were reported using chi-squared and Kruskall-Wallis tests as appropriate, with correction for multiple testing done with the Bonferroni correction.

3.3.4.2 Outcome analysis

Admission to hospital and mortality were analysed using Cox proportional-hazard regression models to calculate hazard ratios (HRs) and 95% confidence intervals (CI). Univariate Kaplan-Meier curves for admission to hospital are shown stratified per comorbidity cluster. Differences were tested with the log-rank test and adjusted for multiple testing using the Bonferroni correction.

For admission analyses, patients were followed up for 12 months after their HF diagnosis or censored at disenrollment or death.

For mortality analyses, patients were followed-up to a censoring date of 1st of January 2019, or at disenrollment, whichever came first. The maximum follow-up date was therefore 120 months (median and inter-quartile range [IQR]: 30 months, 18-51 months). The proportional hazards assumption was assessed using Schoenfeld residual plots [101]. Where this assumption was not

met (i.e., modelling of HF-specific admission, mortality), outcomes were modelled using time-dependent coefficients [102]. All models were adjusted for baseline covariates: age, sex, race, education, medical insurance status, place of diagnosis (in/outpatient), HF recommended medications and comorbidities not used in the clustering step: hypertension, dementia, peptic ulcer, and alcohol misuse disorder.

Incidence of death was calculated as the number of patients who died divided by the total person-months. Negative binomial regressions were used to assess the association between comorbidity clusters and the rate of outpatient, office and ER visits, long-term stays, inpatient admissions and length of stay during one-year follow-up. The negative binomial distribution assumes that each patient has recurrent events according to an individual-specific Poisson event rate and that those vary according to a gamma distribution. Rate ratios and 95% CI were calculated, adjusting for confounders as mentioned previously.

3.3.4.3 Sensitivity analysis: LVEF subset

In a subset of patients with recorded LVEF data, I further adjusted for LVEF as a continuous variable (denoted as % LVEF) and smoking status and tested for interaction between comorbidity cluster and LVEF. If the interaction was non-significant, I did not further categorise this variable[103] and presented the initial model only. This was done as to not underestimate the extent in variation in outcome associated across the spectrum of LVEF which may not be fully captured in a dichotomised approach[104] (i.e., considering LVEF groups such as HFrEF or HFpEF).

3.3.4.4 Sensitivity analysis: pseudo-class draws

I used latent class variables to assess association with outcomes. Usual practice is to assign observations (i.e., patients) to one of the latent classes (clusters) based on the maximum posterior probabilities. The assigned class membership is thus treated as an observed variable, however this method ignores the uncertainty of being in each cluster, for each patient.

Due to the uncertainty in predicted class membership, I employed a multiple imputation (pseudo-class) approach, in a sensitivity analysis, in order to account for any uncertainty that comorbidity cluster classification would add to the outcome statistical analysis. "Pseudo-class draws" is a method to reduce the errors introduced by ignoring the probability of each observation being assigned to classes other than "highest probability" considered in our main approach. With the pseudo-class approach, multiple random draws from the posterior probability distributions of observations are made (in the present case, each patient has five probabilities of belonging to each of the clusters we identified). The random draws are used as multiple imputations of each observation's class membership as if the class membership was missing. I used 20 random draws from a uniform distribution to generate 20 simulated class memberships for each patient (given their original partial class probabilities).

Using each imputed class membership as the exposure to test the association between class membership (comorbidity cluster) and outcome (time-to-admission), I fitted 20 Cox regression models, adjusting for the same covariates used in the main outcome analysis. Estimates from the 20 models fitted to imputed datasets were combined using Rubin's rule. This allowed for the standard error of the association between comorbidity cluster and time to admission to be

calculated. Results from the imputation analysis were attenuated, but similar to the main analysis. Statistical analyses were performed using R v3.6.2 [105].

3.4 Results

3.4.1 Baseline characteristics

The study population comprised of a total of 318,384 patients with incident HF between 1st of January 2008 and 1st of January 2018. Baseline characteristics presented in **Table 3.4**. The median age was 73 years (IQR 63-80) and 48.6% were male. Hypertension (95.2%) was the most common comorbidity, followed by CAD (67.7%), PAD (44.5%) and diabetes (43.7%).

TABLE 3.4: Baseline characteristics stratified by HF comorbidity cluster

	Low-burden (n=83577)	Metabolic-vascular (n=73284)	Ischemic (n=83283)	Anaemia (n=14959)	Metabolic (n=63281)	Overall (n=318384)
Age						
Median [IQR]	71 [60, 79]	73 [66, 80]	78 [70,82]	73 [62, 81]	67 [57, 74]	73 [63, 80]
Sex						
Female	42440 (50.8%)	36716 (50.1%)	40818 (49.0%)	9529 (63.7%)	34017 (53.8%)	163520 (51.4%)
Male	41137 (49.2%)	36568 (49.9%)	42465 (51.0%)	5430 (36.3%)	29264 (46.2%)	154864 (48.6%)
Comorbidities at baseline						
AF	26090 (31.2%)	35031 (47.8%)	44233 (53.1%)	1968 (13.2%)	16844 (26.6%)	124166 (39.0%)
CAD	43999 (52.6%)	63890 (87.2%)	73417 (88.2%)	1771 (11.8%)	32617 (51.5%)	215694 (67.7%)
CVA	15165 (18.1%)	44157 (60.3%)	58088 (69.7%)	3691 (24.7%)	8314 (13.1%)	129415 (40.6%)
PAD	10766 (12.9%)	56137 (76.6%)	64058 (76.9%)	4010 (26.8%)	6676 (10.5%)	141647 (44.5%)
Hypertension	74082 (88.6%)	72855 (99.4%)	81502 (97.9%)	13890 (92.9%)	60897 (96.2%)	303226 (95.2%)
Anaemia	7609 (9.1%)	30174 (41.2%)	33804 (40.6%)	14415 (96.4%)	10224 (16.2%)	96226 (30.2%)
Diabetes	281 (0.3%)	73081 (99.7%)	0 (0%)	2597 (17.4%)	63263 (100.0%)	139222 (43.7%)
Obesity	2854 (3.4%)	25323 (34.6%)	1688 (2.0%)	259 (1.7%)	36812 (58.2%)	66936 (21.0%)
Renal failure	3585 (4.3%)	31489 (43.0%)	16081 (19.3%)	6059 (40.5%)	9854 (15.6%)	67068 (21.1%)
COPD	19045 (22.8%)	37795 (51.6%)	46656 (56.0%)	4779 (31.9%)	18113 (28.6%)	126388 (39.7%)
Cancer	11227 (13.4%)	18097 (24.7%)	25782 (31.0%)	4947 (33.1%)	7599 (12.0%)	67652 (21.2%)
Liver disease	4506 (5.4%)	13861 (18.9%)	8447 (10.1%)	3212 (21.5%)	8353 (13.2%)	38379 (12.1%)
Peptic ulcer	2274 (2.7%)	5168 (7.1%)	5418 (6.5%)	1074 (7.2%)	2089 (3.3%)	16023 (5.0%)
Dementia	4708 (5.6%)	5905 (8.1%)	10913 (13.1%)	1897 (12.7%)	1567 (2.5%)	24990 (7.8%)
Depression	7950 (9.5%)	15019 (20.5%)	14723 (17.7%)	3947 (26.4%)	9647 (15.2%)	51286 (16.1%)

	Low-burden (n=83577)	Metabolic-vascular (n=73284)	Ischemic (n=83283)	Anaemia (n=14959)	Metabolic (n=63281)	Overall (n=318384)
Alcohol misuse disorder	2335 (2.8%)	1862 (2.5%)	2845 (3.4%)	866 (5.8%)	1480 (2.3%)	9388 (2.9%)
No. comorbidities at baseline						
2 or less	31692 (37.9%)	0 (0%)	0 (0%)	374 (2.5%)	2773 (4.4%)	34849 (10.9%)
3 to 4	46386 (55.5%)	1413 (1.9%)	12859 (15.4%)	6939 (46.4%)	27130 (42.9%)	94727 (29.8%)
5 to 6	5453 (6.5%)	23548 (32.1%)	46257 (55.5%)	6426 (43%)	27668 (43.7%)	109352 (34.3%)
7 to 8	46 (0.1%)	33594 (45.8%)	20804 (25%)	1151 (7.7%)	5540 (8.8%)	61135 (19.2%)
Over 9	0 (0%)	14729 (20.1%)	3363 (4%)	69 (0.5%)	160 (0.3%)	18321 (5.8%)
Inpatient diagnosis (vs. outpatient diagnosis)	38052 (45.5%)	40079 (54.7%)	45411 (54.5%)	8057 (53.9%)	31845 (50.3%)	163444 (51.3%)
Insurance type						
Medicare Advantage	50158 (60.0%)	58336 (79.6%)	63766 (76.6%)	10467 (70.0%)	37752 (59.7%)	220479 (69.2%)
Commercial	33419 (40.0%)	14948 (20.4%)	19517 (23.4%)	4492 (30.0%)	25529 (40.3%)	97905 (30.8%)
Race						
White	60104 (71.9%)	48509 (66.2%)	61596 (74.0%)	9517 (63.6%)	41694 (65.9%)	221420 (69.5%)
Black	10277 (12.3%)	12043 (16.4%)	9772 (11.7%)	2828 (18.9%)	11322 (17.9%)	46242 (14.5%)
Hispanic	5200 (6.2%)	6786 (9.3%)	4711 (5.7%)	1162 (7.8%)	4916 (7.8%)	22775 (7.2%)
Asian	2064 (2.5%)	1332 (1.8%)	1619 (1.9%)	398 (2.7%)	947 (1.5%)	6360 (2.0%)
Missing	5932 (7.1%)	4614 (6.3%)	5585 (6.7%)	1054 (7.0%)	4402 (7.0%)	21587 (6.8%)
Education						
Less than 12th grade	213 (0.3%)	333 (0.5%)	202 (0.2%)	50 (0.3%)	249 (0.4%)	1047 (0.3%)
High School Diploma	26027 (31.1%)	27893 (38.1%)	27614 (33.2%)	5239 (35.0%)	23724 (37.5%)	110497 (34.7%)
Less than Bachelor Degree	44827 (53.6%)	37696 (51.4%)	44452 (53.4%)	7643 (51.1%)	33086 (52.3%)	167704 (52.7%)
Bachelor Degree +	11994 (14.4%)	6811 (9.3%)	10511 (12.6%)	1918 (12.8%)	5801 (9.2%)	37035 (11.6%)

	Low-burden (n=83577)	Metabolic-vascular (n=73284)	Ischemic (n=83283)	Anaemia (n=14959)	Metabolic (n=63281)	Overall (n=318384)
Missing	516 (0.6%)	551 (0.7%)	503 (0.6%)	109 (0.7%)	421 (0.7%)	2101 (0.7%)
Income (in U.S. dollars)						
<$40,000	23672 (28.3%)	25282 (34.5%)	27664 (33.2%)	4762 (31.8%)	20137 (31.8%)	101517 (31.9%)
$40,000-$74,000	21529 (25.8%)	19643 (26.8%)	21849 (26.2%)	3600 (24.1%)	16672 (26.3%)	83293 (26.2%)
$75,000-$124,999	17020 (20.4%)	12704 (17.3%)	14310 (17.2%)	2435 (16.3%)	12621 (19.9%)	59090 (18.6%)
$125,000-$199,999	6551 (7.8%)	3684 (5.0%)	4341 (5.2%)	891 (6.0%)	4102 (6.5%)	19569 (6.1%)
$200,000+	3602 (4.3%)	1360 (1.9%)	1957 (2.3%)	423 (2.8%)	1642 (2.6%)	8984 (2.8%)
Missing	11203 (13.4%)	10611 (14.5%)	13162 (15.8%)	2848 (19.0%)	8107 (12.8%)	45931 (14.4%)
Medication at baseline						
Cardioselective beta-blockers	26936 (32.2%)	32949 (45.0%)	36051 (43.3%)	4351 (29.1%)	22095 (34.9%)	122382 (38.4%)
Non-cardioselective beta-blockers	11602 (13.9%)	13169 (18.0%)	11643 (14.0%)	1882 (12.6%)	9463 (15.0%)	47759 (15.0%)
ACEi/ARBs	33005 (39.5%)	41120 (56.1%)	37711 (45.3%)	5925 (39.6%)	31073 (49.1%)	148834 (46.7%)
MRA	3091 (3.7%)	3893 (5.3%)	2864 (3.4%)	733 (4.9%)	3233 (5.1%)	13814 (4.3%)
Thiazide	9444 (11.3%)	12071 (16.5%)	10997 (13.2%)	1964 (13.1%)	9809 (15.5%)	44285 (13.9%)
Loop diuretics	19171 (22.9%)	28629 (39.1%)	24597 (29.5%)	4772 (31.9%)	21361 (33.8%)	98530 (30.9%)
Potassium sparing diuretics	44 (0.1%)	90 (0.1%)	71 (0.1%)	23 (0.2%)	72 (0.1%)	300 (0.1%)
Double therapy (ACEi/ARBs and any beta-blocker)	19842 (23.7%)	27291 (37.2%)	24207 (29.1%)	2990 (20.0%)	18142 (28.7%)	92472 (29.9%)

	Low-burden (n=83577)	Metabolic-vascular (n=73284)	Ischemic (n=83283)	Anaemia (n=14959)	Metabolic (n=63281)	Overall (n=318384)
Triple therapy (ACEi/ARB + any beta blocker + MRA)	1530 (1.8%)	1905 (2.6%)	1273 (1.5%)	179 (1.2%)	1475 (2.3%)	6362 (2.0%)

ACEis= angiotensin-converting-enzyme inhibitors; AF= atrial fibrillation; ARB= angiotensin receptor blocker; CAD= coronary artery disease; COPD=chronic obstructive pulmonary disease; CVA= cerebrovascular disease; IQR= inter-quartile range; PAD= peripheral artery disease; No.= number; MRA= mineralocorticoid receptor antagonist; US= United States.

A five-group solution was the best fit to describe comorbidity patterns. The five clusters were each characterised by a different combination of comorbidities and socio-demographic factors and thus, were named according to their dominant elements: low-burden, metabolic-vascular, ischemic, anaemic and metabolic (see **Figure 3.4).**

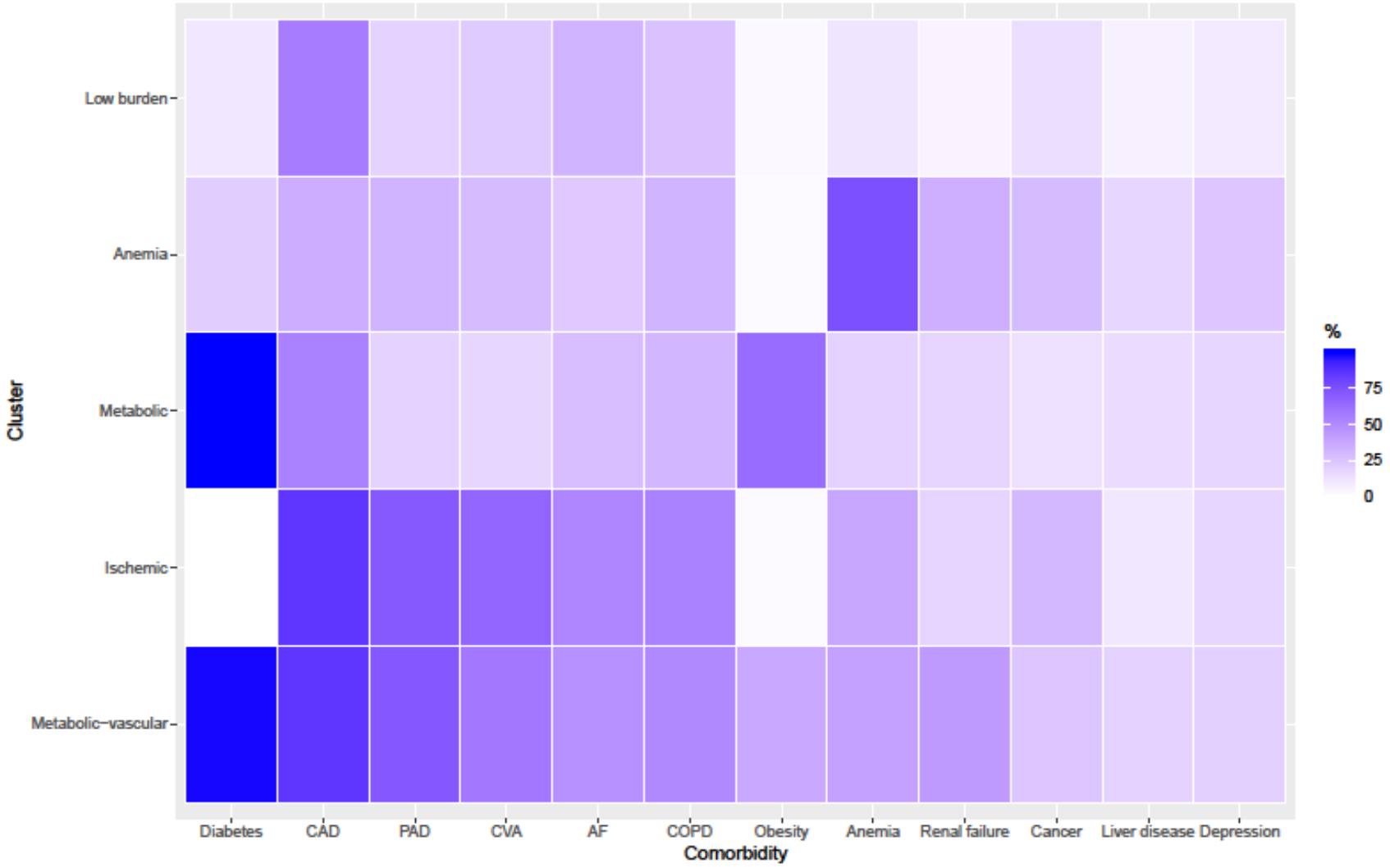

FIGURE 3.4: Five comorbidity clusters identified in patients with heart failure.

Tile plot illustrating cluster-specific comorbidity percentages from the latent class analysis results.

Patients in the low-burden group had relatively less comorbidities compared to the other groups. Amongst these, CAD was most common condition (52.6% of patients). Individuals in this group were least likely to have received their HF diagnosis as an inpatient or to have prescriptions for any HF pharmacological treatments. Nearly all patients in the metabolic-vascular cluster had diabetes (99.7%) and 34.6% had a diagnosis of obesity. This group also had the highest prevalence of renal failure and proportion of Medicare Advantage enrolees as opposed to a commercial insurance plan. The metabolic-vascular cluster also had the highest proportion of Hispanic patients (9.3%) and the highest percentage of prescriptions across the whole spectrum of HF recommended medications.

The ischemic cluster was the oldest group on average (median 78 years) and included no patients with diabetes, though there was a comparably high prevalence of CAD (88.2%) and PAD (76.9%) as in the metabolic-vascular cluster as well as similar proportion of patients with cardioselective beta-blocker prescriptions. The highest proportion of White patients (75%) was observed in this cluster.

The highest proportions of women (63.7%), cancer (33.1%) and depression (26.4%) were found among the anaemic group. This cluster had an intermediate prescription rate for HF medications, compared to the other clusters.

Patients in the metabolic cluster were on average the youngest (median age 67 years), all were diabetic, and 58.2% were obese. Among this group there was the lowest prevalence of PAD (10.5%), CVA (13.1%) and cancer (12%), with intermediate prescription rates for HF medications (see **Table 3.4**).

Patients in the low-burden cluster had relatively fewer comorbidities compared to all others (93.4% of all patients had less than five comorbidities), while fewer patients in the anaemic (48.9%) and metabolic groups (40.7%) had less than five comorbidities.

In contrast, the overall comorbidity burden was higher in the metabolic-vascular and ischemic groups. 98% all patients in the metabolic-vascular group and a majority in the ischemic group (84. 5%) had five or more additional chronic diseases.

Across all comorbidity clusters there was a surge in the number of patients who were prescribed HF medications from baseline to one-year follow-up, except potassium-sparing diuretics. The highest increases were seen in MRA prescriptions, though levels were still overall quite low (only between 8.2% and 12% of patients across each group were prescribed these), followed by increases in loop diuretics and beta-blockers (see **Figure 3.5**).

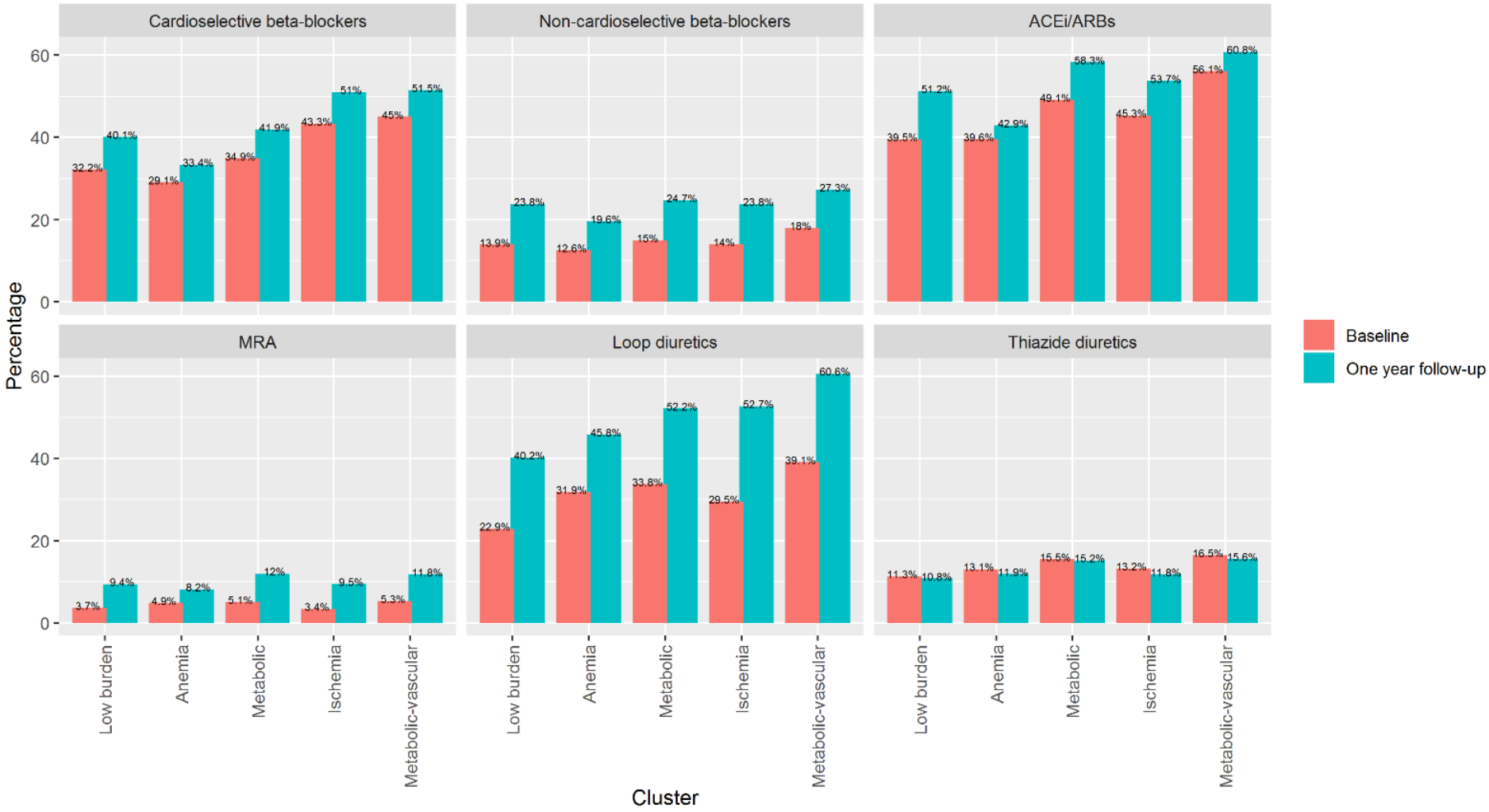

FIGURE 3.5: Prescription patterns for heart failure recommended medications across comorbidity clusters

Potassium-sparing not shown due to <0.1% patients receiving this medication class.

3.4.2 Hospitalisation

The crude frequencies for all-cause and HF-specific admission to hospital are presented in **Table 3.5**. and **Figure 3.6**.

From the overall population, 38.7% of patients were hospitalised within one-year follow-up after their HF diagnosis; 8.8% were HF-specific admissions. Overall, 25.1% of the low-burden group and 51.1% of the metabolic-vascular group were admitted; the remaining groups had lower admission rates.

TABLE 3.5: Frequency of admission to hospital across HF comorbidity clusters, at one-year follow-up

	Low-burden (n=83577)	**Metabolic-vascular (n=73284)**	**Ischemic (n=83283)**	**Anaemia (n=14959)**	**Metabolic (n=63281)**	**Overall (n=318384)**	**P Value [a]**
All-cause admission	20990 (25.1%)	37472 (51.1%)	39645 (47.6%)	5637 (37.7%)	19473 (30.8%)	123217 (38.7%)	<0.001
HF-specific admission	4594 (5.5%)	8921 (12.2%)	9384 (11.3%)	915 (6.1%)	4352 (6.9%)	28166 (8.8%)	<0.001

[a] Bonferroni adjusted
HF= heart failure

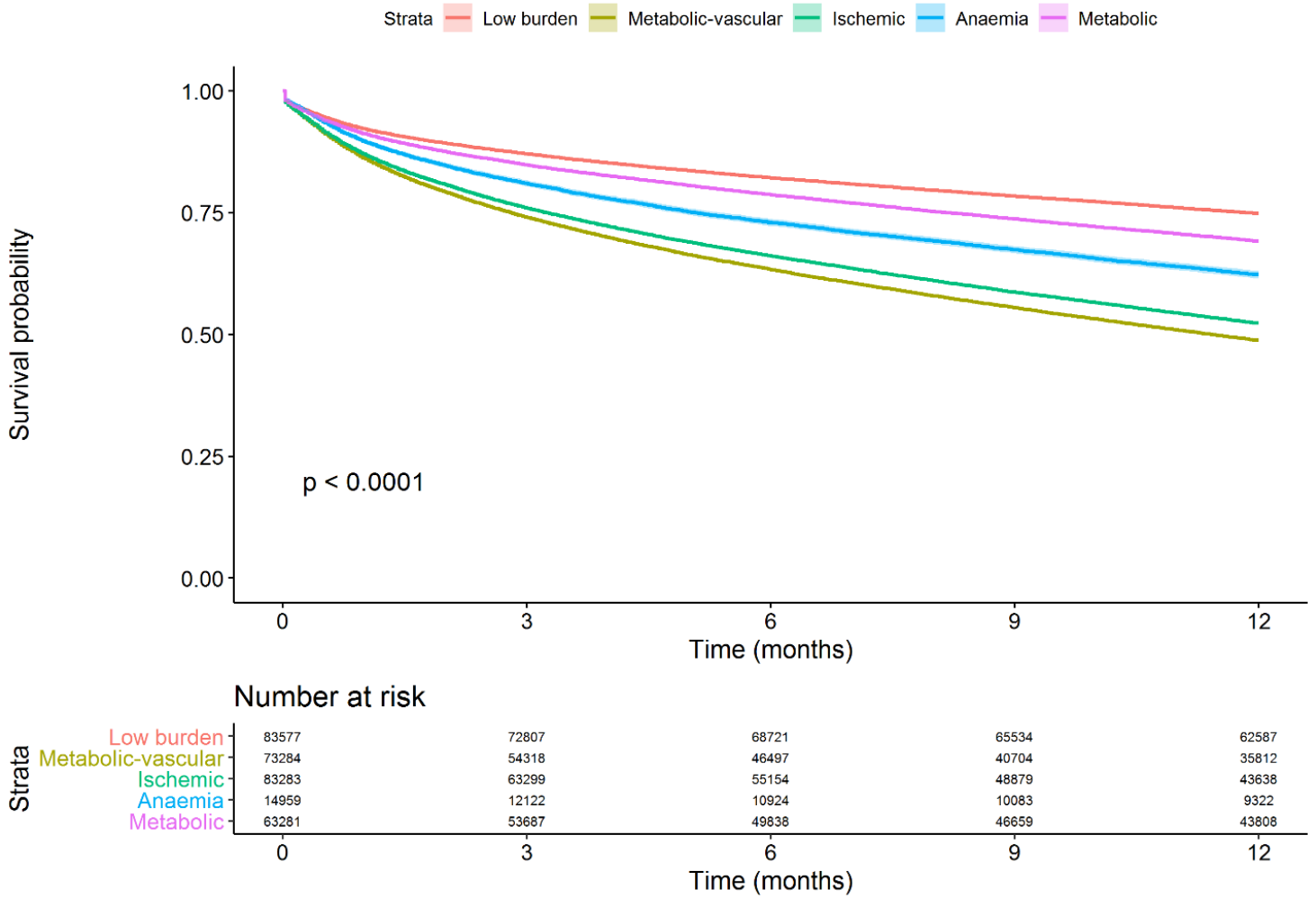

FIGURE 3.6: Kaplan-Meier curve for all-cause admission to hospital by HF comorbidity cluster at one-year follow-up

Differences in risk of admission remained after adjusting for baseline confounders. The metabolic group had the lowest risk (HR_{adj} 95%CI: 1.16, 1.14 to 1.19) while the metabolic-vascular exhibited the highest risk of admission (HR_{adj}, 95%CI: 2.21, 2.17 to 2.25), compared to the low-burden, reference group (see **Figure 3.7**).

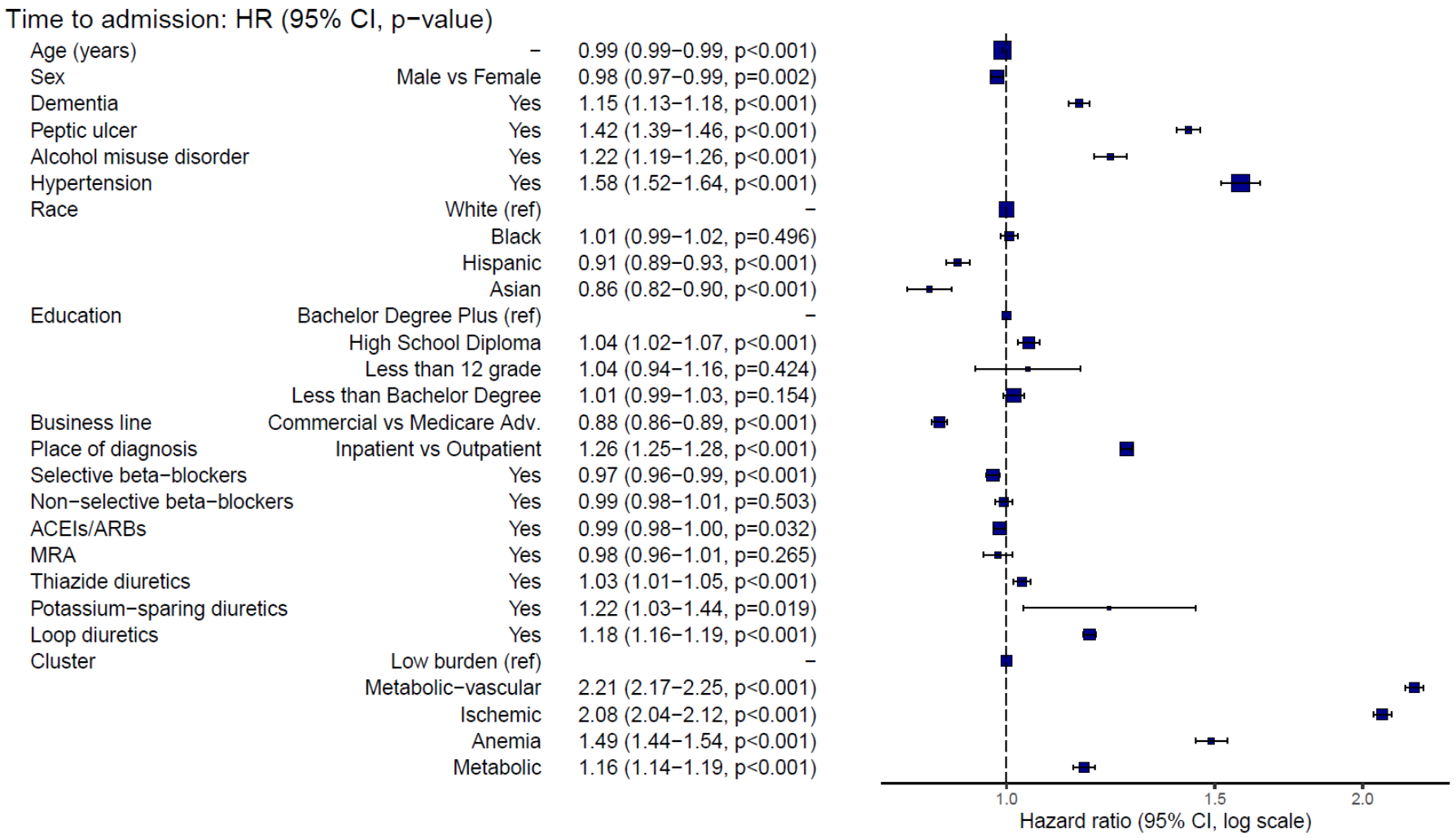

FIGURE 3.7: Association between time to all-cause admission and HF comorbidity clusters, adjusted for baseline covariates

Patients with missing data excluded (N=295,972).

3.4.3 HF-specific hospitalisation

The metabolic-vascular and ischemic clusters were associated with similarly high risk of HF-specific admission (increase of 85% respectively 81%) followed by the metabolic cluster (increase of 14%) (see **Table 3.6**).

TABLE 3.6: Association between HF comorbidity clusters and heart failure-specific admission to hospital with time-varying coefficient due to non-proportional hazards, at one-year follow-up.

	Unadjusted HR (95% CI)	**Adjusted HR (95% CI)**
Age (years)	1.01 (1.00-1.01, p<0.001)	1.01 (1.00-1.01, p<0.001)
Male vs. Female	0.98 (0.97-0.99, p<0.001)	1.08 (1.06-1.11, p<0.001)
Dementia	1.25 (1.23-1.28, p<0.001)	0.87 (0.83-0.91, p<0.001)
Peptic ulcer	1.65 (1.62-1.69, p<0.001)	1.10 (1.05-1.16, p<0.001)
Alcohol misuse disorder	1.32 (1.28-1.36, p<0.001)	0.86 (0.80-0.93, p<0.001)
Hypertension	2.06 (1.99-2.14, p<0.001)	2.02 (1.83-2.22, p<0.001)
Race (ref: White)		
Black	1.06 (1.04-1.07, p<0.001)	1.14 (1.11-1.18, p<0.001)
Hispanic	0.93 (0.91-0.95, p<0.001)	1.02 (0.97-1.07, p=0.498)
Asian	0.83 (0.79-0.86, p<0.001)	1.05 (0.86-1.14, p=0.255)
Education (ref: Bachelor Degree Plus)		
High School Diploma	1.15 (1.12-1.17, p<0.001)	1.03 (0.99-1.08, p=0.134)
Less than 12 grade	1.08 (0.98-1.19, p=0.133)	1.06 (0.86-1.30, p=0.596)
Less than Bachelor Degree	1.08 (1.06-1.10, p<0.001)	1.01 (0.96-1.05, p=0.789)
Business line (Commercial vs. Medicare Advantage)	0.81 (0.80-0.82, p<0.001)	1.02 (0.99-1.06, p=0.135)
Place of diagnosis (inpatient vs outpatient)	1.32 (1.31-1.34, p<0.001)	1.23 (1.20-1.26, p<0.001)
Medication at baseline		
Cardioselective beta-blockers	1.07 (1.06-1.08, p<0.001)	0.99 (1.00-1.01, p=0.372)

	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Non-cardioselective-selective beta-blockers	1.03 (1.01-1.04, p=0.001)	1.15 (1.11-1.19, p<0.001)
ACEIs/ARBs	1.06 (1.05-1.07, p<0.001)	1.02 (1.00 -1.05, p=0.151)
MRA	1.03 (1.00-1.06, p=0.036)	0.94 (0.88 – 0.99, p<0.05)
Thiazide diuretics	1.07 (1.05-1.08, p<0.001)	1.10 (1.06-1.14, p<0.001)
Potassium-sparing diuretics	1.35 (1.15-1.59, p<0.001)	0.88 (0.59-1.30, p=0.525)
Loop diuretics	1.21 (1.20-1.23, p<0.001)	1.37 (1.33-1.41, p<0.001)
Cluster (ref: Low-burden)		
Metabolic-vascular	2.43 (2.39-2.47, p<0.001)	1.85 (1.78-1.92, p<0.001)
Metabolic-vascular * time [a]	1.16 (1.13- 1.19, p<0.001)	1.16 (1.13-1.19, p<0.001)
Ischemic	2.20 (2.17-2.24, p<0.001)	1.81 (1.75-1.88, p<0.001)
Ischemic * time [b]	1.13 (1.10-1.15, p<0.001)	1.13 (1.10-1.15, p<0.001)
Anaemia	1.62 (1.58-1.67, p<0.001)	1.02 (0.94 -1.10, p=0.622)
Anaemia * time [c]	1.05 (1.00-1.10, p<0.05)	1.05 (1.00-1.10, p<0.05)
Metabolic	1.16 (0.88-1.52, p=0.289)	1.14 (1.09 -1.20, p<0.001)
Metabolic * time [d]	1.05 (1.02-1.08, p<0.001)	1.05 (1.03-1.08, p<0.001)

ACEi= angiotensin-converting-enzyme inhibitors; ARB= angiotensin receptor blockers; CI= confidence intervals; HR= hazard ratio; ref= reference; MRA= mineralocorticoid receptor antagonists.
Coefficients for interaction with time:
[a] 0.147 , p-value<0.001
[b] 0.130 , p-value <0.001
[c] 0.051 , p-value=0.034
[d] 0.050 , p-value<0.001

3.4.4 Mortality

26% of individuals died over a median follow up of 30 months. Unadjusted death rates were lowest in the metabolic (3.76 per 1000 person-months [3.68-3.84]), and low-burden groups (5.05 per 1000 person-months [4.97-5.12]) and highest in the anaemic (8.45 per 1000 person-months [8.21-8.70] and ischemic groups (10.08 per 1000 person-months [9.96-10.18]).

Time-dependent coefficient analysis showed a statistically significant time-varying association between clusters and time-to-death for all but the anaemic cluster. This means the relationship between cluster and death was not constant over time except for the anaemic cluster. The effect of time on the association between cluster and death was diminished for the metabolic and metabolic-vascular clusters (as denoted by the negative coefficients for the time*cluster interaction from the Cox regression, see **Table 3.7**). The opposite was observed for the ischemic cluster, where there was an increase in the risk of death over time, on average.

TABLE 3.7: Association between mortality and HF comorbidity cluster with interaction between cluster and time

	Multivariable model* HR (95% CI) and coefficients for interaction
Cluster (ref: Low-burden)	
Metabolic-vascular	1.87 (1.74-2.01, p<0.001)
Metabolic-vascular * time	Coef -0.086; p<0.001
Ischemic	1.24 (1.16-1.33, p<0.001)
Ischemic * time	Coef 0.020, p<0.001
Anaemia	1.46 (1.30-1.64, p<0.001)
Anaemia * time	Coef 0.061, p=0.258
Metabolic	1.18 (1.09-1.29, p<0.001)
Metabolic * time interaction	Coef -0.075, p<0.001

ACE= angiotensin-converting-enzyme inhibitors; ARB= angiotensin receptor blocker; Coef: coefficient; HR= hazard ratio; CI= confidence intervals; ref= reference; MRA= mineralocorticoid receptor antagonists;
* Adjusted for: age, sex, race, education, medical insurance status, whether diagnosis was gained in-patient or in out-patient and HF medications; time-varying coefficient model; excludes patients with missing data on race (21,557) and education (2,097)
Median 30 months follow-up, coefficients from adjusted model.

To explore the effect of the interaction, I used a step function for estimating the variation with time over one-year intervals and obtained stratified HRs per each time group, presented in Appendix B, **Figure B1**.

In analyses adjusted for baseline covariates (**Table 3.8**), the metabolic-vascular cluster had the highest increased hazard of death compared to the low-burden group (HR_{adj}: 1.87 [95% CI 1.74 to 2.01]), while the anaemic and ischemic groups had intermediate risk, on average, during follow-up. The metabolic group displayed the lowest risk of death, though, when further adjustment for smoking status and LVEF was performed in Model 2, the estimate was no longer statistically significant (HR_{adj} [95% CI]: 0.96 [0.84 to 1.10]).

TABLE 3.8: Association between any-cause mortality and HF comorbidity cluster

	Low-burden	Metabolic-vascular	Ischemic	Anaemia	Metabolic	Overall
Model 1[a]	*N=77325*	*N=68414*	*N=77425*	*N=13850*	*N=58635*	*N=295649*
Deaths (%)	17291 (22.4%)	16414 (24.7%)	30510 (39.4%)	4325 (31.2%)	8251 (14.1%)	77276 (26.1%)
Adjusted HR[a] (95% CI)	1.00 (ref)	1.87 (1.74-2.01)	1.24 (1.16-1.33)	1.46 (1.30-1.64)	1.18 (1.09-1.29)	
Model 2[b]	*N=2707*	*N=3267*	*N=3265*	*N=247*	*N=2483*	*N=12091*
Deaths n (%)	510 (20.1%)	755 (24.6%)	1,166 (38%)	98 (28.3%)	281 (12.1%)	3478 (28.8%)
Adjusted HR[b] (95% CI)	1.00 (ref)	1.60 (1.44, 1.79)	1.62 (1.47, 1.80)	1.60 (1.30, 1.96)	0.96 (0.84, 1.10, p=0.569)	

CI= confidence intervals; HR= hazard ratio; ref= reference

[a] Adjusted for: age, sex, race, education, medical insurance status, whether diagnosis was gained in-patient or in out-patient and HF medications; time-varying coefficient model; excludes patients with missing data on race (21,557) and education (2,097).

[b] Adjusted for variables above, left ventricular ejection fraction, smoking status; proportional hazards met; excludes patients with missing data on race (21,557), education (2,097), left ventricular ejection fraction (304,477) and smoking status (282,333).

3.4.5 Healthcare resource use

Results from the negative binomial regressions, which relate each utilisation rate with the comorbidity clusters, are presented in **Table 3.9**.

Table 3.9. Association between healthcare utilisation and HF comorbidity cluster at one year follow-up

	Rate ratio (95% CI)		
	Unadjusted RR	**Model 1[a] Adjusted RR**	**Model 2[b] Adjusted RR**
	N=314936	N=292768	N=11955
Outcome and comorbidity cluster			
Outpatient visits			
Low-burden	Ref.	Ref.	Ref.
Metabolic-vascular	2.33 (2.30, 2.36)	2.01 (1.98, 2.04)	1.96 (1.84, 2.08)
Ischemic	1.91 (1.89, 1.93)	1.73 (1.71, 1.75)	1.70 (1.60, 1.81)
Anaemia	2.32 (2.26, 2.37)	2.11 (2.06, 2.16)	1.89 (1.67, 2.14)
Metabolic	1.24 (1.22, 1.25)	1.17 (1.15, 1.20)	1.13 (1.06, 1.21)
Office visits			
Low-burden	Ref.	Ref.	Ref.
Metabolic-vascular	1.29 (1.28, 1.31)	1.32 (1.31, 1.33)	1.23 (1.17, 1.28)
Ischemic	1.30 (1.29, 1.31)	1.35 (1.34, 1.37)	1.28 (1.23, 1.34)
Anaemia	1.15 (1.13, 1.17)	1.16 (1.15, 1.18)	1.26 (1.16, 1.38)
Metabolic	1.08 (1.07, 1.09)	1.05 (1.04, 1.06)	1.05 (1.00, 1.10)
Long-term care stays			
Low-burden	Ref.	Ref.	Ref.
Metabolic-vascular	2.87 (2.78, 2.96)	2.54 (2.46, 2.62)	2.75 (2.32, 3.26)
Ischemic	3.06 (2.95, 3.14)	2.26 (2.19, 2.33)	2.38 (2.01, 2.82)
Anaemia	2.22 (2.10, 2.33)	1.77 (1.67, 1.86)	2.41 (1.81, 3.21)
Metabolic	1.02 (0.98, 1.06)	1.21 (1.17, 1.26)	1.12 (0.90, 1.38)
Hospitalisations			
Low-burden	Ref.	Ref.	Ref.
Metabolic-vascular	2.86 (2.78, 2,96)	2.11 (2.08, 2.15)	2.02 (1.86, 2.19)
Anaemia	2.22 (2.78, 2.96)	1.64 (1.59, 1.68)	1.85 (1.59, 2.16)
Ischemia	3.04 (2.95, 3.14	2.11 (2.07, 2.15)	1.99 (1.83, 2.17)

	Rate ratio (95% CI)		
	Unadjusted RR	**Model 1[a] Adjusted RR**	**Model 2[b] Adjusted RR**
Metabolic	1.01 (0.97, 1.05)	1.07 (1.04, 1.09)	1.09 (0.99, 1.19)
Length of stay for hospitalisations			
Low-burden	Ref.	Ref.	Ref.
Metabolic-vascular	2.70 (2.97, 3.08)	2.58 (2.52, 2.65)	2.60 (2.28, 2.95)
Ischemic	2.43 (2.37, 2.49)	2.48 (2.41, 2.54)	2.44 (2.14, 2.77)
Anaemia	2.39 (2.29, 2.50)	2.08 (2.01, 2.16)	2.29 (1.85, 2.80)
Metabolic	1.25(1.21, 1.27)	1.09 (1.06, 1.13)	1.17 (1.00, 1.35)

CI= confidence intervals; RR= rate ratio; ref= reference

[a] Adjusted for: age, sex, race, education, medical insurance status, whether diagnosis was gained in-patient or in out-patient and HF medications; patients with missing data were excluded

[b] Adjusted for age, sex, race, education, medical insurance status, whether diagnosis was gained in-patient or in out-patient and HF medications, left ventricular ejection fraction, smoking status; patients with missing data were excluded

Overall, in adjusted analyses, all comorbidity clusters exhibited significantly increased rates of utilisation, in comparison to the low-burden group. The metabolic-vascular and ischemic clusters had the highest rates of hospitalisations and related cumulative length of stay, long-term care stays and office visits, whilst the anaemic group was associated with highest incidence rate of outpatient visits. Cost differences also reflected utilisation results, as the metabolic-vascular cluster had the highest median charges, followed by the ischemic, anaemic, metabolic and low-burden clusters (Appendix B, **Table B4**).

3.4.6 Sensitivity analyses

Pseudo-draws approach

Differences in admission were attenuated but remained significant in sensitivity analysis accounting for uncertainty in class membership (see **Table 3.10**).

TABLE 3.10: Adjusted association between admission to hospital and HF comorbidity cluster, at one-year follow-up.

	Imputation model					**Main analysis**				
	Estimate	SE	Lower 95%CI	Upper 95%CI	P Value	Estimate	SE	Lower 95%CI	Upper 95%CI	P Value
Model covariate										
Age (years)	-0.006	0.0003	-0.006	-0.005	<0.001	-0.007	0.0003	-0.008	-0.007	<0.001
Sex (Male vs. Female)	-0.005	0.006	-0.017	0.006	0.384	-0.018	0.006	-0.030	-0.006	<0.05
Dementia	0.168	0.010	0.147	0.189	<0.001	0.141	0.010	0.120	0.162	<0.001
Peptic ulcer	0.382	0.012	0.359	0.405	<0.001	0.353	0.011	0.331	0.376	<0.001
Alcohol misuse disorder	0.215	0.016	0.183	0.247	<0.001	0.202	0.016	0.170	0.233	<0.001
Hypertension	0.506	0.019	0.468	0.544	<0.001	0.456	0.019	0.417	0.493	<0.001
Race (ref: White)										
Black	0.005	0.008	-0.011	0.022	0.517	0.005	0.008	-0.001	0.021	0.496
Hispanic	-0.088	0.011	-0.112	-0.065	<0.001	-0.09	0.011	-0.118	-0.072	<0.001
Asian	-0.149	0.022	-0.192	-0.105	<0.001	-0.149	0.022	-0.193	-0.106	<0.001
Education (ref: Bachelor Degree +)										
High School Diploma	0.049	0.011	0.029	0.070	<0.001	0.043	0.010	0.022	0.063	<0.001
Less than 12 grade	0.050	0.053	-0.053	0.154	0.343	0.041	0.052	-0.060	0.144	0.424
Less than Bachelor Degree	0.016	0.009	0.003	0.036	0.09	0.014	0.009	-0.005	0.033	0.153
Insurance type Commercial vs. Medicare Advantage	-0.140	0.008	-0.155	-0.124	<0.001	-0.130	0.007	-0.145	-0.114	<0.001
Place of diagnosis Inpatient vs. outpatient	0.248	0.006	0.235	0.260	<0.001	0.233	0.006	0.221	0.245	<0.001

Medications at baseline										
Cardioselective beta- blockers	-0.009	0.006	-0.022	0.003	0.130	-0.026	0.006	-0.038	-0.013	<0.001
Noncardio-selective beta-blockers	0.007	0.009	-0.009	0.024	0.395	-0.005	0.008	-0.022	0.011	0.502
ACEIs/ARBs	0.008	0.006	-0.020	0.003	0.175	-0.013	0.006	-0.025	-0.001	<0.05
MRA	-0.018	0.015	-0.046	0.010	0.215	-0.016	0.145	-0.044	0.012	0.265
Thiazide diuretics	0.029	0.008	0.013	0.047		0.030	0.008	0.013	0.046	<0.001
Potassium-sparing diuretics	0.213	0.086	0.044	0.383	<0.05	0.199	0.085	0.032	0.367	<0.05
Loop diuretics	0.168	0.007	0.155	0.181	<0.001	0.162	0.006	0.149	0.174	<0.001
Cluster (ref: Low-burden)										
Metabolic-vascular	0.657	0.011	0.638	0.680	<0.001	0.793	0.010	0.775	0.811	<0.001
Ischemic	0.581	0.012	0.556	0.604	<0.001	0.731	0.009	0.713	0.749	<0.001
Anaemia	0.295	0.018	0.259	0.330	<0.001	0.398	0.015	0.368	0.429	<0.001
Metabolic	0.147	0.012	0.122	0.172	<0.001	0.151	0.010	0.130	0.171	<0.001

ACEi= angiotensin-converting-enzyme inhibitors; ARB = angiotensin receptor blockers; CI= confidence interval; SE= standard error; ref= reference; MRA= mineralocorticoid receptor antagonists

Results from 20 models using imputed class assignments (estimates combined using Rubin's rule) and results from the main analysis.

Competing risk of death before hospitalisation

In the presence of competing risk of death, cluster membership showed an unchanged association with admission to hospital one year after initial HF diagnosis (Appendix B, **Figure B2, Table B5**).

Subset of patients with LVEF recorded in OLDW

Baseline characteristics

LVEF group data was available in 13,560 patients. More patients with HFpEF were diagnosed outpatient compared to the other two groups and were more likely to be on Medicare rather than commercial insurance plans. The highest prevalence of HFpEF was observed in the metabolic-vascular cluster, whilst the prevalence of HFrEF appeared to be relatively uniform, with the exception of the anaemic subgroup, where prevalence was lower compared to all other clusters (although this comparison may be limited by the relatively small number of patients in this group, see **Table 3.11**).

TABLE 3.11: Distribution of ejection fraction group and smoking status across HF comorbidity clusters in patients with data available

Comorbidity Cluster	Low-burden	Metabolic-vascular	Ischemic	Anaemia	Metabolic	Overall	P-Value[a]
LVEF (n=13,560)							
HFrEF	981 (1.2%)	610 (0.8%)	775 (0.9%)	60 (0.4%)	674 (1.1%)	3100 (1.0%)	
HFmEF	421 (0.5%)	375 (0.5%)	418 (0.5%)	31 (0.2%)	314 (0.5%)	1559 (0.5%)	
HFpEF	1728 (2.1%)	2597 (3.5%)	2459 (3.0%)	325 (2.2%)	1792 (2.8%)	8901 (2.8%)	
Missing	80447 (96.3%)	69702 (95.1%)	79631 (95.6%)	14543 (97.2%)	60501 (95.6%)	304824 (95.7%)	

HFmEF= Heart failure with mid-range ejection fraction [EF] [40 %<EF<50%]; HFpEF= heart failure with preserved ejection fraction HFpEF [EF≥50%; HFrEF= heart failure with reduced ejection fraction HFrEF [EF≤40%]

[a] Non-significant pairwise Bonferroni adjusted comparisons: metabolic-vascular vs. anaemia; anaemia vs. metabolic; ischemic vs. metabolic

Hospitalisation

Differences in admission were attenuated but remained significant after further adjustment for LVEF in the sensitivity analysis (see **Table 3.12**). The interaction between LVEF and comorbidity cluster was not significant (Appendix B, **Table B6**).

TABLE 3.12: Association between all-cause admission to hospital and HF comorbidity cluster, further adjusted for LVEF and smoking status, at one-year follow-up (N=11,294)

	Univariable HR (95% CI)	**Adjusted HR (95% CI)**
Age (years)	1.01 (1.00-1.01, p<0.001)	0.99 (0.99-1.00, p<0.001)
Sex (Male vs. Female)	0.98 (0.97-0.99, p<0.001)	0.86 (0.81-0.91, p<0.001)
Dementia	1.25 (1.23-1.28, p<0.001)	1.32 (1.18-1.48, p<0.001)
Peptic ulcer	1.65 (1.62-1.69, p<0.001)	1.53 (1.39-1.70, p<0.001)
Alcohol misuse disorder	1.32 (1.28-1.36, p<0.001)	1.43 (1.24-1.64, p<0.001)
Hypertension	2.06 (1.99-2.14, p<0.001)	1.66 (1.37-2.01, p<0.001)
Race (ref: White)		
Black	1.06 (1.04-1.07, p<0.001)	1.07 (0.98-1.17, p=0.118)
Hispanic	0.93 (0.91-0.95, p<0.001)	0.89 (0.75-1.05, p=0.162)
Asian	0.83 (0.79-0.86, p<0.001)	1.01 (0.77-1.32, p=0.958)
Education (ref: Bachelor Degree +)		
High School Diploma	1.15 (1.12-1.17, p<0.001)	1.05 (0.95-1.16, p=0.363)
Less than 12 grade	1.08 (0.98-1.19, p=0.133)	1.81 (0.58-5.65, p=0.307)
Less than Bachelor Degree	1.08 (1.06-1.10, p<0.001)	1.02 (0.93-1.11, p=0.719)
Commercial vs Medicare Advantage	0.81 (0.80-0.82, p<0.001)	0.88 (0.81-0.96, p=0.005)
Inpatient vs Outpatient	1.32 (1.31-1.34, p<0.001)	1.14 (1.07-1.21, p<0.001)
Medications at baseline		
Cardioselective beta-blockers	1.07 (1.06-1.08, p<0.001)	0.95 (0.89-1.01, p=0.093)
Non-cardioselective beta-blockers	1.03 (1.01-1.04, p=0.001)	0.97 (0.89-1.05, p=0.451)
ACEIs/ARBs	1.06 (1.05-1.07, p<0.001)	0.96 (0.91-1.02, p=0.216)
MRA	1.03 (1.00-1.06, p=0.036)	0.95 (0.83-1.08, p=0.408)
Thiazide diuretics	1.07 (1.05-1.08, p<0.001)	1.04 (0.95-1.13, p=0.396)
Potassium-sparing diuretics	1.35 (1.15-1.59, p<0.001)	1.10 (0.52-2.31, p=0.806)
Loop diuretics	1.21 (1.20-1.23, p<0.001)	1.16 (1.08-1.23, p<0.001)
Cluster (ref: Low-burden)		
Metabolic-vascular	2.43 (2.39-2.47, p<0.001)	2.11 (1.92-2.32, p<0.001)
Ischemic	2.20 (2.17-2.24, p<0.001)	1.90 (1.72-2.08, p<0.001)
Anaemia	1.62 (1.58-1.67, p<0.001)	1.70 (1.43-2.03, p<0.001)

	Univariable HR (95% CI)	Adjusted HR (95% CI)
Metabolic	1.26 (1.24-1.29, p<0.001)	1.17 (1.05-1.30, p=0.004)
Smoking status (ref: Current smoker)*	-	-
Never smoked	0.80 (0.76-0.84, p<0.001)	0.87 (0.80-0.95, p=0.003)
Not currently smoking	0.88 (0.83-0.93, p<0.001)	0.94 (0.84-1.04, p=0.238)
Previously smoked	0.85 (0.81-0.89, p<0.001)	0.87 (0.80-0.95, p=0.001)
LVEF	1.00 (1.00-1.00, p=0.015)	1.00 (1.00-1.00, p=0.817)

ACEis= angiotensin-converting-enzyme inhibitors; ARB= angiotensin receptor blockers; CI= confidence intervals; HR= hazard ratio; LVEF= left ventricular ejection fraction; MRA= mineralocorticoid receptor antagonist; ref, reference.
LVEF was introduced as continuous term - interaction between LVEF and cluster not significant (model not shown).
*this variable was adjusted for in the present analysis only, due to availability of data for the LVEF subgroup.

3.5 Discussion

3.5.1 Main findings

This is the largest study of model-based clustering in HF published to date, using routinely available variables in a population sample generalisable to insured people living in the US. In this analysis, I identified five distinct comorbidity clusters of patients with HF, namely: the low-burden, metabolic-vascular, anaemic, ischemic and metabolic groups. These comorbidity clusters were differentially associated with risk of hospital admission and death, suggesting comorbidity patterns reflect variable HF clinical patterns and have prognostic relevance.

3.5.2 Comparison with previous studies

Previous studies have identified subgroups in HF: Tromp et al. (2018)[96] included registry patients from various locations in Asia and found five clusters, with differential quality of life and rates of a composite outcome of death or HF hospitalisation within one year follow-up.

Authors identified ischemic and metabolic subgroups – similarly to the present study - but with significantly different characteristics to the current cohort. Particularly, the Asian metabolic group had lower rates of diabetes (63.5% vs. 100%) and obesity (45.1% vs. 58%) and was on average 10 years younger than the US sample. The Asian ischemic cluster had similar prevalence of CAD; however, the US group had a higher prevalence of non-cardiovascular chronic disease including cancer and liver disease. The remaining three clusters identified by Tromp et al. (2018)[96]: elderly/AF; young and lean diabetic did not have direct correspondence in the U.S., indicating clustering of comorbidities could be specific to geographical area.

Another study, from the US, found four subgroups in a hospitalised HF sample: a common disease group, with high prevalence of hypertension; a lifestyle group with high diabetes and obesity; a renal group, and a neurovascular group with increased frequency of cerebrovascular disease[95]. The neurovascular cluster was at highest risk of in-patient mortality and incurred the highest medical cost. However, this cohort may reflect a more severe population as it included hospitalised patients exclusively and was additionally limited by examining inpatient outcomes only without considering longer-term implications.

3.5.3 Clinical outcomes

In this population-wide study, I identified two new US-specific comorbidity clusters: the anaemic and metabolic-vascular groups. It is the first time a principally anaemic group has been detected using model-based clustering techniques in HF. The second most frequent comorbidity in this group was renal failure, with a prevalence second only to the metabolic-vascular group. It is not surprising that these two comorbidities co-occurred, as the cardio-renal anaemia syndrome is well-recognised in HF and is associated with increased admission to hospital and worse

prognosis compared to patients without these additional chronic diseases [106-108]. Compared to the low-burden cluster, the anaemic group was at increased risk of both hospitalisation and risk of death (49% and 46% increased risk respectively). Remarkably, the risk of death in this group was numerically higher than for patients in the ischemic group, suggesting this triangle of comorbidities (HF, anaemia, renal failure) incurs an amplified clinical burden compared with patients fitting an older profile with higher prevalence of cardiovascular disease, such as the ischemic group.

On average, patients in the metabolic-vascular phenotype had the worst clinical prognosis, indicated by the highest risk of hospitalisation and mortality compared to the low-burden cluster. The association with admission was significant after adjusting for HF medications, suggesting that therapies aimed at congestion relief as well as those modifying mortality and morbidity risk, do not necessarily decrease admission risk in this patient group. Although data on compliance with medical or management of comorbidities was not available, the particular combination of high-risk cardiovascular (PAD, CAD) and non-cardiovascular diagnoses (renal failure, diabetes) may incur a doubled risk of risk of admission in these patients, compared to those with lower-burden comorbidities.

The metabolic group had the lowest risk of admission or death, despite all patients being diagnosed with diabetes and over half with obesity. This cluster was the youngest among all groups, which may explain the relatively favourable prognosis. Other studies [109, 110] have reported on the “obesity paradox” in HF where higher BMI appears to act as a protective factor against mortality or admission, though this has been described as either wrongly diagnosing HF in obese individuals, or lead-time bias (earlier symptom onset attributable to added metabolic demands of obesity/diabetes), which is probable in a younger HF subgroup.

Nearly two thirds of the overall cohort had five or more comorbidities, similar to previous analyses [111]. The total number of additional chronic diseases differed across clusters and was highest in those with the poorest prognosis (metabolic-vascular, ischemic groups), suggesting that increases in comorbidity burden worsen prognosis. However, individual comorbidity counts insufficiently describe the differences in clinical burden incurred by comorbid diseases (i.e., anaemia may be associated with a lower level of disability compared to CAD, but the two illnesses contribute equally when using a counting approach). Individual comorbidity counts may also fail to convey the severity of diseases or interactions between comorbidities that may give rise to distinct clinical trajectories. Therefore, identification of specific patterns or clusters of comorbidities, as performed in this study, may capture some of these interactions and provide more granular information that could identify priorities for HF management.

3.5.4 Healthcare resource use

Healthcare resource utilisation has not previously been reported in clustering studies of HF. These data suggest a substantial association of comorbidity patterns with healthcare utilisation in HF. I found that individuals with higher occurrence of cardiovascular disease (metabolic-vascular, ischemic clusters) were more often admitted to hospital, in contrast to the metabolic and anaemic patients, who had comparatively more outpatient visits during follow-up. The lowest utilisation rate was observed in the metabolic group. This may be partially explained by the average younger age of patients in this group, and/or a low requirement for healthcare use for metabolic conditions in the absence of vascular complications (i.e., no CAD, PAD, and CVA). These may reflect different intensity of care and surveillance needed for the management of specific comorbidities of variable severity associated HF across the clusters.

The anaemic subgroup experienced the highest adjusted rate of outpatient visits and high mortality. The main distinguishing characteristics of this cluster (specifically anaemia-depression-cancer) have been independently linked to heightened use of outpatient services, explained in part, by care-seeking behaviours, poor medication adherence in depression[112] or under-treatment of HF due to deteriorating in health status in malignancy[113]. Indeed, the anaemic cluster had some of the lowest proportions of medication prescriptions across all clusters, suggesting less than optimal HF management in this particular subgroup.

Cost of care was mainly driven by inpatient and ER visits and was highest in the metabolic-vascular profile, intermediate in the anaemic and ischemic groups, and lowest in the metabolic and low-burden clusters, respectively. The identification of this "ranking" of cost associated with comorbidity patterns calls for a targeted approach of resource allocation: thus, patients fitting profiles exhibiting high inpatient use should be the focus of community interventions targeting lifestyle changes such as providing nutritional advice, encouraging exercise regimens and compliance with HF treatment, which may, in turn, help to prevent hospitalisations.

3.5.5 LVEF subgroup

LVEF is undoubtedly an important metric, specifically as it informs treatment choice in HF. Furthermore, previous data[114] show that comorbidities may cluster differentially in the two main groups of HFrEF and HFpEF. In order to verify whether LVEF status was associated with comorbidity clusters, I carried out a sensitivity analysis, including only those with LVEF measurement available (13,560 patients out of a total of 318,384). Due to lack of data, I could not verify whether there were differences in the distribution of LVEF groups across the clusters, across the whole sample. However, in this subgroup of patients, I tested an interaction between

LVEF and cluster membership with regards to the main clinical outcome and showed it was not significant.

Among patients with LVEF data available, none of the clusters mapped seamlessly to either LVEF group, although there was some preferential distribution of HFpEF onto the metabolic-vascular or ischemic groups, and a greater preponderance of HFrEF in the low-burden subgroup, highlighting the complexity and interrelatedness of comorbidity in HF [35]. Notably, differences in hospitalisation and survival persisted after adjusting for LVEF, which also did not act as an effect modifier, supporting previous reports showing that most comorbidities have a similar impact on both LVEF-defined HF groups.[114]. Although LVEF is the primary basis for recruitment into therapeutic trials as well as for classifying patients with HF, there are still no proven disease modifying treatments for up to half of all patients with the illness – those with HFpEF. The present findings suggest a potential for clinical trials to include patients and test therapies based on prognostic comorbidity patterns, not just limited to LVEF.

3.5.6 Future work

This clustering analysis may serve as a hypothesis-generating paradigm in identifying comorbidity patterns, which may be improved upon in further studies. It would be interesting to assess whether membership to comorbidity cluster changes over time in patients with HF and to map their trajectories, similar to the study by Vetrano et al. (2020), who investigated elderly persons' transitions among multimorbidity clusters over time [115]. However, to assess whether cluster membership changes over time, accurate recording of comorbidities at specific intervals of time is needed, with standardised investigations and complete medical records for all patients in the original cohort – and this cannot be guaranteed with the data source I used. Another issue

would be that mortality shapes the movement of clusters - as more people die and exit the cohort, I would naturally expect a regrouping of patients.

Second, the temporal relationship between comorbidity and HF as prevalent versus incident comorbidities has differential implications either through their roles in direct causation or acting as risk factors. It has been suggested that HFpEF may result from a combination of comorbidities such as obesity, diabetes, COPD and hypertension, whilst HFrEF is primarily a result of an abnormality in heart structure or/and function (i.e., reduced ability of the heart to pump blood), in some cases due to a MI or CAD. Conversely, HF may give rise to comorbidities, which are known to affect outcomes. Further, illnesses such as AF or COPD may be either a cause of a consequence of HF, whilst anaemia has a multifactorial aetiology and includes interactions between renal dysfunction, chronic inflammation, and iron deficiency. The picture is complex and in the present study I did not specifically considered development of comorbidities after HF as patients who experience these are, from a clinical perspective, different, compared to those that develop comorbidities before HF. If a dynamic pattern is found in cluster assignment, it would therefore be unclear whether it represents a genuine movement of patients from one cluster to another, or whether it would represent the movement of individual patients through different stages of HF.

In conclusion, a temporal assessment of clustering in HF may be addressed in a future study perhaps using registry data to ensure validity standardised tests and questionnaires, with a level of accuracy which would allow a temporal assessment of multimorbidity clusters. It would also be interesting to assess and explore the “incident/prevalent” comorbidity framework in this context perhaps by including comorbidity development as time-varying factors.

3.5.7 Strengths and limitations

The large sample size, comprising of patients with incident HF from the US, is reflective of those who are commercially insured or on Medicare Advantage, unlike previous smaller studies with restricted inclusion criteria. Patients of all ages, ethnic groups and both sexes were included, with a similar distribution to other large national studies [116, 117]. The prevalence of specific risk factors for HF, such as hypertension and CAD were slightly higher compared to other studies of HF [6, 33].

There are some limitations: diagnoses were based on ICD codes only, though they have been validated [118, 119]. However, the use of administrative data means diagnoses can be subject to misclassification and measurement error. By linking outpatient and in-hospital claims, I was able to identify the date of incident HF and identify comorbidities which were diagnosed prior to HF. This resulted in limiting the inclusion of cases where precursors of HF may have been mistakenly labelled as HF. Moreover, changes in diagnostic procedures over time, specific to HF, such as advances in echocardiography and imaging, might have increased likelihood of detecting milder forms of the disease in more recent times, which would be difficult to assess.

Data on severity of HF or control of comorbidities were not available, however, in outcome analyses I adjusted for use of diuretics, which may be act as a surrogate for the presence of congestion.

Data limitations pertaining to mortality recording in OLDW need to be mentioned. There are multiple sources of mortality data in OLDW, including the Social Security Administration Death Master File (SSA DMF), considered a reliable source. However, due to implementation of restrictions in publicly sharing information from the SSA, the availability of this source has

changed since 2011. While the other sources of mortality information have remained unchanged, (for example, patient death status or discharge status available from electronic healthcare records, or disenrollment from medical insurance plan due to death), I therefore thought it would be prudent to approach the mortality data with caution and chose to present death as a secondary outcome. Due to incomplete data on mortality, I considered that a competing risk analysis would be difficult to interpret, and I have not presented these results in the main results section. To investigate whether risk of admission to hospital may be overestimated due to a competing risk of death in this study, is therefore problematic. Despite the potentially incomplete mortality data, I performed a (sensitivity) analysis of the risk of admission to hospital, accounting for the competing risk of death within the first year of HF diagnosis, which showed a similar result to the main analysis.

Ultimately, the aim of this analysis was not to create a novel prediction model for outcomes in HF, which already exist and have been validated[120]. The approach used to derive the comorbidity clusters was data-driven, with no a priori theory driving expectations on how the comorbidities would cluster. My aim was to identify novel, potentially "hidden" patterns that may guide clinical management and resource allocation in a real-world setting. HF patients typically present with a constellation of overlapping characteristics– this is reflected presently, as several comorbidities were observed across the five identified clusters, albeit in different proportions.

3.6 Conclusions

In this large population-based study of patients with HF from the US, I have demonstrated that EHR data may be used to generate a classification of HF based on comorbidities and their combinations. I identified five comorbidity clusters that were associated with different risk of

hospital admission, mortality and diverging levels of healthcare resource utilisation. These findings suggest an opportunity for future RCTs to incorporate comorbidity patterns in their enrolment criteria and a need for tailored comorbidity-management and prevention plans to accompany existing evidence-based medical therapy for patients with HF, in particular, targeting the clusters with the poorest prognosis.

Overall, it is challenging to manage patients with HF with co-occurring disease. This analysis emphasises that the specific knowledge of how comorbidities cluster together and their association with clinical outcomes may assist clinicians who manage these complex patients to further refine and target their treatment. Patients within each cluster are more similar, on a group level, compared to those in other clusters - whether these subgroups may benefit from similar preventative and care plans needs to be evaluated in future studies.

Upcoming characterisations of HF may benefit from integrating data on comorbidities ideally derived from large, real-world populations in relevant and local geographical settings, to derive a more granular taxonomy, enabling multidimensional and personalised HF care and resource allocation.

Chapter 4 DIFFERENCES IN OUTCOMES IN COPD PATIENTS WITH HF AND REDUCED VERSUS PRESERVED LEFT VENTRICULAR EJECTION FRACTION

The results presented in the previous chapter indicated that COPD was not a strong driver in determining any of the identified comorbidity clusters, compared to other chronic diseases (such as coronary artery disease [CAD], anaemia or diabetes). Nonetheless, the clusters with the highest risk of admission to hospital and death included over 50% of patients with COPD. Previous literature has shown individuals with COPD are more commonly diagnosed with HFpEF than HFrEF, though the nature of relationship is not entirely elucidated. Furthermore, the left ventricular ejection fraction (LVEF) based dichotomy in HF and its purpose beyond treatment recommendation has been subject to debate recently, particularly in the context of COPD as this additional diagnosis is related with underuse of HF treatments such as beta-blockers. I therefore wanted to further characterise a subgroup of patients with HF and COPD, through the LVEF status lens, and thus compared clinical, healthcare use and therapeutical management between patients with COPD-HFpEF and COPD-HFrEF. This analysis was written up as a publication and is under review in an academic journal (Appendix G, Paper 2).

4.1 Introduction

The previous chapter presented evidence to support the finding that HF represents a dynamic syndrome, representing a spectrum of phenotypes which display unique patient characteristics

and heterogeneous disease trajectories [104] which are not completely captured by the main HF dichotomy based on LVEF. Despite this, LVEF remains an important marker of HF as it directs treatment pathways [10]. The co-occurrence of COPD and HF has important therapeutic consequences. HFrEF medications such as beta-blockers are frequently under-utilised in patients with COPD and HF[79, 121, 122], while COPD medication such as beta-agonists are associated with an greater frequency of adverse cardiovascular events [82] in those with existing HFrEF[45] or precursors such as left ventricular systolic dysfunction[123]. Additionally, when COPD is present, low-grade systemic inflammation may additionally contribute to the progression of atherosclerosis, ischemia and adverse cardiovascular events [50]. The impact of HF phenotype, according to LVEF, is poorly described in patients with COPD, but may have relevant implications for treatment planning.

In this study, I describe the clinical and sociodemographic characteristics of a cohort of patients with HF and comorbid COPD according to LVEF-based phenotype and assess the association between LVEF phenotypes and admission to hospital, mortality, overall healthcare resource use and prescriptions for guideline-recommended treatments.

4.2 Study aims

(1) To compare any-cause and HF-specific hospitalisation, AECOPD and mortality between LVEF phenotypes in a population of COPD-HF patients.

(2) To compare healthcare resource use and HF-specific medication prescriptions between LVEF phenotypes in a population of COPD-HF patients.

4.3 Methods

4.3.1 Data source

I used the OptumLabs Data Warehouse (OLDW[74]) (previously described in Chapter 2 and Chapter 3, Methods) to identify commercially insured and Medicare Advantage patients at least 18 years old with incident HF in the United States (U.S).

4.3.2 Population

Incident HF was defined as having at least one episode of acute HF resulting in hospitalisation, or two outpatient claims on different dates within the study period (1/1/2008 to 1/1/2018) containing any ICD-9/ICD-10 HF code in any position on the claim (Chapter 3, Methods) and availability of LVEF data from clinical records. Additional inclusion criteria were having a COPD diagnosis (see **Table 4.1**) before HF (see **Figure 4.1).**

TABLE 4.1: List of ICD-9 and ICD-10 codes used to identify COPD patients.

ICD-9 code	Diagnosis
491	Chronic bronchitis
4910	Simple chronic bronchitis
4911	Mucopurulent chronic bronchitis
49122	Obstructive chronic bronchitis with acute bronchitis
4912	Obstructive chronic bronchitis with acute exacerbation
4918	Other chronic bronchitis
4919	Unspecified chronic bronchitis
492	Emphysema
492	Emphysematous bleb
4928	Other emphysema
496	Chronic airway obstruction, not elsewhere classified
ICD-10 code	**Diagnosis**
J43	Emphysema
J418	Mixed simple and mucopurulent chronic bronchitis
J449	Chronic obstructive pulmonary disease, unspecified
J430	Unilateral emphysema, MacLeod's
J431	Panlobular emphysema
J432	Centrilobular emphysema
J438	Other emphysema
J439	Emphysema, unspecified
J440	Chronic obstructive pulmonary disease with acute lower respiratory infection
J441	Chronic obstructive pulmonary disease with (acute) exacerbation

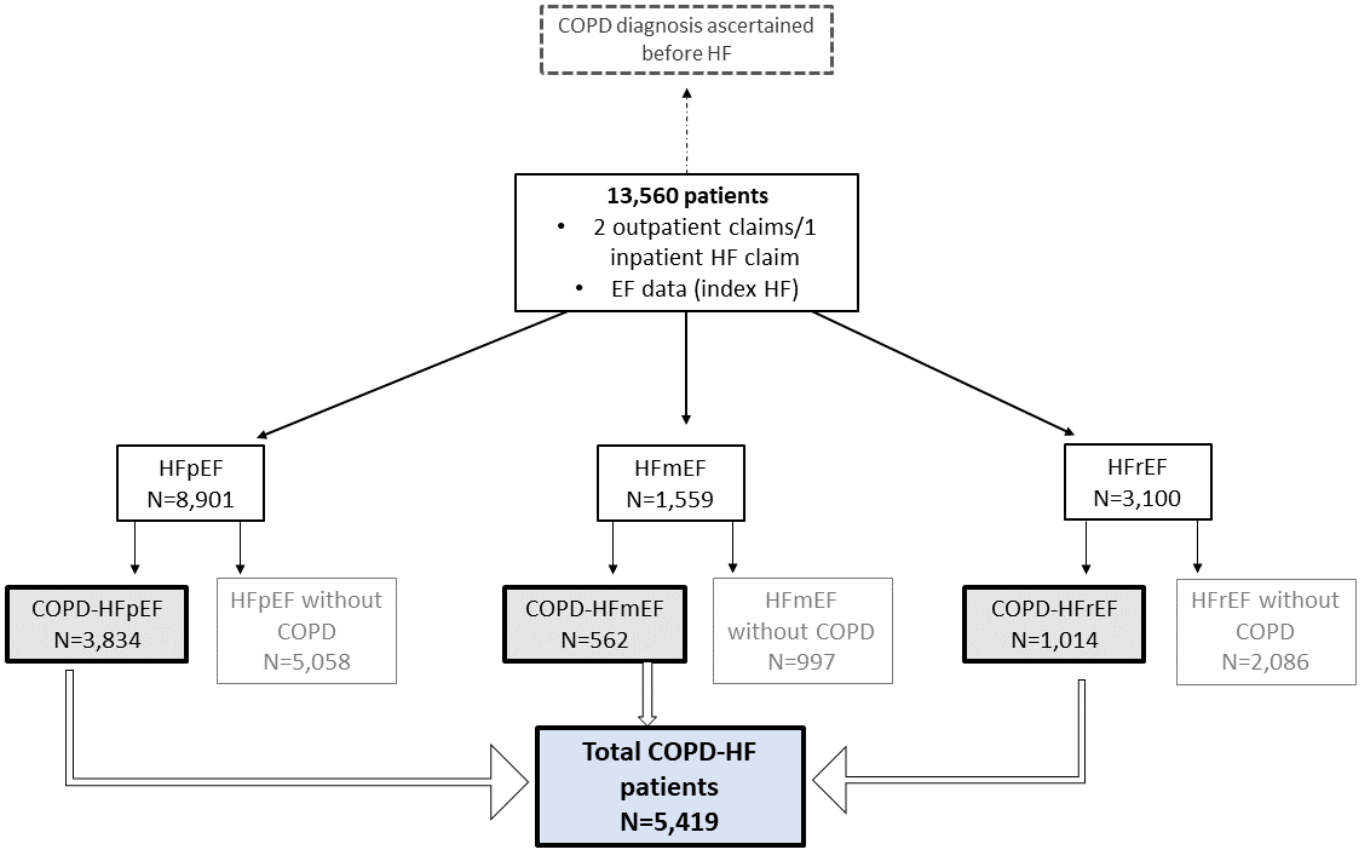

FIGURE 4.1: Study flow, patient inclusion

4.3.3 Covariates

Similar to the analysis presented in Chapter 3, for each patient, I assessed sociodemographic characteristics such as: age, sex, race, type of insurance (payer or Medicare Advantage), place of diagnosis (in or outpatient), education and the following comorbidities: AF, CAD, PAD, CVA, hypertension, diabetes mellitus, obesity, depression, alcohol misuse disorder, dementia, cancer, peptic ulcer, liver disease and renal failure. These were identified using ICD-9 or ICD-10 codes recorded any time before the diagnosis of HF (obesity and anaemia were assessed in the previous

12 months only, see Appendix B, Table B1). Pharmacy prescription claims included: beta-blockers, ACEi, ARBs, MRA, thiazide, potassium sparing and loop diuretics, short and long-acting beta-agonists and inhaled corticosteroids (ICS) containing regimens (see Appendix B, Table B2, Appendix C, Table C1).

4.3.4 Outcomes

The main outcome was all-cause hospitalisation within one-year of HF diagnosis, defined similarly as in Chapter 3, Methods. Secondary outcomes included HF-specific hospitalisation, AECOPD, mortality and in-patient and outpatient healthcare resource use and costs. AECOPD was defined as either an inpatient admission with a primary diagnosis of COPD (severe), or an outpatient visit with a COPD code (see **Table 4.1**) in any position and a procedure code for administration of a steroid or antibiotic (Appendix C, Table C2), or a pharmacy claim for oral corticosteroid or antibiotic[1] within 10 days of the visit (moderate). This method has been used and validated previously using the OLDW[124] as well as in UK data sources[125].

4.3.5 Statistical analysis

Differences in baseline characteristics between HF groups were presented using chi-squared and Kruskall-Wallis tests as appropriate, using the Bonferroni correction for multiple testing. I used Cox proportional-hazard regression models to calculate hazard ratios (HRs) and 95% confidence intervals (CI) to analyse hospitalisation, AECOPD and mortality. Proportional hazards assumption was verified with Schoenfeld residual plots. For admission to hospital and AECOPD

[1] List available: https://www.ncqa.org/hedis/measures/hedis-2019-ndc-license/hedis-2019-final-ndc-lists/

analyses, patients were followed up for 12 months after receiving a HF diagnosis or censored at disenrollment or death. For mortality, patients were followed-up to a censoring date of 01 January 2019, or to disenrollment, whichever came first. This resulted in a maximum follow-up of 120 months (median 27 months, IQR 17 – 42). The competing risk of death before HF admission and AECOPD, was assessed with a Fine and Gray model[126]. Negative binomial regression models were used to assess the association between LVEF groups and the rate of outpatient, office and emergency room (ER) visits, long-term stays, inpatient admissions and length of stay during one-year follow-up. Rate ratios and 95% CI were calculated. Confounders were added cumulatively in all analyses: first I adjusted for age, sex, race, education, medical insurance type, place of diagnosis, comorbidities and HF medications. In a second step I added COPD medications and the finally adjusted models included smoking status. Statistical analyses were performed using R v3.6.2.

4.4 Results

4.4.1 Baseline characteristics

Of 5,419 patients with COPD and HF with LVEF recorded in OLDW, 70% had HFpEF, 20% had HFrEF and 10% had HFmEF. An assessment of patient characteristics of HF patients with and without LVEF measurement in OLDW is available in Appendix C, Table C3.

The median age was 74 years (IQR 67 – 80) and 50.1% of patients were male. Patients with COPD-HFpEF had higher overall proportions of comorbidities compared with either COPD-HFmEF or COPD-HFrEF patients, except for CAD, which was more frequent in HFrEF and HFmEF, respectively. A total of 62% of patients in the COPD-HFpEF group were diagnosed

with HF in an inpatient setting, compared to 56.3% patients with reduced and 52.8% of patients with mid-range EF (see **Table 4.2**)

TABLE 4.2: Baseline characteristics of patients with COPD-HF stratified by LVEF phenotype

	HFpEF (N=3843)	HFmEF (N=562)	HFrEF (N=1014)	Overall (N=5419)	P-Value
Age (years)					<0.001
Median [IQR]	75 [67, 81]	73 [66.3, 79]	72 [65, 79]	74 [67., 80]	
Male	1684 (43.8%)	365 (64.9%)	668 (65.9%)	2717 (50.1%)	<0.001
Comorbidities at baseline					
AF	1911 (49.7%)	278 (49.5%)	481 (47.4%)	2670 (49.3%)	0.428
Alcohol misuse disorder	175 (4.6%)	33 (5.9%)	41 (4.0%)	249 (4.6%)	0.245
Anaemia	1368 (35.6%)	133 (23.7%)	258 (25.4%)	1759 (32.5%)	<0.001
CAD	2909 (75.7%)	493 (87.7%)	896 (88.4%)	4298 (79.3%)	<0.001
CVA	1949 (50.7%)	257 (45.7%)	449 (44.3%)	2655 (49.0%)	<0.001
Liver disease	625 (16.3%)	89 (15.8%)	118 (11.6%)	832 (15.4%)	<0.01
Cancer	984 (25.6%)	141 (25.1%)	227 (22.4%)	1352 (24.9%)	0.108
Dementia	284 (7.4%)	24 (4.3%)	49 (4.8%)	357 (6.6%)	<0.001
Depression	939 (24.4%)	122 (21.7%)	149 (14.7%)	1210 (22.3%)	<0.001
Diabetes	1905 (49.6%)	249 (44.3%)	400 (39.4%)	2554 (47.1%)	<0.001
PAD	2327 (60.6%)	330 (58.7%)	520 (51.3%)	3177 (58.6%)	<0.001
Hypertension	3747 (97.5%)	546 (97.2%)	978 (96.4%)	5271 (97.3%)	0.189
Renal failure	1169 (30.4%)	154 (27.4%)	209 (20.6%)	1532 (28.3%)	<0.001
Peptic ulcer	322 (8.4%)	38 (6.8%)	54 (5.3%)	414 (7.6%)	<0.05
Obesity	1733 (45.1%)	194 (34.5%)	347 (34.2%)	2274 (42.0%)	<0.001
Place of diagnosis					<0.001
Outpatient	1461 (38.0%)	265 (47.2%)	443 (43.7%)	2169 (40.0%)	
Inpatient	2382 (62.0%)	297 (52.8%)	571 (56.3%)	3250 (60.0%)	
Insurance status					<0.001
Medicare Advantage	3218 (83.7%)	455 (81.0%)	788 (77.7%)	4461 (82.3%)	
Commercial	625 (16.3%)	107 (19.0%)	226 (22.3%)	958 (17.7%)	
Education					0.229
Bachelor's degree Plus	406 (10.6%)	>42 (>7.4%)*	>98 (>9.7%)*	560 (10.3%)	

	HFpEF (N=3843)	HFmEF (N=562)	HFrEF (N=1014)	Overall (N=5419)	P-Value
High School Diploma	1259 (32.8%)	182 (32.4%)	364 (35.9%)	1805 (33.3%)	
Less than bachelor's degree	2160 (56.2%)	327 (58.2%)	541 (53.4%)	3028 (55.9%)	
Missing	18 (0.5%)	<11 (<2%)*	<11 (<2%)*	26 (0.5%)	
Income (U.S dollars)					0.059
<$40,000	1386 (36.1%)	184 (32.7%)	349 (34.4%)	1919 (35.4%)	
$40,000-$74,000	1083 (28.2%)	158 (28.1%)	274 (27.0%)	1515 (28.0%)	
$75,000-$124,999	633 (16.5%)	121 (21.5%)	194 (19.1%)	948 (17.5%)	
$125,000-$199,999	189 (4.9%)	25 (4.4%)	53 (5.2%)	267 (4.9%)	
$200,000+	67 (1.7%)	16 (2.8%)	23 (2.3%)	106 (2.0%)	
Missing	485 (12.6%)	58 (10.3%)	121 (11.9%)	664 (12.3%)	
Race					0.631
White	3037 (79.0%)	456 (81.1%)	815 (80.4%)	4308 (79.5%)	
Black	491 (12.8%)	59 (10.5%)	114 (11.2%)	664 (12.3%)	
Hispanic	92 (2.4%)	13 (2.3%)	27 (2.7%)	132 (2.4%)	
Asian	36 (0.9%)	<11 (<2%)*	<11 (<1%)*	48 (0.9%)	
Missing	187 (4.9%)	>23 (>4.1%)*	>47 (>4.6%)*	267 (4.9%)	
Smoking status					<0.001
Current smoker	828 (21.5%)	146 (26.0%)	303 (29.9%)	1277 (23.6%)	
Never smoked	749 (19.5%)	85 (15.1%)	126 (12.4%)	960 (17.7%)	
Not currently smoking	380 (9.9%)	46 (8.2%)	85 (8.4%)	511 (9.4%)	
Previously smoked	1555 (40.5%)	248 (44.1%)	400 (39.4%)	2203 (40.7%)	
Missing	331 (8.6%)	37 (6.6%)	100 (9.9%)	468 (8.6%)	
COPD medications at baseline					<0.001
No COPD treatment	2127 (55.3%)	354 (63.0%)	630 (62.1%)	3111 (57.4%)	
Short-acting bronchodilator	560 (14.6%)	83 (14.8%)	144 (14.2%)	787 (14.5%)	<0.001
Long-acting bronchodilator	198 (5.2%)	19 (3.4%)	51 (5.0%)	268 (4.9%)	

	HFpEF (N=3843)	HFmEF (N=562)	HFrEF (N=1014)	Overall (N=5419)	P-Value
ICS containing regimen	958 (24.9%)	106 (18.9%)	189 (18.6%)	1253 (23.1%)	

ACEis=angiotensin converting-enzyme-inhibitors; AF= atrial fibrillation; ARBs =angiotensin-receptor blockers; CAD=coronary artery disease; COPD= chronic obstructive pulmonary disease; CVA= cerebrovascular disease; HFmEF= heart failure with mid-range ejection fraction; HFpEF= heart failure with preserved ejection fraction HFrEF= heart failure with reduced ejection fraction; ICS= inhaled corticosteroids; IQR= inter-quartile range; PAD= peripheral artery disease; MRA= mineralocorticoid receptor antagonist; US= United States.
Bonferroni correction was used to correct for multiple testing.
* Exact numbers not presented in order to comply with OptumLabs cell size suppression policy.

4.4.2 Hospitalisation and AECOPD

In total, 1,980 (50.5%) of patients were admitted to hospital within one-year of HF diagnosis, with no significant differences in the crude frequency of all-cause admission by LVEF status. When assessing cause-specific admission, 16.4% of patients of all patients were admitted for HF; a higher proportion of patients with HFrEF experienced this outcome compared to HFpEF (20% vs. 15.5%). Overall, 35.6% of all patients experienced either a moderate or severe exacerbation of COPD, making this the most frequent outcome in the cohort. AECOPD prevalence (either severe or moderate) among those with HFrEF was similar in the HFmEF group, but lower compared to patients with HFpEF (29.4% in HFrEF and 29.9% in HFmEF vs. 38% in HFpEF). Moderate AECOPD was observed in similar proportions across all LVEF categories whereas severe AECOPD admissions were less frequent in the HFrEF group compared with the HFpEF group (7.2% vs 11.6%) **(see Table 4.3)**.

TABLE 4.3: Frequency of clinical outcomes according to LVEF phenotype, in patients with COPD-HF, at one-year follow-up

Outcome	HFpEF (n=3843)	HFmEF (n=562)	HFrEF (n=1014)	Overall (n=5419)	*P*-value
All-cause admission	1980 (51.5%)	269 (47.9%)	485 (47.8%)	2734 (50.5%)	0.555
HF-specific admission	595 (15.5%)	89 (15.8%)	203 (20.0%)	887 (16.4%)	<0.01
Any AECOPD*	1462 (38%)	168 (29.9%)	298 (29.4%)	1928 (35.6%)	<0.001
Severe AECOPD	446 (11.6%)	52 (9.3%)	73 (7.2%)	571 (10.5%)	<0.001
Moderate AECOPD	1265 (32.9%)	138 (24.6%)	254 (25.0%)	1657 (30.6%)	0.639

AECOPD= acute exacerbation of COPD; COPD= chronic obstructive pulmonary disease; HF= heart failure; HFpEF= heart failure with preserved ejection fraction; HFmEF= heart failure with mid-range ejection fraction; HFrEF= heart failure with reduced ejection fraction; LVEF = left ventricular ejection fraction.
*Only first AECOPD counted, regardless of severity

There was an incremental rise in the risk of AECOPD associated with use of short, long-acting bronchodilators and ICS-regimens, compared to no use of COPD medication. HF-admission was not impacted by COPD medication use (see **Table 4.4**).

TABLE 4.4: Association between COPD medication regimens and AECOPD, HF-admission, respectively, in patients with COPD-HF, at one year follow-up

	AECOPD unadjusted HR (95%CI)	AECOPD adjusted* HR (95%CI)	HF admission, unadjusted HR (95%CI)	HF admission, adjusted* HR, (95%CI)
No COPD treatment (ref)	-	-	-	-
Short-acting bronchodilator	2.00 (1.76-2.28, p<0.001)	1.95 (1.70-2.25, p<0.001)	0.82 (0.71-0.95, p=0.009)	0.87 (0.73-1.03, p=0.106)
Long-acting bronchodilator	2.92 (2.44-3.50, p<0.001)	2.65 (2.18-3.22, p<0.001)	0.80 (0.65-0.99, p=0.038)	0.93 (0.73-1.18, p=0.565)
ICS containing regimen	3.22 (2.91-3.57, p<0.001)	3.00 (2.68-3.36, p<0.001)	0.91 (0.78-1.07, p=0.242)	1.07 (0.88-1.30, p=0.492)

AECOPD= acute exacerbation due to chronic obstructive pulmonary disease; COPD= chronic obstructive pulmonary disease; CI= confidence intervals; HR= hazard ratio; ICS= inhaled corticosteroid; ref= reference. *Adjusted for age, sex, race, education, medical insurance status, whether diagnosis was gained in-patient or in out-patient, HF medications, COPD medications, smoking status; patients with missing data were excluded.

Results from the competing risk analysis showed that patients with COPD-HFrEF had an increased incidence of HF-admission and lower incidence of AECOPD, compared to those with COPD-HFpEF, when the competing risk of death was accounted for (see **Figure 4.2**).

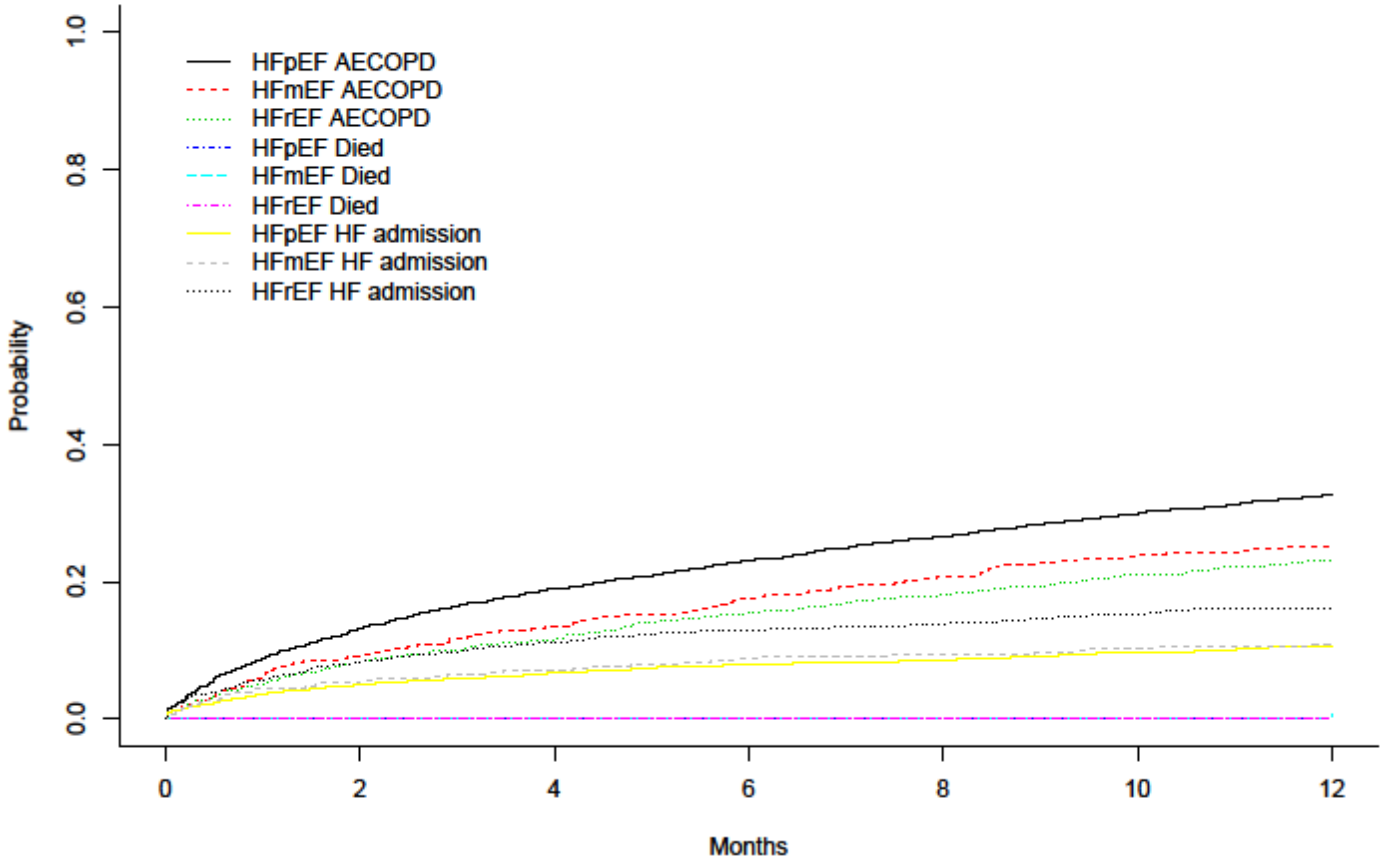

FIGURE 4.2: Cumulative incidence for competing risk events (HF-admission, AECOPD, death) in patients with COPD-HF, within one-year of HF diagnosis

Table 4.5 and **Figure 4.3** highlight the main results. In the two partially adjusted models (model 1 and 2) and the fully adjusted model 3, there were no significant differences in the risk of hospitalisation across all COPD-HF groups. However, the COPD-HFrEF group, were, on average, more likely to be admitted to hospital due to HF versus patients with COPD-HFpEF (model 3, HR_{adj}: 1.54, 95% CI 1.29 – 1.84). The opposite relationship was observed for

AECOPD risk: patients with COPD-HFrEF were less likely to experience an AECOPD, compared with patients with COPD-HFpEF (model 3, HR_{adj} 0.75, 95% CI 0.66 – 0.87).

TABLE 4.5: Association between LVEF phenotype and all-cause admission, HF-admission and AECOPD in patients with COPD-HF, at one year follow-up.

Outcome and LVEF group	Univariable HR (95% CI)	Model 1* HR (95% CI)	Model 2† HR (95% CI)	Model 3‡ HR (95% CI)
All-cause admission	Ref.	Ref.	Ref.	Ref.
HFmEF	0.91 (0.80 - 1.04, p=0.168)	1.01 (0.88 - 1.15, p=0.924)	1.01 (0.88 - 1.15, p=0.925)	1.01 (0.88 - 1.16, p=0.888)
HFrEF	0.91 (0.82 - 1.01, p=0.064)	1.05 (0.95 - 1.17, p=0.343)	1.05 (0.95 - 1.17, p=0.352)	1.07 (0.96 - 1.20, p=0.224)
HF-hospitalisation	Ref.	Ref.	Ref.	Ref.
HFmEF	1.03 (0.82-1.28, p=0.812)	1.09 (0.87-1.38, p=0.451)	1.09 (0.86 - 1.38, p=0.609)	1.03 (0.81-1.32, p=0.799)
HFrEF	1.34 (1.14-1.57, p<0.001)	1.54 (1.30-1.83, p<0.001)	1.53 (1.29 - 1.82, p<0.05)	1.54 (1.29-1.84, p<0.001)
AECOPD	Ref.	Ref.	Ref.	Ref.
HFmEF	0.74 (0.63-0.86, p<0.001)	0.78 (0.66-0.92, p=0.003)	0.83 (0.71-0.99, p=0.033)	0.82 (0.69-0.97, p=0.024)
HFrEF	0.72 (0.64-0.82, p<0.001)	0.75 (0.66-0.86, p<0.001)	0.78 (0.68-0.89, p<0.001)	0.75 (0.65-0.97, p<0.001)

AECOPD= acute exacerbation due to chronic obstructive pulmonary disease; CI= confidence intervals; HR= hazard ratio; HF= heart failure; HFmEF= heart failure with mid-range ejection fraction; HFpEF= heart failure with preserved ejection fraction; HFrEF= heart failure with reduced ejection fraction; LVEF= left ventricular ejection fraction.
Ref = reference category (HFpEF)
*Adjusted for: age, sex, race, education, medical insurance status, whether diagnosis was gained in-patient or in out-patient and HF medications; patients with missing data on race were excluded (267) and education (26)
†Adjusted for age, sex, race, education, medical insurance status, whether diagnosis was gained in-patient or in out-patient and HF medications, COPD medications
‡Adjusted for age, sex, race, education, medical insurance status, whether diagnosis was gained in-patient or in out-patient and HF medications, COPD medications; smoking status; patients with missing data were excluded

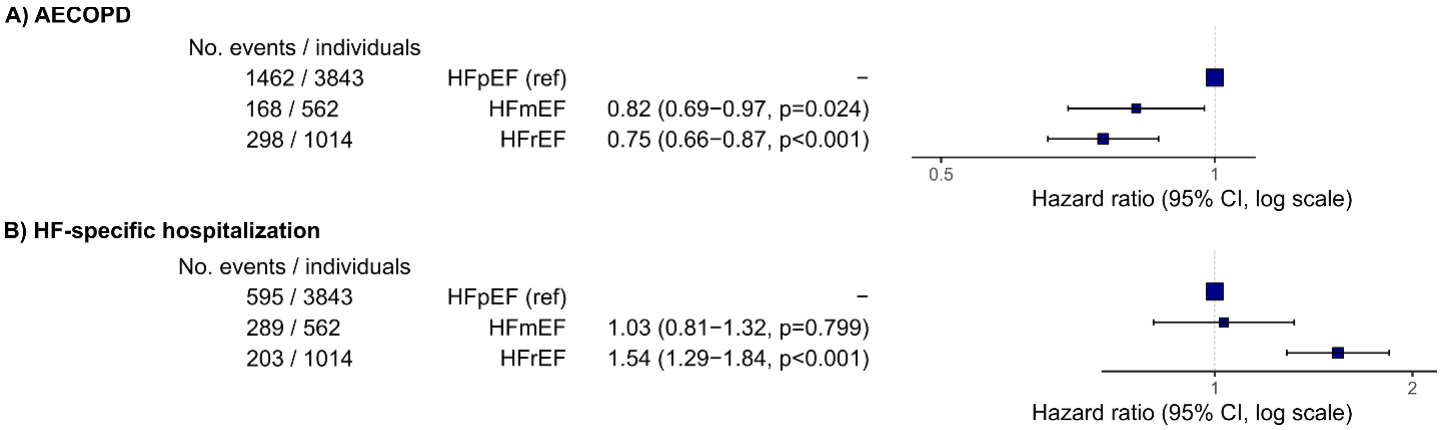

FIGURE 4.3: Association between LVEF phenotype and risk of A) AECOPD and B) HF-admission, in patients with COPD-HF, at one year follow-up

4.4.3 Mortality

Unadjusted mortality estimates did not differ significantly across LVEF groups (see **Table 4.6**).

TABLE 4.6: Frequency of death according to LVEF phenotype in patients with COPD-HF, within a median follow-up of 26.9 months (IQR 16.9 - 42.4)

	HFpEF (n=3841)	**HFmEF (n=562)**	**HFrEF (n=1014)**	**Overall (n=5417)**	**P-Value**
Died (n, %)	1449 (37.7%)	190 (33.8%)	399 (39.2%)	2038 (37.6%)	NS
Person-months	124035.6	17902.6	34367.5	176305.7	
Deaths per 1000 person months (95% CI)	11.7 (11.1 - 12.3)	10.6 (9.2 - 12.2)	11.61 (10.5 - 12.8)	11.56 (11.1 - 12.1)	

CI= confidence interval; HFpEF= heart failure with preserved ejection fraction; HFmEF= heart failure with mid-range ejection fraction; HFrEF= heart failure with reduced ejection fraction; IQR= inter-quartile range; NS= not significant

However the fully adjusted model revealed that patients with COPD-HFrEF had a heightened risk of death compared to those with COPD-HFpEF (HR_{adj} 1.16, 95% CI 1.03, 1.32, (see **Figure 4.4**), within a median survival of 27 months (IQR 16.9 – 42.3).

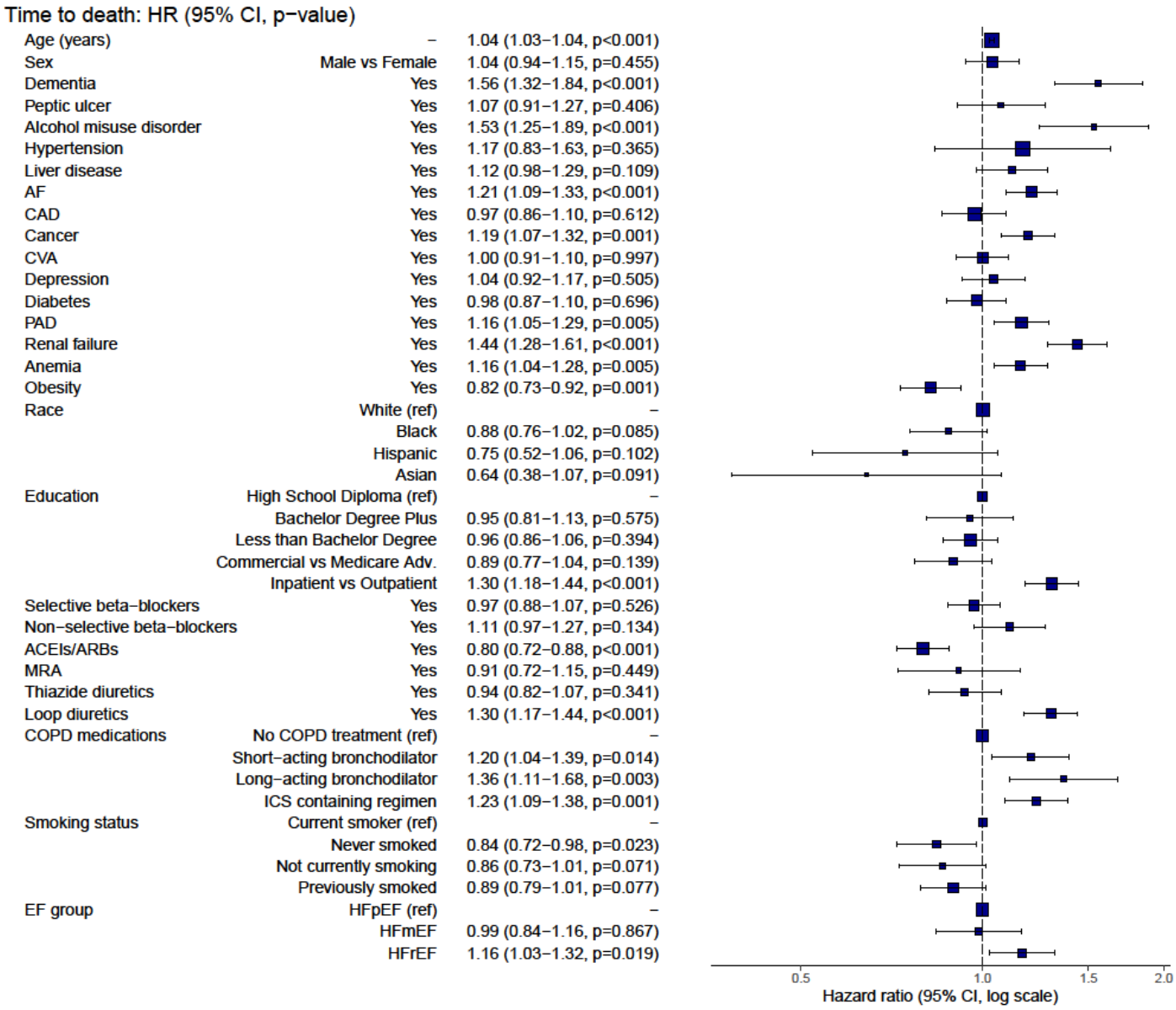

FIGURE 4.4: Association between LVEF phenotype and time to death, in patients with COPD-HF, within a median 27 months follow-up

ACEi s= angiotensin-converting-enzyme inhibitors; ARB= angiotensin receptor blockers; AF, atrial fibrillation, CAD, coronary artery disease; CI, confidence interval; COPD= chronic obstructive pulmonary disease; CVA, cerebrovascular accident; EF, ejection fraction; HFpEF= heart failure with preserved ejection fraction; HFmEF= heart failure with mid-range ejection fraction; HFrEF= heart failure with reduced ejection fraction; HR, hazard ratio; PAD, peripheral artery disease; ICS= inhaled corticosteroids; MRA= mineralocorticoid receptor antagonists.

4.4.4 Healthcare resource use

In unadjusted analyses, rates of outpatient visits, long-term care stays, inpatient stays and associated length of stay and ER admissions, differed by LVEF group. After adjusting for potential confounders, significant differences remained in the rates of long-term hospital stays in skilled nursing facilities (with an overall decreased rate of events in COPD-HFrEF compared to COPD-HFpEF, RR_{adj}, 0.76, 95%CI 0.62 - 0.94) and ER visits, which were lower for both COPD-HFrEF (RR_{adj} 0.86, 95%CI 0.76 - 0.97) and COPD-HFmEF patients (RR_{adj} 0.85, 95%CI 0.76 - 0.93) compared to COPD-HFpEF. Those with COPD-HFrEF experienced shorter lengths of inpatient stay, on average, compared to those with COPD-HFpEF (RR_{adj} 0.80, 96% CI 0.67-0.93, see **Table 4.7**).

TABLE 4.7: Association between LVEF phenotype and healthcare resource use in patients with COPD-HF, at one-year follow-up

	Rate ratio (95% CI)	
	Unadjusted RR (95% CI) N=5,149	Adjusted RR (95%CI) N=4,446
Outpatient visits		
HFpEF	Ref.	Ref.
HFmEF	0.77 (0.69 - 0.85)	0.92 (0.82 - 1.02)
HFrEF	0.88 (0.81- 0.95)	1.04 (0.95 - 1.14)
Office visits		
HFpEF	Ref.	Ref.
HFmEF	1 (0.93 - 1.08)	1.01 (0.93 - 1.1)
HFrEF	0.98 (0.92 - 1.04)	1 (0.94 - 1.07)
Long-term care stays		
HFpEF	Ref.	Ref.
HFmEF	0.65 (0.50 - 0.83)	0.80 (0.61 - 1.03)
HFrEF	0.58 (0.48 - 0.71)	0.76 (0.62 - 0.94)
Hospitalisations		
HFpEF	Ref.	Ref.
HFmEF	0.81 (0.72 - 0.92)	0.91 (0.80 - 1.03)
HFrEF	0.84 (0.76 - 0.92)	0.92 (0.82 - 1.01)
Length of stay for hospitalisations		
HFpEF	Ref.	Ref.
HFmEF	0.76 (0.63 - 0.92)	0.91 (0.75 - 1.11)
HFrEF	0.75 (0.65 - 0.88)	0.80 (0.67 - 0.93)
ER admissions		
HFpEF	Ref.	Ref.
HFmEF	0.73 (0.64 - 0.82)	0.86 (0.76 - 0.97)
HFrEF	0.72 (0.66 - 0.80)	0.85 (0.76 - 0.93)

CI=confidence intervals; ER= emergency room; HFpEF= heart failure with preserved ejection fraction; HFmEF= heart failure with mid-range ejection fraction; HFrEF= heart failure with reduced ejection fraction; RR= rate ratio; ref= reference.

* Adjusted for: age, sex, race, education, medical insurance status, whether diagnosis was gained in-patient or in out-patient, HF medications, COPD medications, smoking status.

Patients with missing data were excluded.

Median costs for outpatient visits were significantly higher for COPD-HFrEF compared to the other two LVEF groups (Appendix C, Table C4).

4.4.5 Management – medication prescriptions

Patients with COPD-HFrEF experienced the highest increase in HF-related prescriptions from the baseline period (defined as 12 months before HF diagnosis) to one-year follow-up. ACEi/ARB prescriptions increased from 54.6% to 74.7% and non-cardioselective beta-blockers prescriptions from 26.7% to 49.4%. The COPD-HFrEF and HFmEF groups had lower levels of short-acting and long-acting beta-agonists as well as steroids prescribed compared to the COPD-HFpEF group. However, levels of COPD pharmacotherapy remained overall low, as not more than 44% of patients in any group had a prescription (see **Figure 4.5**).

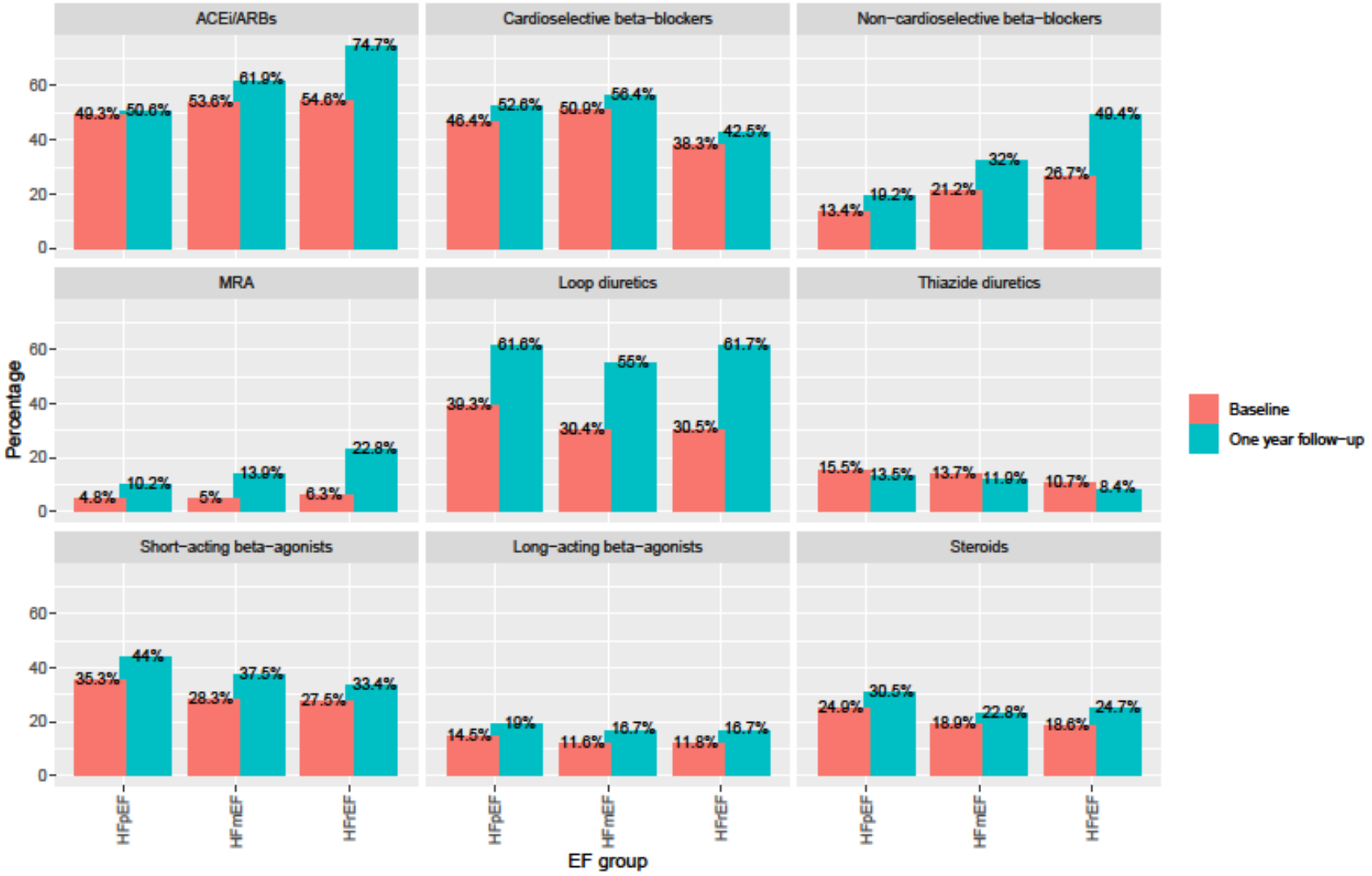

FIGURE 4.5: Heart failure and COPD medication prescription frequency in patients with COPD-HF, according to LVEF phenotype

4.5 Discussion

4.5.1 Main findings

This is the largest study to describe characteristics of patients with coexisting COPD and HF according to LVEF-based phenotype. The most common HF LVEF phenotype in this COPD population was HFpEF. Patients in the COPD-HFrEF group had on average, lower overall burden of comorbidities and prescriptions for COPD medication, compared with patients with COPD-HFpEF. COPD-HFrEF patients had lower risk of AECOPD, and lower rates of long-term and ER visits and longer inpatient stays. In contrast, patients with COPD-HFrEF were at increased risk of admission due to HF decompensation and had worse survival compared to patients with COPD-HFpEF.

4.5.2 Baseline characteristics

Prevalence of HFrEF compared to HFpEF in COPD has been shown to be lower in cohort studies [35, 50, 127, 128], however, the majority of the previous literature on COPD-HF focused on evaluating characteristics and outcomes of patients with COPD-HFrEF [48, 129]. To date, the present study is the largest comparison of both characteristics and outcomes across all HF phenotypes.

A previous, smaller study reported a distinct pattern of baseline characteristics associated with COPD-HFpEF and COPD-HFrEF, compared to the present report. Kuown and colleagues[130] included 184 highly selected patients from an outpatient clinic in South Korea, excluding those with severe comorbidities and thus limiting generalisability to the greater COPD-HF population. The use of a LVEF cut-off of 50% EF value to classify patients as either HFrEF (<50%) or

HFpEF (≥50%), may have masked potentially distinct findings for HFmEF. Comorbidity patterns differed across their study and the present one, likely due to differences in study design, sample size and geographical location. For example, cardiovascular disease (AF: 49.3% OLDW vs. 38% Kwon et al, hypertension: 97.3% vs. 49%) and non-cardiovascular comorbidities (diabetes: 47.1% vs. 32%) were more prevalent in the current sample while anaemia was more prevalent in the Asian sample (53% Kwon vs. 32.5% OLDW). The overall prevalence of comorbid conditions in my analysis was also higher than previously reported rates. In comparison to Kuown and colleagues[130], I observed those in the COPD-HFpEF group had a higher uptake of COPD medications, particularly ICS-containing regimens, which are prescribed to some of the most severe cases, according to GOLD guidelines[39]. Therefore, results suggest there was a higher proportion of severe COPD patients with HFpEF compared to COPD-HFrEF.

4.5.3 Hospitalisation

In the OLDW sample of COPD-HF patients, there was no difference in all-cause hospitalisation according to LVEF phenotype, which reflects previously reported findings from the broader HF population[114, 128]. However, there were differences in cause-specific admission risk between COPD-HF LVEF based phenotypes. Patients with COPD-HFrEF were more likely to experience a HF-admission compared with those with COPD-HFpEF (see **Figure 4.2**).

The greater proportion of CAD in the COPD-HFrEF may be associated with a higher predisposition towards cardiovascular outcomes[131, 132] compared to COPD-HFpEF. Conversely, individuals with COPD-HFrEF were less likely to experience an AECOPD compared with those with COPD-HFpEF. This suggests differences in COPD disease burden or presentation depending on the LVEF phenotype in patients with concomitant HF.

Results therefore suggest that on average, the clinical trajectory of patients with COPD-HFpEF appears to be led by COPD outcomes. One potential explanation is the presence of more severe COPD[133] in this subgroup, compared with those with COPD-HFrEF, suggested by a higher requirement for COPD-related medication. It is also possible that some misclassification of the cause of admission may have influenced results, and this is related to coding practices such as a lack of documentation of HF decompensation during admission in the presence of AECOPD treatment, or assigning HF as a secondary cause of admission, thus possibly underestimating HF admission risk in COPD-HFpEF. However, an analysis exploring the relationship between COPD-medications and cause-specific outcomes showed steroid use was related to a three-fold increased risk of AECOPD (HR_{adj}, 95% CI: 3, 2.68-3.36), but not to HF-admission (HR_{adj}, 95%CI 1.07, 0.88-1.30) suggestive of a possible association of COPD severity rather than misclassification in our cohort.

HFpEF is a particularly difficult diagnosis to adjudicate, due to a lack of standardised criteria and non-specific symptoms which involve validation and clinical interpretation from several investigations[50, 128]. This is more challenging in the presence of COPD. The tendency to attribute respiratory symptoms to an underlying pulmonary disease rather than a cardiovascular one may be more frequent in situations where echocardiography quality is limited, as may occur in patients with COPD[50]. There is ongoing debate regarding the optimal diagnostic workup for HF with coexisting COPD [134]. Future prospective studies are needed to investigate the degree to which COPD symptoms may be misclassified as HFpEF (and vice versa), as well as whether the increase in AECOPD risk observed in those with HFpEF is true versus misattribution of cardiac events.

The proportion of patients diagnosed with HFpEF inpatient was larger compared with those with HFrEF. It is likely that, due to high variation in clinical characteristics and the existence of many comorbidities, patients with COPD-HFpEF are more difficult to accurately diagnose or manage in ambulatory, generalist settings as compared to COPD-HFrEF. Incorrect diagnosis or delay in diagnosis may be additionally aggravated by the presence of COPD, with greater diagnostic uncertainty for HFpEF versus HFrEF (for which more established diagnostic criteria are defined[10]. Alternatively, HFpEF patients may have less contact within primary care, as reported previously, providing less opportunities for diagnosis in outpatient settings [32].

4.5.4 Mortality

There was a 16% elevated risk of mortality for patients with COPD-HFrEF compared with COPD-HFpEF, within a median follow-up of 27 months. Data regarding mortality rates between HF LVEF phenotypes are conflicting, as most observational studies in the general HF population suggest no overall difference between the two EF groups [128], while a large meta-analysis, based on clinical trial results, revealed a 50% lower risk of death for HFpEF compared to HFrEF [135].

The present results suggest that in patients with COPD, HFrEF is associated with poorer overall survival compared with a diagnosis of HFpEF. As there are proven therapies for patients with HFrEF (regardless of presence of other comorbidities), the low uptake of guideline-recommended medication in this cohort may underlie this result. Management of HFpEF is currently directed at symptom alleviation, since there are no evidence-based disease-modifying treatments as yet. Surprisingly, these patients fared better than those with HFrEF, suggesting that in patients with COPD, a reduced EF may carry a heavier mortality burden compared with a

status of preserved EF. This interpretation would be in agreement with the observation that those with HFpEF experience a higher proportion of deaths due to non-cardiovascular causes versus those with HFrEF, as a consequence of a higher burden of non-cardiovascular comorbidities[136].

4.5.5 Healthcare resource use

COPD-HFrEF patients were less likely to experience long-term or ER visits, but not inpatient stays; however, when they were hospitalised, they had a shorter length of stay, on average, compared to those with COPD-HFpEF.

These results highlight different clinical trajectories between the two LVEF groups and may reflect the lower prevalence of comorbidities and higher levels of guideline-recommended prescription medication for COPD-HFrEF in addition to likely management uncertainty for COPD-HFpEF. In turn, this may increase vulnerability towards longer admission duration compared with the COPD-HFrEF group.

Additionally, higher overall healthcare costs observed in the COPD-HFpEF group also reflect the overall greater disease burden seen in this group (i.e., higher prevalence of diabetes, renal failure, depression).

4.5.6 Strengths and limitations

A large number of patients with COPD-HF were included, making these results generalisable to the US commercially insured and Medicare Advantage population. While LVEF was assessed as an effect modifier in the relationship between COPD and HF and clinical outcomes such as

death, previously[114] , there are no large studies assessing patients with coexisting COPD-HF according to LVEF-based HF groups.

Most patients with HF claims did not have a diagnostic test such as LVEF recorded in OLDW; thus, to ensure validity of HF diagnosis, the sample was limited to patients with echocardiographic data. Comparison with previous data from OLDW[137] suggests patients with HF who have a LVEF recording in the database had increased prevalence of obesity and AF and were more often insured by Medicare or White; however, patients were largely similar on key variables such as age, sex, the majority of sociodemographic factors and other comorbidities.

The non-differential distribution of a majority of characteristics of patients with HF with LVEF versus no LVEF data suggests therefore that the population included in our study did not differ from the overall HF population captured by the OLDW. This may reflect a "system-level" wide missingness for this variable rather than a significant selection bias due to LVEF recording.

Spirometry data was not available for this cohort, however, the use of validated COPD codes, which have up to 85% accuracy and are considered suitable for epidemiological research [80] and assessment of COPD-related medication improved the precision of diagnosis, which is difficult in HF. This is due to potential obstruction related to cardiac decompensation [50], which can confound pulmonary testing and thus, COPD ascertainment [50, 121, 138].

Overdiagnosis of COPD due to underlying, but unrecognised HF cannot be excluded[139]. Nonetheless, the assessment of the lung disease as prevalent (i.e., which was present before HF diagnosis) limited potential diagnosis misclassification. Even so, future studies where lung function measurements are performed on euvolemic patients with HF are needed to validate the accuracy of COPD diagnosis.

Given that this study used claims data, it was not possible to capture prescriptions that were not submitted to insurance; therefore, an underestimation of prescription rates cannot be ruled out. However, previous studies suggest that uptake of guideline recommended medication is low for patients with either HF[140, 141], COPD[142-144] or those with both diseases[130].

Duration or severity of COPD were not available either and thus could not be accounted for in adjusted analyses. However, I adjusted for use of diuretics, which may be considered a proxy for the presence of congestion, and COPD medication regimens, which may serve as a proxy for severity of disease (or GOLD stage). However, residual confounding cannot be excluded.

Finally, cause-specific outcomes are dependent on ICD-9 and ICD-10 coding which are subject to misclassification.

4.6 Conclusions

Amongst patients with COPD and HF, HFpEF is the most common LVEF-phenotype. Outcomes in the COPD-HFpEF group were principally driven by COPD, as AECOPDs were more frequent compared to the COPD-HFrEF group, possibly due to more severe COPD. Given the lack of treatments specifically directed at HFpEF, a more comprehensive primary care assessment to discriminate between cardiovascular and respiratory symptoms is needed. A greater precision and emphasis on the recognition and management of COPD, may provide an opportunity to reduce AECOPD and improve outcomes for these patients. Patients with COPD-HFrEF were more likely be hospitalised for a HF decompensation, and had overall worse survival, compared with their COPD-HFpEF counterparts, emphasising the importance of optimising guideline-recommended HF disease-modifying medication in this group.

Chapter 5 IMPACT OF BETA-BLOCKER THERAPY ON OUTCOMES IN PATIENTS WITH COPD

Systematic literature review and meta-analysis

This chapter reports the findings of a systematic review and meta-analyses on the effect of beta-blocker use on outcomes in patients with COPD. Despite improving mortality in patients with cardiovascular disease, beta-blockers are underused in those with coexistent COPD, due to concerns regarding respiratory side-effects and interactions with COPD treatments such as beta-agonists. These fears are not supported by recent evidence, which suggests that cardioselective beta-blockers don't negatively impair lung function or respiratory outcomes in patients with COPD.

While others have conducted similar reviews[56], they have not provided a comprehensive assessment including a wide range of patient-centred outcomes, and have not evaluated the within-class effect of beta-blocker therapy (by comparing effects of individual beta-blockers).

Some individuals receive beta-blocker prescriptions for indications which are precursors to HF (such as myocardial infarction [MI], coronary artery disease [CAD]and hypertension). To capture this population, which represents essentially a population of pre-HF patients, I included data on all individuals with COPD with an indication for beta-blockers, ensuring

representativeness of the sample. Therefore, this work allows for exploration into how HF management may be affected by concurrent COPD comorbidity.

The review protocol was registered with PROSPERO (CRD42018098983) and was published, as well as the systematic review itself (see Appendix G, Paper 3, and Paper 4). Another publication related to this Chapter is a Letter to Editor discussing implications on clinical and methodological rigorousness of conducting meta-analyses of beta-blocker use in individuals with COPD (Appendix G, Paper 5).

5.1 Introduction

Beta-blockers are recommended in several cardiovascular disease states due to their beneficial effects on mortality and morbidity, as demonstrated in clinical trials of patients with HF[10], post MI [145] and acute coronary syndrome (ACS) [146]. Among those with an indication for treatment, prescription rates of beta-blockers are lower for people with concomitant COPD compared to those without COPD. This is in part due to concerns regarding adverse respiratory effects (i.e., reduced lung function) despite accumulating evidence to the contrary[39]. Further, patients with COPD and coexistent cardiovascular disease are at increased risk of mortality and hospitalisation, further adding to the clinical burden and complexity of treatment pathways in these patients[46, 147].

COPD guidelines recommend the use of cardioselective beta-blockers when needed, supported by evidence gathered in a Cochrane review indicating lung function is not significantly affected by use of these agents [57].

Data regarding the relationship between beta-blocker therapy and mortality as well as AECOPD are derived mostly from observational studies and previous reviews have aggregated results for cardio and non-cardioselective agents [148, 149]. However, a recent single RCT[58] reported more hospitalisations due to acute exacerbations of COPD (AECOPD) in patients treated with metoprolol as compared to placebo, though results on mortality and FEV_1 were inconclusive.

This study expands on previous literature by evaluating the effects of beta-blockers from both clinical trials and observational studies, on a wide-ranging spectrum of clinical endpoints (mortality, AECOPD, FEV_1, all-cause hospitalisation) and quality of life outcomes such as St.

George's Respiratory Questionnaire (SGRQ), The 6-minute walking test (6MWT) and 12-minute walking test (12MWT) and The Short-Form Health Survey Questionnaire (SF-36).

5.2 Study aims

There were two overarching aims:

(1) To identify and assess the class-effect of beta-blockers on a broad range of patient outcomes in individuals with COPD.

(2) To compare within-class effects of beta-blockers and to identify whether specific agents are particularly beneficial for patients with COPD.

If all studies have at least one intervention in common with another, it is possible to create a network of treatments, allowing both direct and indirect evidence to be used in deriving comparisons between beta-blockers not compared in a head-to-head manner, by conducting a network-meta-analysis (NMA).

5.3 Methods

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines[150]. This protocol for this review was registered with PROSPERO. (CRD42018098983). Inclusion and exclusion criteria are presented in **Table 5.1**.

TABLE 5.1: Inclusion and exclusion criteria for systematic literature review

Category	Inclusion Criteria	Exclusion Criteria
Population	Adult patients with COPD (Defined as post-bronchodilator FEV1/FVC of <0.70, or as being in accordance with current or previous GOLD guidelines, patients with a clinical diagnosis of COPD) Studies including a mixed population (e.g., COPD and asthma) were excluded unless they reported outcomes separately COPD	Publications that do not report data specific to adults with COPD
Interventions	Beta-blockers	Publications that do not report data specific to beta-blockers
Comparators	Placebo or beta-blocker	Studies reporting on treatments other than beta-blockers
Outcomes	Mortality, AECOPD, FEV1, all-cause hospitalisation, adverse events, SGRQ, 12 and 6MWT, SF-36, CAT, EQ-5D, CRQ, ISWT	Publications that do not report clinical efficacy or safety data on potential comparators
Study design	Observational studies, RCTs	Animal studies In-vitro/ex-vivo studies Case studies/case series Reviews, editorials, conference abstracts (we will include only peer-reviewed publications)
Language	English-language articles only	Journal articles with non-English full texts
Geographical regions	No limitation based on geographic region(s)	N/A
Publication date	N/A	N/A

6/12MWT= 6/12-minute walking test; AECOPD= acute exacerbation of COPD; CAT= COPD assessment test; COPD= chronic obstructive pulmonary disease; CRQ= Chronic respiratory disease questionnaire; EQ-5D= Euro-QoL-5-Dimension; FEV1= Forced expiratory volume in 1 second; FVC= forced vital capacity; ISWT= Incremental shuttle walking test; N/A= not applicable; SF-36= Short-Form Health Survey Questionnaire; SGRQ=St. George's Respiratory Questionnaire.

5.3.1 Search strategy

The search algorithm was generated using the Patient Intervention Comparators and Outcomes (PICO) framework outlined above and are available in the Appendix D, Table D1. Searches were conducted from inception to January 2021 in MEDLINE, Embase and Cumulative Index to

Nursing and Allied Health Literature via Ovid and The Cochrane Collection Central Register of Clinical Trials. Reference lists of accepted publications and published systematic reviews were manually searched for additional references.

5.3.2 Selection of eligible studies

Title and abstract screening

I (main investigator for this work) reviewed each title and abstract to assess eligibility for inclusion in the study according to the pre-defined inclusion and exclusion criteria. A quarter of titles and abstracts were additionally screened by a second collaborator. Any disagreements were resolved through discussion or by a third senior investigator (main supervisor) if a judgment could not be made. For all abstracts deemed eligible for inclusion during the first level of review, full-text articles were retrieved and reviewed.

Full-text screening

I reviewed the full texts included in the previous step, alongside other three collaborators. For each excluded study, a specific reason for exclusion was provided and was validated by the main investigator. The main supervisor was consulted to resolve any disagreements.

5.3.3 Data extraction

I developed a Microsoft Excel template for data extraction, with input from two senior investigators (supervisors for this thesis). For each included study, data was extracted on study design, patient characteristics, interventions, and outcomes. Extracted elements were:

- Study characteristics (country, study design, follow-up time, aims, statistical analysis).

- Population: demographic information (sex, age, ethnicity), inclusion/exclusion criteria, disease severity, comorbidities.
- Interventions and comparators: type of medication administered (beta-blocker or placebo), treatment duration.
- Outcomes: definition of outcome, time point of assessment, value at baseline/time point, change in value from baseline/time point.

Authors were contacted to clarify ambiguously reported data from published reports.

5.3.4 Outcomes

While I aimed to include data on all outcomes outlined in **Table 5.1**, searches identified studies reporting on the following outcomes only:

- All-cause mortality
- AECOPD
- FEV_1
- All-cause hospitalisation
- St. George's Respiratory Questionnaire (SGRQ)
- The 6-minute walking test (6MWT) and 12-minute walking test (12MWT)
- The Short-Form Health Survey Questionnaire (SF-36)

I extracted data from 85% of included studies and validated the remaining 15% extracted by three collaborators.

5.3.5 Risk of bias

The Risk of Bias in Non-randomized Studies of interventions (ROBIN-I) [151] tool was used to assess risk of bias in cohort studies and the Risk of Bias (ROB) tool[152] was employed for RCTs. Bias domains evaluated confounding, reporting, attrition, and measurement of outcomes. Each domain was assigned to a risk category for instance “low”, “moderate”, “high” or “unclear” for observational studies and “low”, “high” or “some concerns” for RCTs. Additionally, the certainty of the evidence was assessed using the Grading of Recommendations Assessment Development and Evaluation (GRADE) criteria [153].

5.3.6 Data analysis

Where included studies were reasonably statistically and clinically similar, I used meta-analysis to pool results to investigate class-effect of beta-blocker treatment, or NMA, where data on individual therapeutic compounds was available. Publication bias was assessed using funnel plots if there were at least 10 studies included in meta-analysis [154]. For binary outcomes I initially included studies that reported on outcomes in any format (HR, OR, RR, IR); however, the final inclusion list contains only studies reporting HRs since this was the most common amongst included studies. Heterogeneity was assessed using I^2 [155].

5.3.6.1 FEV1 - Network meta-analysis of RCTs

I performed a random-effects Bayesian NMA to estimate mean change in FEV_1 between patients who received individual beta-blockers compared with placebo with 95% Credible intervals (CrI), using package gemtc[156] in R v3.6. CrIs represent the 95% probability that the true underlying effect lies in the specified interval. Where the standard deviation (SD) for the FEV_1 measure was

not reported, it was extrapolated by averaging the SDs from other studies with similar characteristics.

Random-effect analyses are widely accepted as the appropriate, more conservative approach when there is heterogeneity across study methods. In comparison, fixed-effect models presume that effect size associated with an intervention does not vary across studies, thus this method may be appropriate when only few studies are available for analysis.

The best model fit for each network was selected based on a review of the deviance information criterion (DIC) and an evaluation of the different model assumptions. For transparency I present both random and fixed effects.

NMAs include direct and indirect evidence from trials to determine the best available treatment with respect to an outcome of interest. NMA assumptions need to be met in order for the results to be valid, including transitivity and consistency. For the transitivity assumption to be met, the studies that contribute direct evidence must be similar in distribution of covariates and effect modifiers across the study cohorts. Inconsistency occurs when the indirect evidence in a network is different compared to the direct evidence. Assessing consistency of data in the network model is done implicitly in package “gemtc” which uses a decision rule - the node-splitting method - to choose which comparisons may be potentially inconsistent. Small study effects were explored by looking at comparison-adjusted funnel plots[157] and publication bias was assessed by Egger’s test among comparisons of beta-blockers and placebo. A value of $p<0.1$ suggested significant publication bias.

To assess the probability that a treatment is the best within a network, rank probabilities were determined, that is, the probability for each treatment to obtain each possible rank in terms of

their relative effects. There is a caveat to this as a treatment may have a high probability of being first or last treatment and its benefit over other treatments may be of little clinical value [158]. For this reason, I report a full ranking profile (where each treatment is assigned a probability of being first, second, and so on, best treatment in the network) which was derived using the surface under the cumulative ranking curve (SUCRA)[159].

Sensitivity analyses

I conducted two meta-regressions to establish whether FEV_1 at baseline, study duration, or cardiovascular disease status affected the main NMA results. The following variables were added, separately, as covariates in the main NMA model:

a) FEV_1 as a continuous variable.
b) Follow-up dichotomised into short follow-up (< than 24 hours) and long follow-up (> than 24 hours).
c) Cardiovascular disease status entered as a dichotomous variable indicating presence or absence of cardiovascular disease.

Model fits were compared between models with and without covariates, using the DIC.

5.3.6.2 AECOPD – Meta-analysis of observational studies

I pooled Hazard ratios (HRs) quantifying the association between beta-blocker treatment (vs. no beta-blocker treatment) among patients with COPD, using random-effects meta-analysis with the DerSimonian-Lard estimator in "metafor" [160] package in R v3.6. For transparency, I also present the fixed-effect model.

5.3.6.3 Mortality & quality of life - Narrative synthesis

If studies were too heterogeneous (I^2>75%), or where outcomes were reported in under three studies per treatment comparison, quantitative analysis was not reported, but summary results were graphed on forest plots without pooling the results (mortality) and/or synthesised qualitatively, as was the case for quality-of-life endpoints.

5.4 Results

The search employed on the aforementioned databases identified 2932 articles whilst other sources revealed six additional ones. After title and abstract screening, 187 articles were selected for full-text review. Finally, 23 observational studies and 14 RCTs that reported on patients with COPD were included in the systematic literature review. Out of the 23 observational studies, twenty-one reported on mortality [161-181], five reported on AECOPD [161, 170, 172, 182, 183] three reported on all-cause hospitalisation [79, 184, 185], one reported on SGRQ [182] and one reported on SF-36[179]. From14 RCTs, 12 reported on lung function (FEV_1) [186-197], two each reported on 12MWT[195, 198] and 6MWT[58, 192] and two reported on SGRQ[58, 192] (see **Figure 5.1**).

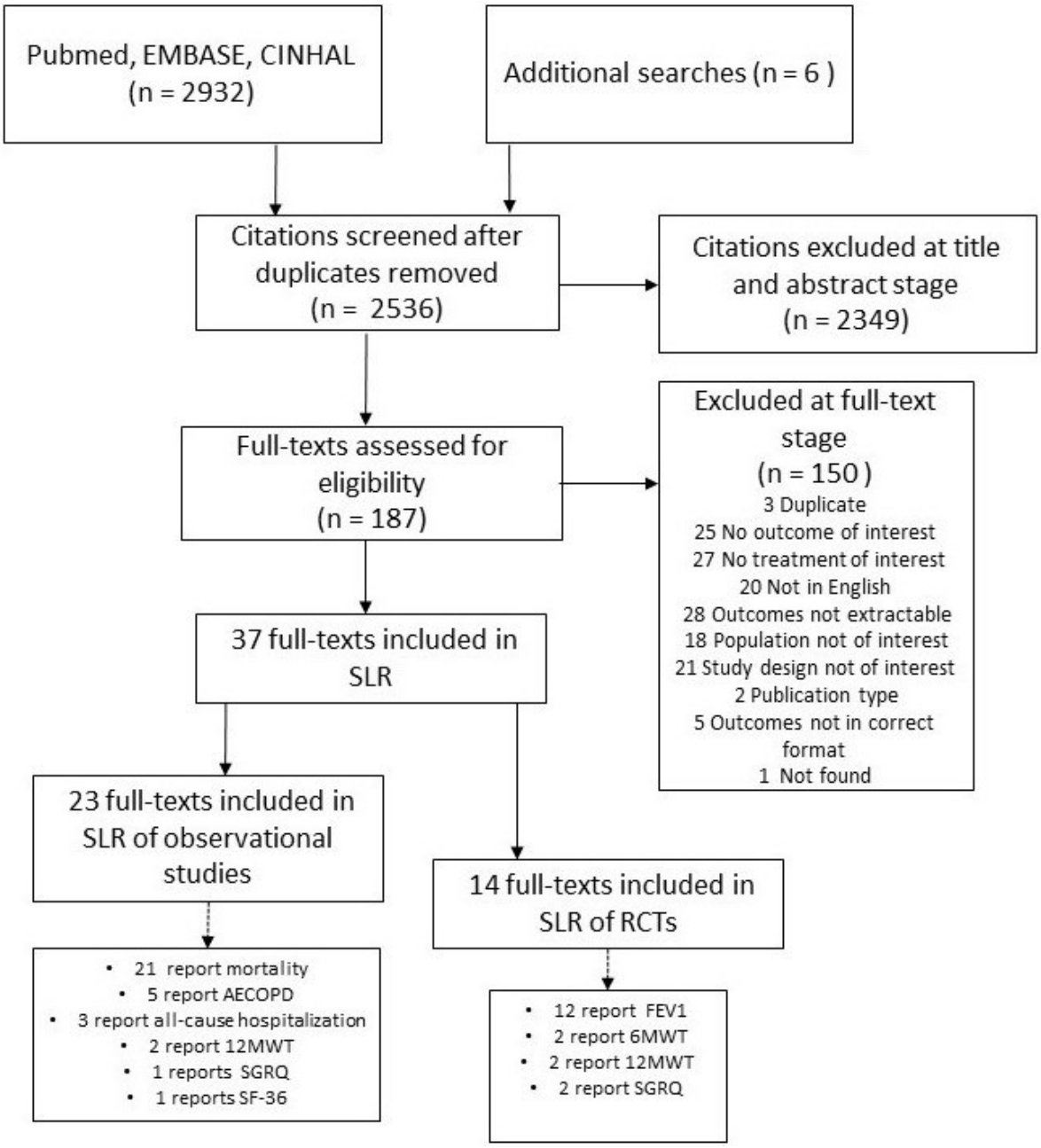

FIGURE 5.1: PRISMA diagram

In line with the protocol[199], I planned to include data on effect of beta-blockers on AECOPD from RCTs, however the search strategy revealed only one study of this type [58]. From a cohort of 532 individuals with moderate to severe COPD, the authors reported no significant difference in time to first AECOPD (of any severity) between metoprolol and placebo. Nonetheless, the use of metoprolol was associated with an increased risk of severe exacerbation (requiring hospitalisation). This study could not be included in the quantitative analysis, as there was no other RCT data to pool.

5.4.1 Quantitative analyses

5.4.1.1 AECOPD

There were five observational studies evaluating the effect of beta-blockers on AECOPD in patients from at least five European countries [161, 170, 172, 182, 183]. Follow-up ranged from 0.76 [183] to 7.2 years[170]. The average age of the patients varied from 62.8[161] to 74[183] years old and the percentage of males from 49.8%[170] to 72.3%[182]. Two studies reported on smoking status[170, 182], which showed most patients were current or former smokers. Cardiovascular comorbidity was frequent, reported in all but one study[172]. Body mass index (BMI) was reported in two studies and ranged between 25.5[182] and 29. 9 kg/m^2[161]. All study characteristics are available in **Table 5.2** below.

TABLE 5.2: Summary of observational studies included in the systematic literature review

Author, country	Beta-blocker evaluated	Outcomes	Follow-up	Population	Sample size	Outcomes assessed
Rutten, 2010; Netherlands	Cardioselective; non-cardioselective	All-cause mortality, AECOPD	Mean 7.2 years (±2.8)	COPD	2230	Mortality, Meta-analysis AECOPD
Maltais, 2018; Multiple countries	Not specified (any BB)	AECOPD, SGRQ	1 year	COPD (GOLD stage 2-4)	5162	Meta-analysis AECOPD
Short, 2011 ; Scotland	Cardioselective (88%); non-cardioselective	All-cause mortality. AECOPD	Mean 4.35 years (±2.28)	COPD	5977	Mortality, Meta-analysis of AECOPD
Bhatt 2016; UK	Not specified (any BB)	AECOPD, all-cause mortality, SGRQ	Median 2.1 years	COPD	3464	Mortality, Meta-analysis of AECOPD
Rasmussen 2020; Denmark	Cardioselective and non-cardioselective (any BB)	AECOPD	Median: 0.76 years	COPD + MI	10,884	Meta-analysis of AECOPD
van Gestel, 2008 ; Netherlands	Cardioselective	All-cause mortality	Median 5 years	COPD + vascular surgery	1265	Mortality
Quint, 2013 ; England	Cardioselective; non-cardioselective	All-cause mortality	Median 2.9 years (range 0.09 - 7.2)	COPD + first MI	1063	Mortality
Zeng, 2013; China	Cardioselective; non-cardioselective	All-cause mortality	Median 1.85 years	COPD	220	Mortality
Mentz, 2013; USA	Cardioselective; non-cardioselective	All-cause mortality	2 months	COPD + HF	725	Mortality
Gottlieb, 1998; USA	Not specified (any BB)	All-cause mortality	2 years	COPD + acute MI	48,480	Mortality
Sin, 2002; Canada	Not specified (any BB)	All-cause mortality	Median: 21 months (IQR, 7 - 39)	COPD + HF	3834	Mortality

Author, country	Beta-blocker evaluated	Outcomes	Follow-up	Population	Sample size	Outcomes assessed
Ekstrom, 2013; Sweden	Cardioselective (98%)	All-cause mortality	Median 1.1 years (IQR 0.6-2)	COPD	1794	Mortality
Coiro, 2016; Multiple countries	Not specified (any BB)	All-cause mortality,	Mean 2.7 years	COPD + acute MI	1573	Mortality
Staszewsky, 2016; Italy	Not specified (any BB)	All-cause mortality	4 years	COPD + HF	2837	Mortality
Su, 2016; Taiwan	Cardioselective; non-cardioselective	Survival	Mean 4.35 years (±2.28)	COPD + HF	11,558	Mortality
Kubota, 2015; Japan	Cardioselective; non-cardioselective	All-cause mortality	Mean 2.75 years	COPD + acute HF	132	Mortality
Hawkins, 2009; Italy	Not specified (any BB)	All-cause mortality	N/R	COPD + history of MI	1258	Mortality
Ellingsen, 2020; Sweden	Not specified (any BB)	All-cause mortality; AECOPD	10 years	COPD + AF	17,745	Mortality
Rodriguez-Manero, 2019; Spain	Not specified (any BB)	All-cause mortality	Mean 1.93 years (±0.28)	COPD	937	Mortality
Su, 2019b; Taiwan	Cardioselective; non-cardioselective	All-cause mortality	9.32 years	COPD + HF	275,436	Mortality
Su 2019; Taiwan	Cardioselective; non-cardioselective	All-cause mortality	Mean: BB group: 3.9 years (± 2.7) Control group: 3.5 years (± 2.7)	COPD + acute MI	22,007	Mortality

Author, country	Beta-blocker evaluated	Outcomes	Follow-up	Population	Sample size	Outcomes assessed
Wang 2019; Taiwan	Cardioselective; non-cardioselective	All-cause mortality	N/R	COPD + first acute MI	23,116	Mortality
Scrutinio, 2019; Italy	Cardioselective; non-cardioselective	All-cause mortality	N/R	COPD + HF	396	Mortality
Farland, 2013; USA	Cardioselective; non-cardioselective	All-hospitalisation	1 year	COPD	412	Outcome not reported in suitable format (OR); only two observational studies per this outcome
Brooks, 2007; USA	Cardioselective; non-cardioselective	All-cause hospitalisation	N/R	COPD	Not reported per population of interest	Only two observational studies per this outcome
van Gestel 2009; Netherlands	Not specified (any BB)	SF-36	6.4 years	COPD + PAD	1310	Only one observational study reporting on this outcome

AECOPD= acute exacerbation of COPD; AF= atrial fibrillation; BB= beta-blocker; DM= diabetes mellitus, GOLD= Global Initiative for Chronic Obstructive Lung Disease; HF= heart failure; IQR= inter-quartile range; MI= myocardial infarction, N/R= not reported; PAD= peripheral artery disease; SF-36= Short-Form Health Survey Questionnaire; SGRQ=St. George's Respiratory Questionnaire; USA=United States of America.

In the presence of low statistical heterogeneity (<25%), the random effects and fixed effects method for pooling effect estimates give identical results. Due to low heterogeneity (I^2=0, owing to the large weight attributed to one study only[183]) and the small overall number of studies, I report both random and fixed-effects meta-analyses of AECOPD. In random-effects analysis, the pooled risk of AECOPD associated with beta-blocker use from 27717 patients, was HR 0.78 [95%CI 0.74 – 0.82] suggesting a reduction in relative risk in the presence of beta-blockers (see **Figure 5.2**, **Table 5.3**).

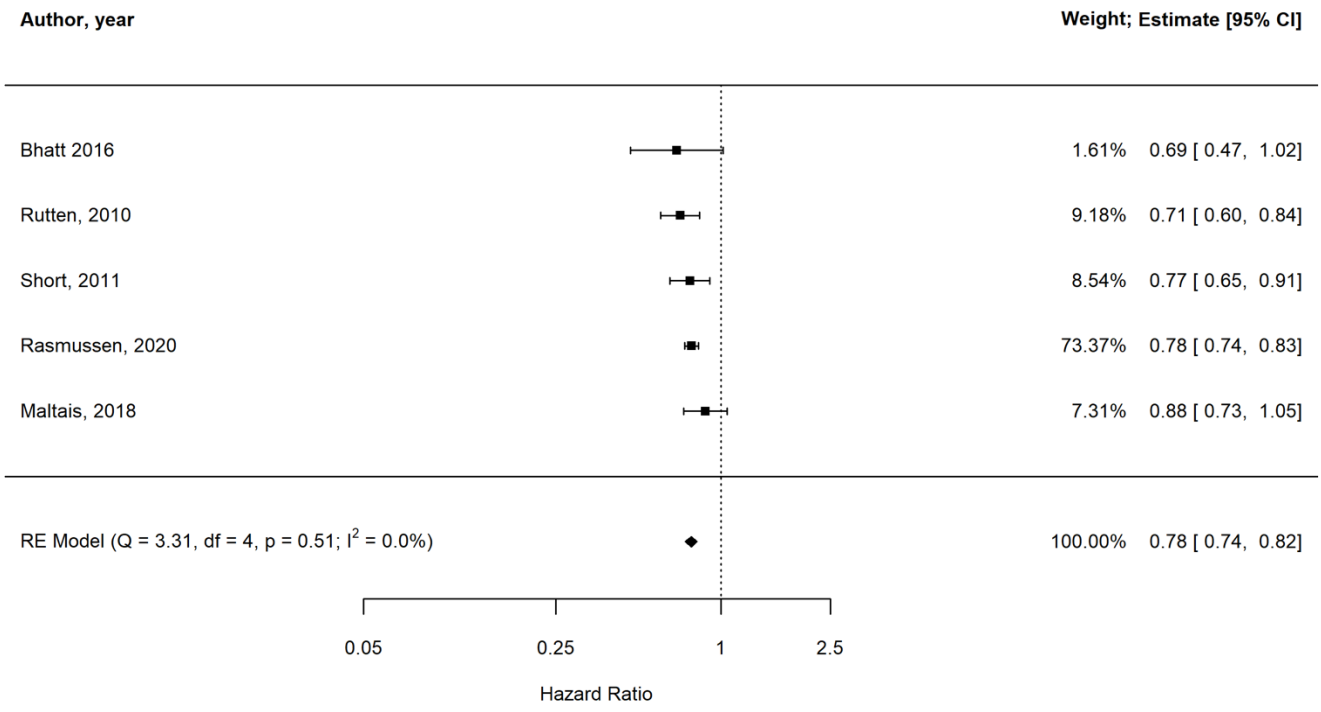

FIGURE 5.2: Association between beta-blocker use and risk of AECOPD in patients with COPD, random effects model showing HRs with 95% CI

TABLE 5.3: AECOPD estimates for beta-blocker versus no beta-blocker use, from individual observational studies

Author	Comparison	Follow-up (months)	AECOPD HR [95 CI]	Covariates adjusted for in analysis
Rutten, 2010	BB vs. no BB	86.4	0.71 [0.6 – 0.83]	Age, sex, smoker, diabetes, hypertension, cardiovascular disease, pulmonary drugs, referral to pulmonologist
Maltais, 2018	BB vs. no BB	12	0.88 [0.73 – 1.05]	Age, sex, COPD treatment, BMI, race, GOLD stage, cardiac disorders, hypertension, ACEi, ARB, lipid-modifying agents
Short, 2011	BB vs. no BB	52 (27)	0.77 [0.65 -0.91	History of hospital admission for cardiovascular disease, diabetes, smoking, age, sex, FEV_1, resting Sa02 and deprivation index
Bhatt 2016	BB vs. no BB	Median 25.2	0.69 [0.47 – 1.02]	Age, race, HF, FEV_1, % emphysema on CT, respiratory medications, log CAC and the propensity to prescribe BB
Rasmussen, 2020	BB vs. no BB	Mean 9.1	0.78 [0.74 – 0.83]	Age, sex, history of AECOPD, inhaled therapy, comorbidities, type of MI, revascularisation procedures, income, calendar year

ACEI= angiotensin-converting-enzyme inhibitors; ARB= angiotensin receptor blockers; AECOPD= acute exacerbation due to COPD; BB= beta-blockers; BMI= body mass index; CAC= coronary artery calcification; CI,= confidence interval; CT= computed tomography; FEV_1= forced expiratory volume in 1 second; HF= heart failure; HR= hazard ratio; GOLD= Global Initiative for Chronic Obstructive Lung Disease; MI= myocardial infarction; Sa0=, arterial oxygenation saturation;

The fixed-effects meta-analysis yielded similar results (see **Figure 5.3**).

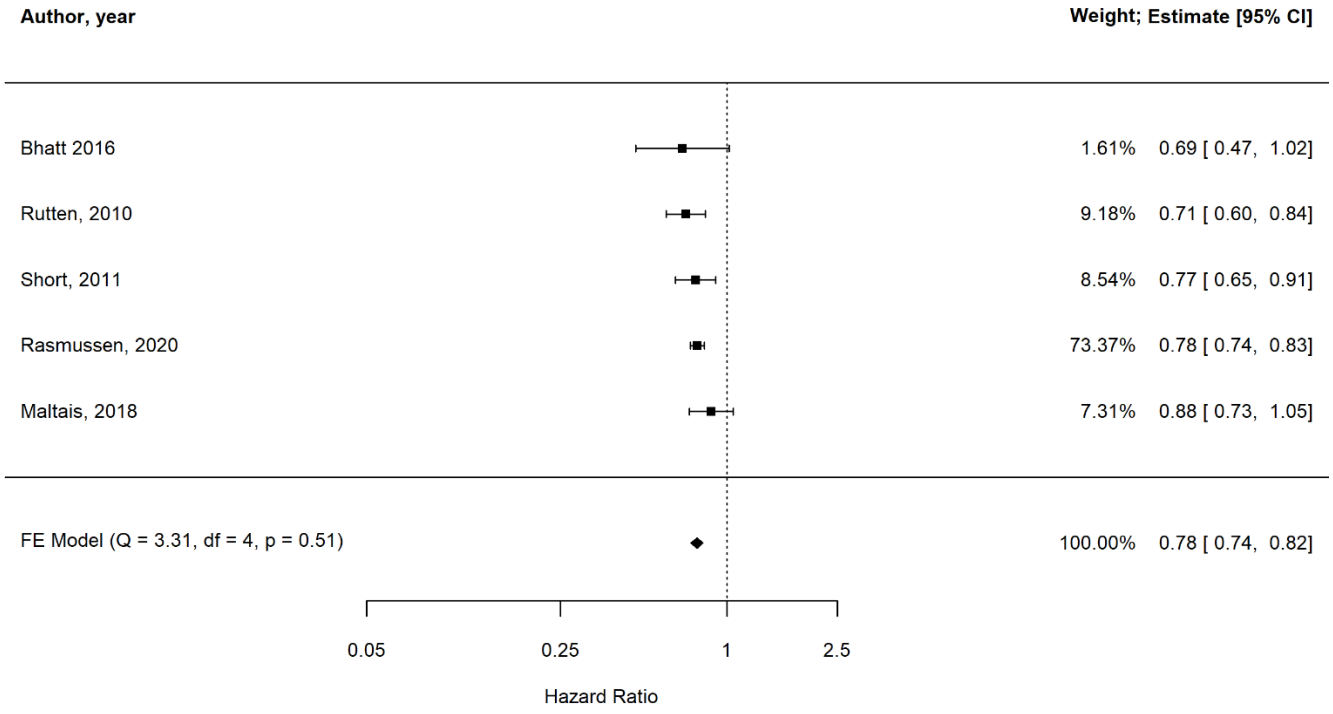

FIGURE 5.3: Association between beta-blocker use and risk of AECOPD in patients with COPD, fixed effects model showing HRs with 95% CI

Due to the low number of studies, I did not formally assess publication bias.

5.4.1.2 FEV1

FEV_1 was investigated in 12 RCTs and a total of 199 patients. Seven beta-blockers (atenolol, bisoprolol, carvedilol, celiprolol, metoprolol, propranolol, labetalol) were evaluated [186-191, 193-197, 200]. Duration of trials varied from 1 hour [189, 195] to 3-4 months[193] and FEV_1 measurement at baseline between 1.15[195] and 2.41 litres (l)[197] (see **Table 5.4**).

TABLE 5.4: Study characteristics (RCTs)

Author, year, country	Primary Outcome	Secondary Outcomes	Study design	Population	Drug	Included in NMA	Notes
Adam 1982, Australia	FEV_1, 3.5 h after drug administration	Specific AWR	Double-blind, placebo-controlled cross-over	COPD + hypertension	Labetalol, metoprolol, atenolol, propranolol, placebo	Yes	
Hawkins 2009, UK	FEV_1	Other pulmonary function tests, symptoms and quality of life	Double-blind, placebo controlled	COPD + HFrEF	Bisoprolol, placebo	Yes	
Lainscak 2011, Slovenia	FEV_1	Pulmonary function, heart rate, NT-proBNP.	Open-label	COPD + HFrEF	Bisoprolol, carvedilol	Yes	
McGavin 1979, UK	FEV_1	12 MWT; pulse rate; FVC; PEFR	Double-blind cross-over	COPD	Metoprolol, propranolol	Yes	
Van Der Woude 2005, Netherlands	FEV_1	Bronchoconstriction	Double-blind, placebo-controlled cross-over	COPD	Metoprolol, celiprolol, propranolol	Yes	
Mainguy 2012, Canada	Difference in dynamic hyperinflation	Differences in cycle endurance test duration, FEV_1	Double-blinded cross-over	COPD	Bisoprolol	Yes	
Chang 2010, New Zealand	FEV_1	Exercise capacity, salbutamol response curve	Double-blind placebo-controlled cross-over	COPD, moderate	Propranolol, metoprolol	Yes	
Jabbal 2017, UK	AWR	FEV_1, FVC, RVC, SGRQ, TDI, 6MWT	Open-label, cross-over	COPD, moderate to severe	Bisoprolol, carvedilol	Yes	
Trials with SDs extrapolated for NMA analysis							

Author, year, country	Primary Outcome	Secondary Outcomes	Study design	Population	Drug	Included in NMA	Notes
Dorow 1986, Germany	AWR	FEV_1	Double-blind, placebo-controlled cross-over	COPD + stable angina	Bisoprolol, atenolol, placebo	Yes	SD extrapolated*
Sinclair 1979, UK	FEV_1	Symptoms	Double-blind, placebo-controlled cross-over	COPD	Propranolol, metoprolol	Yes	SD extrapolated*
Chester 1981, USA	FEV_1	FVC	Double-blind cross-over	COPD	Propranolol	Yes	SD extrapolated*
Ranchod 1982, South Africa	FEV_1	Pulse rate, FEV_1, MMFR, PFR	Double-blind placebo-controlled cross-over	COPD	Propranolol, atenolol	Yes	SD extrapolated*
Excluded from NMA							
Butland 1980, UK	FEV_1	12MWT	Double-blind placebo-controlled cross-over	Emphysema with severe airway obstruction	Metoprolol, atenolol, placebo	No	Mean change in FEV_1 or data needed to calculate not provided
Dransfield 2019, USA	AECOPD	All-cause mortality, all-cause hospitalisation, spirometry, 6MWT	Double-blind, placebo-controlled	COPD, moderate to severe	Metoprolol	No	Only one RCT reporting on AECOPD

12MWT= 12 minutes walking test; 6MWT= 6 minutes walking test; AECOPD= acute exacerbation of COPD; AWR= airway resistance; FEV_1= forced expiratory volume in 1 second; FVC= forced vital capacity; HFrEF= heart failure with reduced ejection fraction; MMFR= maximal mid-expiratory flow rate; NMA= network meta-analysis; NT-proBNP= N-terminal pro-brain natriuretic peptide; PFR= peak expiratory flow rate; RCT= randomised controlled trial, SD= standard deviation; SE= standard error; SGRQ= St. George's Respiratory Questionnaire; TDI= transition dyspnoea index.
*SD was extrapolated (averaged) from studies with similar characteristics.

The majority of patients were over 40 years old except for one study where mean age was 39[196]. Across all RCTs, over half of the patient population were male and four studies only included patients with cardiovascular disease or hypertension explicitly [186, 190, 191, 193].

BMI was available in two studies of COPD and cardiovascular disease [191, 193] and in one study only which excluded cardiovascular disease [194]. Estimates were however similar across all three studies, and denoted overweight, but not obese patient populations.

Celiprolol was the only treatment which was evaluated patients without cardiovascular disease exclusively, in one trial[197] only.

Sample size, age and proportion of males were all similar across all studies.

Finally, a comparison between studies including patients with cardiovascular disease and COPD and those including patients with COPD only is difficult due to lack of reported data on whether patients had cardiovascular comorbidities. All characteristics are presented in Appendix D, Table D2.

Figure 5.4 below shows the network of eligible comparisons for FEV_1 mean change from baseline to time-point, including the seven individual beta-blockers. All treatments, except carvedilol were evaluated in minimum one placebo-controlled trial.

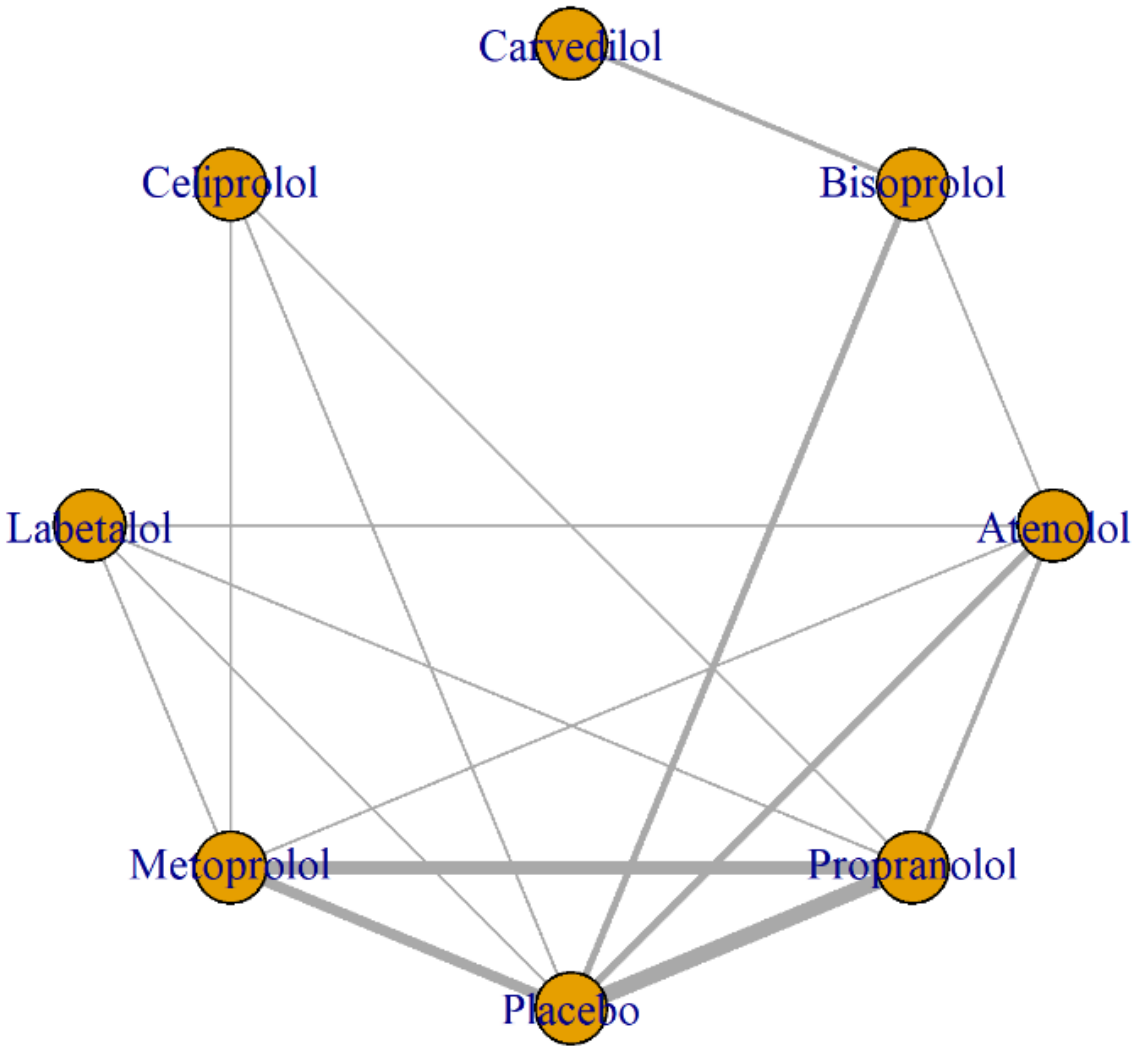

FIGURE 5.4: Network of beta-blockers included in the NMA

Study FEV_1 measurements are presented in **Table 5.5**.

TABLE 5.5: FEV1 measurements (RCTs)

Author	No. arms	Treatment arm	Timepoint	No. randomised	Baseline FEV_1 (SD)	Follow-up FEV_1 (SD)	Mean change in FEV_1 (SD)	SE for mean change in FEV_1
Adam 1982	5	Placebo	3.5h	10	1.69 (N/R)	1.6 (0.03)	-0.09 (N/R)	0.031
Adam 1982	5	Labetalol	3.5h	10	1.69 (N/R)	1.7 (0.033)	0.01 (N/R)	0.033
Adam 1982	5	Metoprolol	3.5h	20	1.69 (N/R)	1.6 (0.047)	-0.09 (N/R)	0.047
Adam 1982	5	Atenolol	3.5h	20	1.69 (N/R)	1.54 (0.045)	-0.15 (N/R)	0.045
Adam 1982	5	Propranolol	3.5h	10	1.69 (N/R)	1.46 (0.06)	-0.23 (N/R)	0.057
Hawkins 2009	2	Placebo	4 months	13	1.26 (0.42)	1.38 (0.026)	0.12 (0.21)	0.116
Hawkins 2009	2	Bisoprolol	4 months	14	1.37 (0.42)	1.3 (0.026)	-0.07 (0.08)	0.11
McGavin 1979	2	Propranolol	1h	9	1.25 (0.49)	1.1 (0.48)	-0.15	N/R
McGavin 1979	2	Metoprolol	1h	9	1.15 (0.43)	1.13 (0.53)	-0.02 (N/R)	N/R
McGavin 1979	2	Propranolol	6h	9	1.25 (0.49)	1.1 (0.45)	-0.15 (N/R)	0.22
McGavin 1979	2	Metoprolol	6h	9	1.15 (0.43)	1.19 (0.38)	0.04 (N/R)	0.19
Van Der Woude 2005	4	Placebo	4 days	15	2.41 (0.36)	2.24 (0.37)	-0.17 (N/R)	0.13
Van Der Woude 2005	4	Celiprolol	4 days	15	2.41 (0.36)	2.32 (0.29)	-0.09 (N/R)	0.12
Van Der Woude 2005	4	Metoprolol	4 days	15	2.41 (0.36)	2.16 (0.36)	-0.25 (N/R)	0.13
Van Der Woude 2005	4	Propranolol	4 days	15	2.41 (0.36)	2.08 (0.31)	-0.33 (N/R)	0.12
Lainscak	2	Bisoprolol	3-4 months	32	1.561 (0.414)	1.698 (0.519)	0.137 (N/R)	0.12
Lainscak	2	Carvedilol	3-4 months	31	1.704 (0.484)	1.734 (0.548)	0.03 (N/R)	0.13
Mainguy 2012	2	Bisoprolol	14 days	27	1.4 (0.45)	1.35 (0.44)	-0.05 (N/R)	0.12
Mainguy 2012	2	Placebo	14 days	27	1.4 (0.45)	1.39 (0.45)	-0.01 (N/R)	0.12
Chang 2010	4	Placebo	7-10 days	14	1.64 (0.53)	1.6 (0.53)	-0.04 (N/R)	0.2
Chang 2010	4	Metoprolol 95 mg	7-10 days	14	1.64 (0.53)	1.54 (0.58)	-0.1 (N/R)	N/R
Chang 2010	4	Propranolol	7-10 days	14	1.64 (0.53)	1.48 (0.5)	-0.16 (N/R)	0.19
Chang 2010	4	Metoprolol 190	7-10 days	14	1.64 (0.53)	1.59 (0.55)	-0.05 (N/R)	0.24
Jabbal 2017	2	Bisoprolol	6 weeks	25	1.5 (0.7)	1.34 (0.67)	-0.16 (N/R)	0.19

Author	No. arms	Treatment arm	Timepoint	No. randomised	Baseline FEV_1 (SD)	Follow-up FEV_1 (SD)	Mean change in FEV_1 (SD)	SE for mean change in FEV_1
Jabbal 2017	2	Carvedilol	6 weeks	25	1.5 (0.7)	1.26 (0.7)	-0.24 (N/R)	0.198
Sinclair 1979	3	Placebo	1 h	10	1.34 (0.56)	1.3 (0.49)	-0.04 (N/R)	0.235
Sinclair 1979	3	Propranolol	1 h	10	1.33 (0.62)	1.13 (0.27)	-0.2 (N/R)	0.213
Sinclair 1979	3	Metoprolol	1 h	10	1.29 (0.48)	1.22 (0.3)	-0.07 (N/R)	0.179
Chester 1981	2	Placebo	3h	13	1.55 (0.85)	1.47 (0.45)	-0.08 (N/R)	0.266
Chester 1981	2	Propranolol	3h	13	1.55 (0.85)	1.39 (0.5)	-0.16 (N/R)	0.273
Dorow 1986	3	Placebo	4h	12	1.59 (0.19)	1.582 (0.34)	-0.008 (N/R)	0.112
Dorow 1986	3	Atenolol	4h	12	1.59 (0.19)	1.42 (0.05)	-0.167 (N/R)	0.056
Dorow 1986	3	Bisoprolol	4h	12	1.59(0.19)	1.61 (0.54)	0.025(N/R)	0.165
Ranchod 1982	3	Placebo	2h	15	2.42 (0.44)	2.39 (0.45)	-0.03 (N/R)	0.162
Ranchod 1982	3	Propranolol	2h	15	2.27 (0.44)	2.15 (0.4)	-0.12 (N/R)	0.153
Ranchod 1982	3	Atenolol	2h	15	2.38 (0.19)	2.25 (0.05)	-0.13 (N/R)	0.05

FEV1= forced expiratory volume in 1 second; SD= standard deviation; SE= standard error; N/R= not reported; No.= number.

There was no significant difference in FEV_1 amongst all beta-blockers except for propranolol, which was the only treatment associated with a decrease in FEV_1 (mean difference [MD] -0.14 ml, 95% CrI -0.28 to -0.016) (see **Figure 5.5)**.

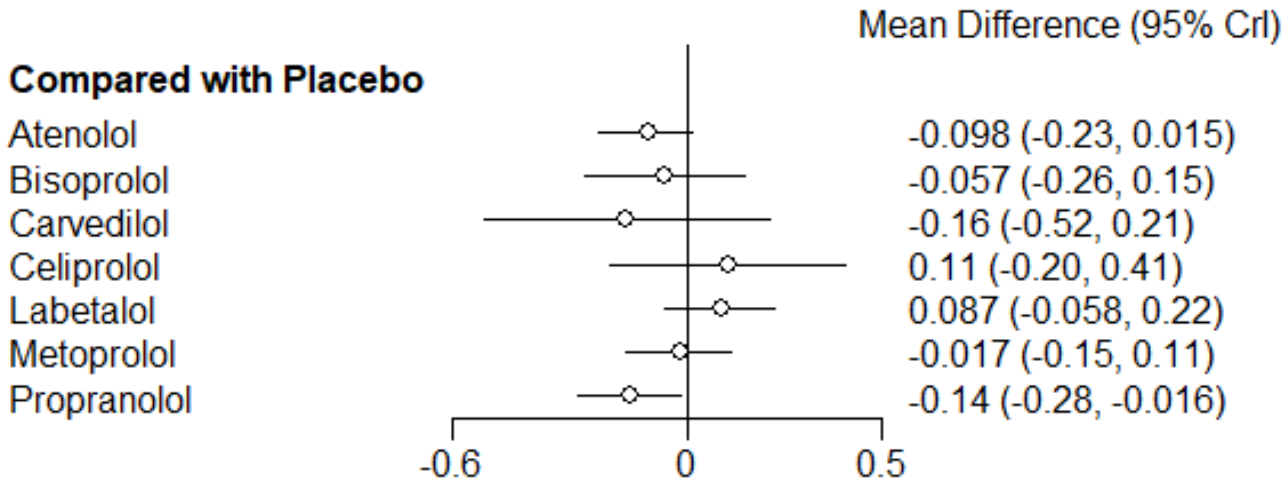

FIGURE 5.5: NMA results showing mean difference in FEV1 (95% Credible Intervals), beta-blockers compared to placebo

The GRADE assessment of RCT data reporting on FEV_1 is available in the Appendix D, Table D3. Consistency results are illustrated in **Figure 5.6** suggesting both direct and indirect evidence contributing to the NMA were in agreement.

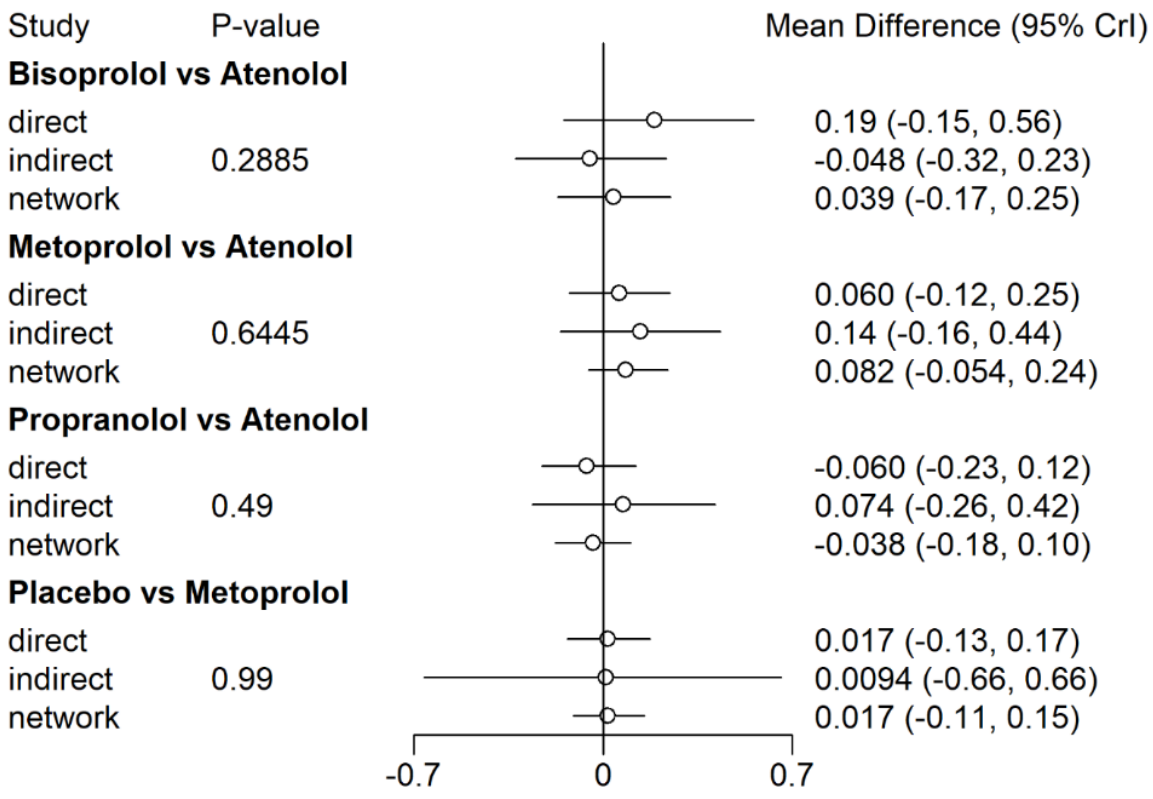

FIGURE 5.6: Consistency results illustrating no significant difference between direct and indirect evidence across all comparisons assessed in the FEV1 NMA

Individual medications were ranked and are presented with estimates of the probability that each is the best treatment (i.e., probability that the treatment improves lung function).

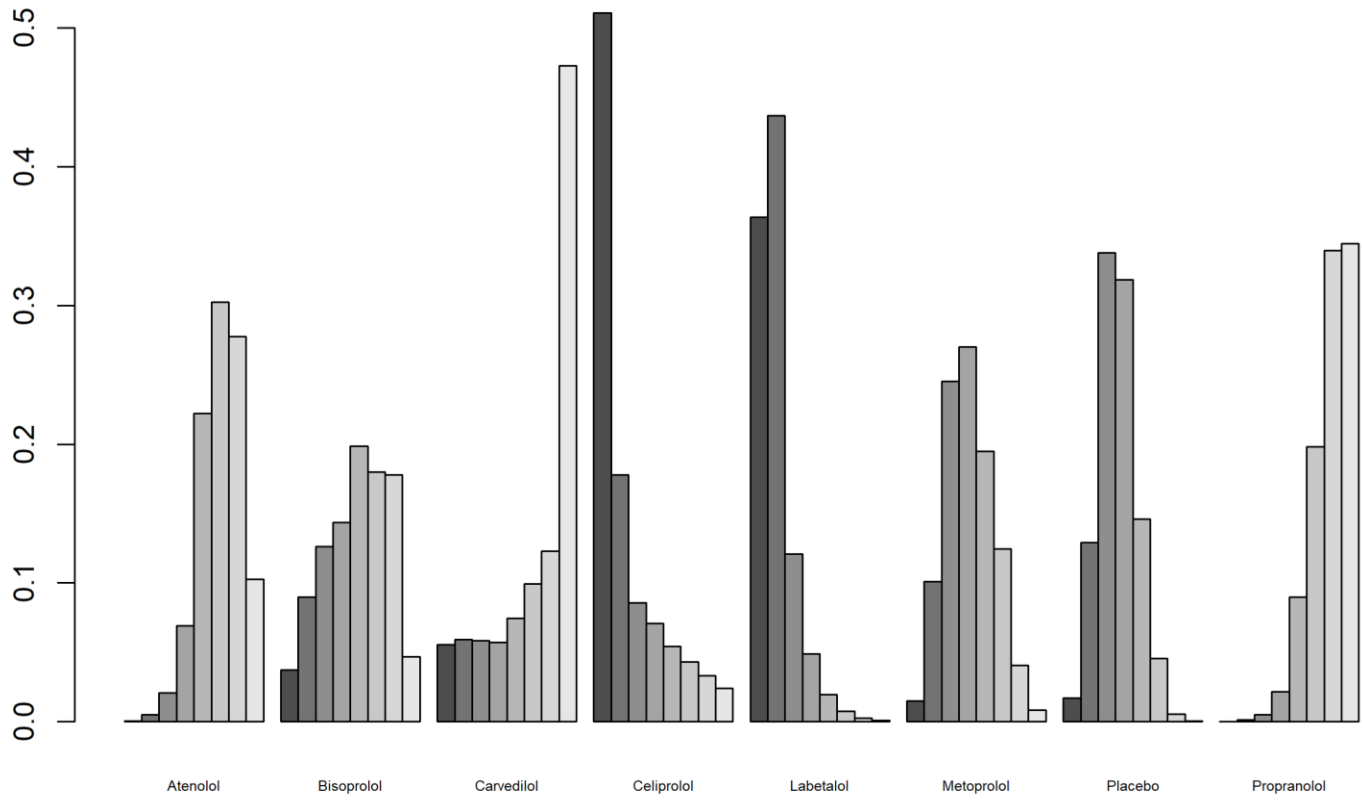

FIGURE 5.7: Rankogram illustrating probabilities that each treatment is first, second, third…eighth with regards to FEV1 improvement

The SUCRA results based on the rankogram values (see **Figure 5.7**) appear to suggest labetalol (86.2%) and celiprolol (80%) were the most likely of being the best treatments to positively affect FEV_1, whilst propranolol was the least likely to do so (16.2% probability of being the best) (**Table 5.6**).

TABLE 5.6: SUCRA ranking probability of being the best treatment (improvement in FEV_1) in patients with COPD

Beta-blocker	Probability best
Labetalol	86%
Celiprolol	80%
Placebo	63%
Metoprolol	56%
Bisoprolol	45%
Atenolol	28%
Carvedilol	26%
Propranolol	16%

According to the comparison-adjusted funnel plot, no publication bias was found for Egger's test (p=0.1286).

Sensitivity analyses FEV_1

The meta-regression analyses, investigating whether baseline FEV_1 measurement, follow-up duration or cardiovascular disease status influenced results showed similar findings to the main analysis (model fit did not improve in none of the models with added covariates).

5.4.2 Narrative synthesis

5.4.2.1 Mortality

Twenty-one observational studies reported on effect of beta-blocker treatment on mortality [161, 162, 164-178, 180, 181, 201] in 422,552 patients from no less than 11 countries. All studies had variable proportions of cardiovascular comorbidities amongst the COPD population.

Mean age ranged between 62.8 [161] and 84.6 [181] years old and the proportion of males between and 37% [163] and 100% [181]. Hypertension was the most widely reported additional chronic disease with proportions ranging between 27.5% [170] and 88.3% [174]. Smoking status was reported in seven studies [162, 163, 165, 168, 170, 178, 181] where most patients were documented as being either current or former smokers, however data was not available consistently. BMI was reported in five studies[161, 165, 166, 178, 181], and varied between 20.4 [166] and 29.9 [161]. Follow-up time was also highly variable, ranging from 2 [167] to 112 months[177].

Adjusted risk estimates for beta-blocker use (vs. lack of beta-blocker) associated mortality ranged from HR 0.46 (95%CI 0.19 -1.11)[166] to 1.19 (95%CI 1.04 to 1.37)[163] (see **Figure 5.7**). Age and sex were the most common confounders adjusted for in analyses in addition to study-specific factors such as medications for specific disease (HF, hypertension), other comorbidities or clinical variables (Appendix D, Table D4).

Two studies reported unadjusted analyses only[164, 165]. There was one study only reporting an increase in death associated with beta-blocker treatment (HR: 1.19, 95% CI 1.04 to 1.37); however the population included in this analysis consisted of severe COPD patients undergoing

long-term oxygen therapy [163]. There was a very high degree of heterogeneity amongst studies (I^2 =99.3%). This was explored by conducting stratified analyses (i.e., stratifying by type of beta-blocker [cardioselective vs. non-cardioselective]; excluding unadjusted estimates; excluding the only study which exclusively included very severe COPD patients). However, due to heterogeneity remaining very high (I^2>75%), results from the outcome analysis are presented graphically only (see **Figure 5.8**).

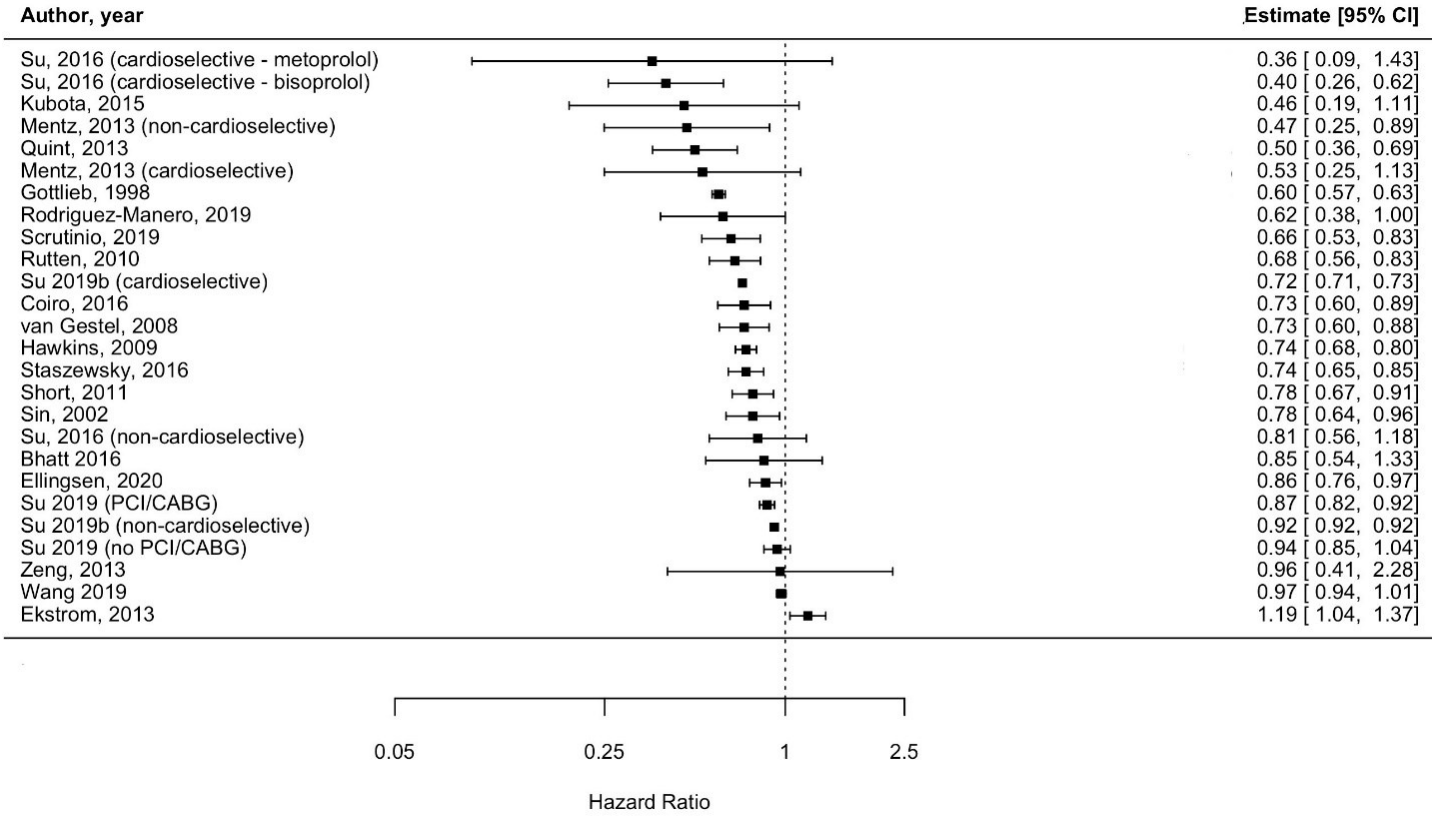

FIGURE 5.8: Forest plot illustrating effect of beta-blocker therapy versus no beta-blocker therapy on mortality, in patients with COPD

Estimate: hazard ratio, 95% CI (confidence interval).

5.4.2.2 All-cause hospitalisation

All-cause hospitalisation was available in three studies[79, 184, 185]. One compared cardioselective to non-selective beta-blockers (reported OR) [185]; one compared non-cardioselective to selective beta-blockers (reported HR) [79] and one compared cardioselective beta-blockers to no beta-blocker treatment (reported relative risk [RR]) [184]. None found significant differences in all-cause hospitalisation associated with the investigated beta-blockers (see **Table 5.7**).

TABLE 5.7: All-cause hospitalisation results

Author	Study design	Comparison	Follow-up	Estimate (95% CI)	Covariates adjusted for in analysis	Notes
Sessa, 2018a ; Denmark	Observational	Non-cardioselective BB vs. cardioselective BB	7567 person-years	HR: 1.01 (0.93–1.10)	Age, year of inclusion in the cohort, vital status, pharmacological treatments, comorbidities	Only study presenting results for non-cardiovascular BB vs. cardioselective BB;
Brooks, 2007	Observational	Cardioselective BB vs. no BB	3611 patient-years	RR: 0.64 (0.43–0.96)		
Farland, 2013	Observational	Cardioselective BB vs. non-cardioselective BB	1 year	OR: 1.41 (0.95 - 2.09)	Age, sex, smoking status, angina, MI, CABG, PCI, AF, HF, PAD, DM, primary care vs. specialist, inhaled anticholinergic, inhaled LABA, inhaled corticosteroid, xanthine derivative, ACEI, ARB, aldosterone antagonist, clopidogrel, statin, thiazide diuretic, loop diuretic, nitrate, CCB, digoxin, vitamin K antagonist)	

ACEI= angiotensin-converting-enzyme inhibitors; ARB= angiotensin receptor blockers; AF= atrial fibrillation; BB= beta-blockers; CABG= coronary artery bypass grafting; CCB= calcium channel blockers; DM= diabetes mellitus; HF= heart failure; HTN= hypertension; LABA= long-acting beta-agonist; PCI=percutaneous coronary intervention; MI= myocardial infarction; PAD= peripheral arterial disease; RR= relative risk; CI= confidence interval; OR= odds ratio; HR= hazard ratio.

5.4.2.3 Quality of life

SGRQ was assessed in two RCTs[58, 192] and one observational study[182] which did not report mean change from baseline to time point per treatment arm. One RCT[202] contrasted the effect of metoprolol to placebo and one observational study[182] evaluated any beta-blocker compared to no beta-blocker treatment; there were no significant difference in SGRQ between the two treatment arms at one-year follow-up (see **Table 5.8**).

TABLE 5.8: SGRQ results

Author, year	Study design	Treatment arm	Time point	Baseline SGRQ (95% CI) [SE] in meters	Follow-up SGRQ (95%CI)	Mean change (95%CI)
Jabbal, 2017	RCT	Bisoprolol	6 weeks	33 (24, 42)	36 (28, 44)	3 (NR)
Jabbal, 2017	RCT	Carvedilol	6 weeks	33 (24, 42)	36 (26, 45)	3 (NR)
Dransfield 2019	RCT	Metoprolol	52 weeks	-	-	Metoprolol vs. placebo, baseline to timepoint: 0.77 (-1.38, 2.92)
Dransfield 2019	RCT	Placebo	52 weeks	-	-	-
Maltais, 2018	Observational	No BB	52 weeks	43.60 [0.28]	37.90 [0.19]	BB vs. no BB, baseline to timepoint: -0.60 (-1.810, 0.602)
Maltais, 2018	Observational	BB	52 weeks	43.58 [0.76]	37.29 [0.58]	

BB= beta-blocker; CI= confidence interval; RCT= randomised controlled trial; SGRQ= St. George Respiratory Questionnaire; SD= standard deviation; SE= standard error; NR= not reported

12MWT was investigated in two RCTs[195, 198]; one evaluated atenolol and metoprolol versus placebo, and did not report mean change in score at four weeks follow-up[198]; the second did not find a significant difference in distance walked between patients that received metoprolol compared with propranolol six hours after treatment administration [195] (see **Table 5.9**).

TABLE 5.9: 12MWT results

Author, year	**Study design**	**Treatment arm**	**Timepoint**	**Baseline 12MWT (SD) in meters**	**Follow-up 12MWT (SD)**	**Mean change (SD)**
Butland 1980,	RCT	Placebo	4 weeks	-	12MWT post mean: 715 (225)	-
	RCT	Atenolol	4 weeks	-	675 (227)	-
	RCT	Metoprolol	4 weeks	-	680 (228)	-
McGavin, 1979	RCT	Propranolol	6 h	1058 (255)	1158 (162)	100 (NR)
	RCT	Metoprolol	6 h	1059 (314)	1154 (199)	95 (NR)

12MWT 12-minute walking-test; RCT= randomised controlled trial, NR= not reported; SD= standard deviation

Data on *6MTW* was reported in two RCTs [192] [58]. The first compared bisoprolol with carvedilol and did not present mean change between treatment groups; however, the calculated difference indicates both treatments decreased distance walked in patients with COPD; the second trial[58] did not report a significant difference between metoprolol and placebo on 6MWT (see **Table 5.10**).

TABLE 5.10: 6MWT results

Author, year	Study design	Treatment arm	Timepoint	Baseline 6MWT (SD) in meters	Follow-up 6MWT (SD)	Mean change (SD)
Jabbal, 2017	RCT	Bisoprolol	6 weeks	495 (101)	469 (101)	-26 (NR)
	RCT	Carvedilol	6 weeks	495 (101)	474 (125)	-25 (NR)
Dransfield 2019	RCT	Metoprolol	52 weeks	-	-	Metoprolol vs. placebo, baseline to timepoint: -5.77 (95% CI –21.59, 10.06)
	RCT	Placebo	52 weeks	-	-	-

6MWT= 6-minute walking test; CI, confidence intervals; RCT= randomised controlled trial; NR= not reported; SD= standard deviation.

Data on *SF-36* was available in one observational study[179]. Authors reported no significant association between beta-blocker treatment and individual domains of the quality-of-life assessment tool, either at baseline or 6.4 years follow-up (see **Table 5.11**).

TABLE 5.11: SF-36 results

Author, year	Study design	Treatment arm	N	Timepoint	Results* notes
van Gestel 2009	Observational	Beta-blocker	191	Median 6.4 years (2.9 - 9.3)	No significant associations between beta-blockers and the individual domains of the SF-36 in patients (PF: OR 1.36; 95% CI 0.72–2.61, RP: OR 1.55; 95% CI 0.78–3.06, BP: OR 1.00; 95% CI 0.52–1.94, GH: OR 1.27; 95% CI 0.67–2.41, VT: OR 1.29; 95% CI 0.68–2.44, SF: OR 1.59; 95% CI 0.87–2.92, RE: OR 1.00; 95% CI 0.50–1.97, MH: OR 1.15; 95% CI 0.62–2.14). Beta-blocker therapy at follow-up was not associated with impaired health status (PF: OR 1.27; 95% CI 0.72–2.27, RP: OR 1.66; 95% CI 0.92–2.98, BP: OR 0.96; 95% CI 0.55–1.69, GH: OR 1.50; 95% CI 0.84–2.66, VT: OR 1.22; 95% CI 0.69–2.14, SF: OR 1.34; 95% CI 0.78–2.29, RE: OR 1.27; 95% CI 0.70–2.30, MH: OR 1.57; 95% CI 0.89–2.75)
van Gestel 2009	Observational	No beta-blocker	135	Median 6.4 years (2.9 - 9.3)	

OR= odds ratio; CI= confidence intervals; SF-36= Short-Form Health Survey Questionnaire.
*Results not presented per treatment arm or per overall SF-36; The SF-36 questionnaire has 8 domains: physical functioning (PF), role physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role emotional (RE) and mental health (MH).

5.4.3 Risk of bias

5.4.3.1 Observational studies

Observational studies were mostly judged to have moderate risk of bias (23 studies[79, 161-163, 165, 167-172, 174-179, 183-185, 201, 203]), two studies[162, 182] had low risk of bias, one[181] had serious risk of bias and one[164] did not provide enough information for a judgment to be produced. The domains of bias which were mostly affected by a "moderate rating" were "bias due to confounding" resulting from the wide-ranging variability in baseline covariates that were adjusted for in analyses and "bias in selection of participants into study" as most studies included patients recruited from databases which relied on ICD coding (without confirming validity of diagnosis with diagnostic tests) (see **Table 5.12**).

TABLE 5.12: Risk of bias assessment, observational studies

Author, year	Bias due to confounding	Bias in selection of participants into study	Bias in classification of interventions	Bias due to departures from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall
Bhatt 2016	Low	Moderate	Moderate	Moderate	NI	Moderate	Low	Moderate
Brooks, 2007	Moderate	Low	Moderate	NI	NI	Low	Low	Moderate
Coiro, 2016	Low	Low	Moderate	Low	Low	Low	Low	Low
Ekstrom, 2013	Moderate	Moderate	Low	NI	Low	Low	Low	Moderate
Ellingsen, 2020	Moderate	Moderate	Low	NI	Low	Low	Low	Moderate
Gottlieb, 1998	NI	NI	Moderate	NI	Moderate	Low	Low	NI
Hawkins, 2009	Moderate	Moderate	Low	Low	Low	Low	Low	Moderate
Maltais, 2018	Low	Moderate	Low	Low	Low	Low	Low	Low
Mentz, 2013	Low	Moderate	Moderate	NI	Low	Low	Low	Moderate
Quint, 2013	Moderate	Moderate	Moderate	NI	Low	Low	Low	Moderate
Rodriguez-Manero, 2019	Moderate	Moderate	Serious	NI	Low	Low	Low	Moderate
Rutten, 2010	Moderate	Serious	Low	NI	Low	Low	Moderate	Moderate
Scrutinio, 2019	Moderate	Moderate	Moderate	NI	Low	Low	Low	Moderate
Short, 2011	Moderate	Moderate	Moderate	NI	NI	Low	Low	Moderate
Sin, 2002	Moderate	Moderate	Low	NI	NI	Low	Low	Moderate

Author, year	Bias due to confounding	Bias in selection of participants into study	Bias in classification of interventions	Bias due to departures from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall
Staszewsky, 2016	Moderate	Moderate	Moderate	NI	NI	Moderate	Low	Moderate
Su 2019	Moderate	Moderate	Moderate	NI	Low	Low	Low	Moderate
Su, 2016	Moderate	Moderate	Moderate	NI	NI	Low	Low	Moderate
Su, 2019b	Moderate	Moderate	Moderate	NI	Low	Low	Low	Moderate
van Gestel, 2008	Moderate	Moderate	Moderate	NI	Low	Low	Low	Moderate
Wang 2019	Moderate	Moderate	Moderate	NI	Low	Low	Low	Moderate
Zeng, 2013	Serious	Serious	Moderate	NI	NI	Moderate	Moderate	Serious
Sessa 2018a	Moderate	Low	Moderate	NI	Low	Low	Low	Moderate
van Gestel 2009	Low	Low	Moderate	NI	Low	Low	Low	Moderate
Farland, 2013	Moderate	Moderate	Moderate	NI	NI	Moderate	Low	Moderate
Rasmussen, 2020	Moderate	Low	Moderate	NI	Low	Low	Low	Moderate

5.4.3.2 RCTs

Ten RCTs[189, 191, 194, 196, 197] had moderate risk of bias; two[192, 193] were had serious risk of bias, both due to the lack of blinding (see **Figure 5.9**).

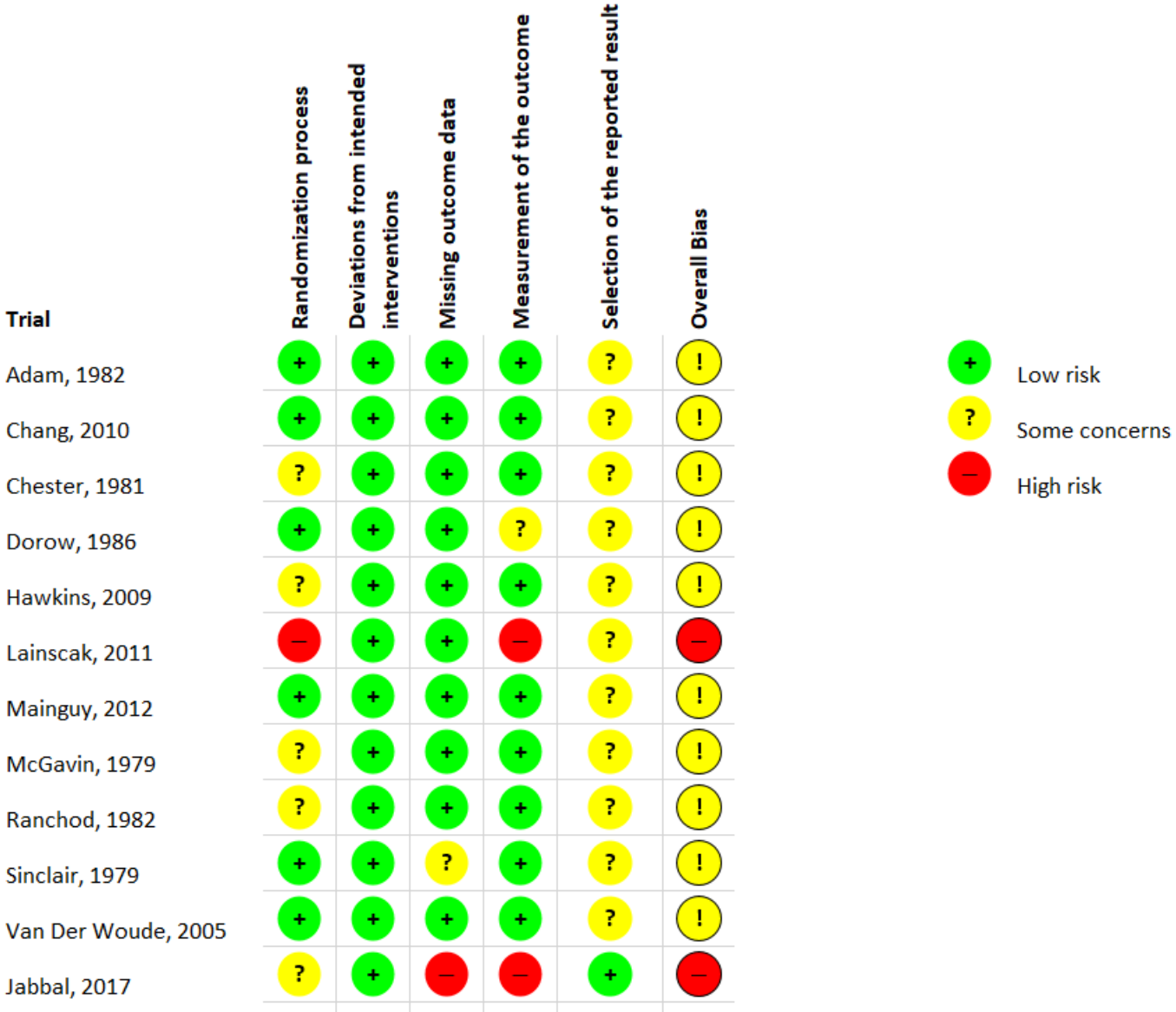

FIGURE 5.9: Risk of bias assessment, RCTs

5.5 Discussion

This contemporary evaluation of beta-blockers in patients with COPD adds to the previous literature from the prism of several important findings: All studies reporting on any type of beta-blocker in patients with COPD were included, showing overall positive effects on AECOPD and mortality. For the first time, a probabilistic approach was used to evaluate the individual effects of beta-blockers on lung function using direct and indirect evidence from RCTs in an NMA. No beta-blocker affected lung function significantly except propranolol, and the treatments less likely to have a detrimental effect on lung function were labetalol and celiprolol. Lastly, data on all-cause hospitalisation and quality of life endpoints such as SGRQ, 12 and 6MWT and SF-36 were rarely reported across the literature and a formal quantitative analysis was not possible - suggesting an area of focus for future research.

5.5.1 Mortality

Despite heterogeneous study design elements such as follow-up time, and geographical location, as well as baseline characteristics, individual results from 17 out of 21 studies reporting on mortality indicated beta-blocker therapy was associated with a decreased risk of death in patients with COPD, compared to those not receiving the medication. However, it was not possible to quantify the effect of beta-blockers on mortality due to considerable heterogeneity (I^2 >75%). Previous studies [148, 149, 204] have provided pooled estimates of the effect of beta-blocker therapy on mortality, however all reported degrees of heterogeneity above the Cochrane I^2 threshold of 75%; 89.3%[148], 83%[149] and most recently 96%[204] bringing into question the validity of these analyses. Reasons for very high heterogeneity in previous meta-analyses include: differences in study populations (such as enrolment of individuals with varying

severity), incorrect risk of bias assessment and inclusion of different comparator arms for the intervention effect of interest (including studies where comparator arms received other HF medications despite, despite aiming to evaluate the effect of beta-blocker treatment versus the lack of treatment)[204].

In this analysis, most studies were affected by bias, mostly due to confounding: two studies did not adjust for any confounders [164, 191], whereas nine did not adjust for COPD severity [162-165, 167, 169, 171, 173, 174]. Therefore, these studies may overestimate the prognostic effect of beta-blocker therapy on patients with COPD. One reason for the lack of adjustment for COPD-related factors may be the use of data from either existing drug-trials or cardiovascular disease-specific registries which included data on subgroups of patients with COPD. This emphasises the need for COPD-specific trials which may allow for a more reliable assessment of the true effect of beta-blockers in these patients. The decrease in mortality observed among these patients could in fact be related to the effect of beta-blockers on other comorbid conditions (i.e., cardiovascular disease), which is established. A previous study[170] suggested long-term treatment with beta-blockers improved survival in COPD individuals without cardiovascular disease, however future studies are needed to confirm this and to evaluate whether beta-blockers provide non-cardiovascular mortality benefits.

5.5.2 AECOPD

I found that patients with COPD who were given beta-blockers were at diminished risk of AECOPD (HR 0.78 [95%CI 0.74 – 0.82]) with the caveat that the GRADE assessment for the observational evidence on which the estimate was derived was of "low" quality (Appendix D, Table D3). Despite this, my analysis is in line with findings from Du and colleagues[148], who

report an even larger reduction in risk, of 37% (RR, 0.63; 95% CI, 0.57 to 0.71). This previous report however, had methodological limitations specific to the observational nature of the included studies (residual confounding, immortal time bias), which limits generalisability of their result. A recent RCT[58], less likely to be affected by bias, found no significant difference between metoprolol and placebo on the time-to-AECOPD of any severity, in patients with COPD without an indication for beta-blocker treatment. It revealed a significant increase in the risk of AECOPD requiring hospitalisation, bringing into question the protective effect of this specific beta-blocker. As this study did not evaluate other beta-blockers, future RCTs assessing multiple regimens are needed to confirm their benefit.

Whether beta-blockers have an indirect effect on exacerbations of COPD could be assessed in clinical trials including patients with COPD and comorbid cardiovascular disease, allowing assessment of these agents in a more representative COPD population.

5.5.3 FEV1

FEV_1 was assessed in 199 patients from 12 RCTs. None of the individual cardioselective beta-blockers included in the NMA (atenolol, bisoprolol, celiprolol, metoprolol) were associated with significant effects on FEV_1 in patients with COPD, regardless of baseline FEV1 or follow-up time. This confirms findings from a Cochrane review[57] which concluded that cardioselective beta-blockers, do not impact FEV_1 in patients with COPD, even in those with the lowest baseline FEV_1 measurements. This report extends to show a lack of association with non-selective beta-blockers such as carvedilol and labetalol. Propranolol was the only beta-blocker associated with a reduction of 140 ml in FEV_1 (95% CrI: -0.28, -0.016), which is larger than the clinically significant threshold of 100 ml change by the American Thoracic Society and

European Respiratory Society guidelines. This result is based on high quality evidence, according to the GRADE and thus supports current recommendations not to use this medication in patients with COPD.

For the first time reported in the literature, I aimed to create a hierarchy of beta-blockers based on their effect on FEV_1. Propranolol had the lowest probability of being ranked first (signalling worse impact on lung function), compared to all other treatments considered in the NMA, including placebo. Labetalol and celiprolol - drugs used in hypertension – were the least likely drugs to negatively impact FEV_1, compared to all other treatments; however, neither impacted on FEV_1 with certainty, compared to placebo. These results are inferred from very low-quality evidence according to GRADE, casting doubt on their leading positions in the ranking. Beta-blocker choice is influenced by cardiovascular comorbidity (carvedilol, metoprolol and bisoprolol are recommended in HF; atenolol is more often prescribed in patients with asymptomatic hypertension, bisoprolol is also used in atrial fibrillation, and propranolol occasionally used in tachyarrhythmias), it is not surprising that a clear "best in class" beta-blocker for COPD was not identified. That beta-blockers less likely to decrease lung function are mainly used to treat hypertension may merely represent a reflection of an attribute trait to a specific subgroup of patients, [less likely to be affected by detrimental side-effects (i.e., indication bias)], compared to others with COPD and more severe comorbidities. Prescription of beta-blockers in COPD needs to consider clinically significant lung function alteration versus mortality benefits in those with cardiovascular disease, particularly MI[205] and HF [206].

Whilst cardiovascular disease is diagnosed in significant proportions of patients with COPD[207], the main analysis included mainly small studies and only three explicitly included patients with a cardiovascular comorbidity (one enrolled angina[190], two HF [191, 193], and

one included hypertension, which is a common cardiovascular risk factor [186]. Reflecting previous literature [57], I report no significant FEV_1 treatment effect according to cardiovascular disease status in patients with COPD.

Eight trials excluded patients with additional cardiovascular disease (or did not report whether this was present), and results were similar as for those with cardiovascular disease.

Since previous clinical data on the effect of beta-blockers on lung function according to cardiovascular disease are limited, these results are encouraging. A recent single RCT including COPD patients without an indication for beta-blockers (therefore those with HF, previous MI or revascularisation) failed to show clear benefits of metoprolol compared with placebo. Observational studies do not present a clear picture either: the population-based Rotterdam Study[208] reported significant decreases in lung function due to both cardio and non-cardioselective beta-blockers, while two other studies [172] [209] reported no difference in FEV_1 due to beta-blockers. Yet, these data may be affected by confounding by indication, which may explain the variability of estimates. Additionally, the longer follow-ups in these studies (ranging from four to six years) may overlook effects of FEV_1 decline specific to patients with COPD, regardless of cardiovascular disease.

Overall, the FEV_1 analysis suggests that regardless of cardiovascular disease status, beta-blockers included in this review do not affect lung function in patients with COPD. Included evidence was based on a relatively small population and some of the studies were conducted decades ago; therefore, large RCTs are needed to assess other beta-blockers which may confer lung function benefits in contemporary COPD patients.

The effect of beta-blocker exposure on all-cause hospitalisation and quality of life in patients with COPD could not be quantified, due to lack of data; narrative results suggest non-significant effect of beta-blockers, from both RCTs and observational data. Clinical studies of beta-blocker treatment in cardiac disease suggests improvements in exercise tolerance and functional status, so whether beta-blockers affect these outcomes in patients with COPD also, is important for clinical management and needs to be evaluated in future studies.

5.5.4 Strengths and limitations

Only published, peer-reviewed literature was included, thus, results may be affected by publication bias as it is more likely that studies reporting positive results (i.e., that did not find beta-blockers were associated with negative outcomes) are more often reported than negative ones. Despite this, the data is based on the most recent available evidence and portray a more nuanced effect of specific beta-blocker treatment in patients with COPD, emphasising the need for a targeted treatment of cardiovascular disease comorbidity in these patients.

Inclusion criteria was limited to stable COPD patients and whilst I demonstrated that FEV_1 was not impacted by beta-blocker exposure, it could not be verified whether these medications reduce the response to COPD regimens such as beta-agonists, nor was I able to investigate long-term effects of co-administration with HF medications.

Another concern is undiagnosed cardiovascular disease in patients with COPD. Symptoms of ischemic heart disease or HF may be wrongly misattributed or concurrent with COPD symptoms, posing difficulties in separating possible non-cardiac effects of beta-blockers, independent of their cardiac benefits. One advantage of the FEV_1 analysis is that RCTs only were included, where concomitant cardiovascular disease is often ascertained more rigorously and therefore

cardiovascular disease status was known with greater confidence compared with observational studies.

Furthermore, no statistically significant effect was detected in sensitivity analyses evaluating the association with cardiovascular disease status, which may be due to limited sample size. Adequately powered RCTs are needed to assess the effect of beta-blockers in a diverse COPD population, allowing for accurate comparisons based on cardiovascular disease status to be made.

A recent RCT[58] comparing metoprolol with placebo failed to find a significant effect on FEV_1 but reported worsening of overall COPD symptoms. This confirms the need to capture a spectrum of respiratory outcomes to fully assess the implications of beta-blocker treatment in patients with COPD, which needs to be addressed in a future study.

Confounding by contraindication is likely to affect interpretation of results – if we assume clinicians knowingly withheld treatment from patients due to concerns regarding breathing difficulty. This may have resulted in a reduced sample size of possible COPD patients who may have been eligible for beta-blocker therapy. Alternatively, healthcare professionals may prescribe beta-blockers to less severe patients, limiting generalisability.

The AECOPD analysis is also limited by a low number of included studies, all of which were observational. This reinstates the need of more carefully conducted RCTs to evaluate a range of beta-blockers and their effects of AECOPD, in order to validate observational data.

5.6 Conclusions

Findings from this analysis represent the most comprehensive evidence synthesis which addresses the effects of beta-blocker use in patients with COPD, spanning data published over four decades. A reduction in AECOPD risk was calculated from observational data while RCT

data were pooled to assess lung function. Mortality and quality of life were narratively described due to high heterogeneity or lack of data, respectively. FEV_1 was significantly impacted by propranolol, but not by atenolol, bisoprolol, carvedilol, celiprolol, labetalol or metoprolol. Treatment choice in patients with COPD should be made according to cardiovascular disease comorbidity guidelines on management.

Chapter 6 IMPACT OF COPD ON IN-HOSPITAL MORTALITY AND MANAGEMENT OF PATIENTS HOSPITALISED FOR HEART FAILURE

In previous chapters, I evaluated the association between COPD - amongst other comorbidities - and outcomes in chronic HF patients.

The next two chapters set out to investigate the effect of COPD on a variety of outcomes, in patients hospitalised for acute decompensated HF. The motivation for these two studies is two-fold: first, acute (or decompensated) and chronic HF represent different manifestations of the HF syndrome, where acute HF refers to a rapid onset or worsening of symptoms, usually requiring emergency hospital admission. Second, management goals differ as, despite advances in long-term care, treatments for acute HF are lacking and pharmacological therapy is mainly aimed at relieving congestion with the aid of diuretics.

Therefore, to better characterise the role of COPD in HF, it is critical to explore this relationship in a secondary-care setting. For this reason, I aimed to evaluate the association between COPD and short-term outcomes related to hospital stay (such as in-hospital death, guideline-directed pharmacotherapy and readmission) in individuals with acute HF.

The first study, presented in this chapter, evaluated the characteristics, in-hospital death and management (HF medications including beta-blockers, referral to specialists) of patients

admitted for HF in the UK, comparing those with COPD with those without COPD. Since misclassification across COPD and asthma is very common in clinical practice, I also present results for patients with asthma versus those without asthma, in order to contextualise the findings for the COPD population. The focus in this chapter will nonetheless be on the effect of COPD.

Part of this analysis has been written up for publication in an academic journal and is currently under peer-review (see Appendix G, Paper 6).

6.1 Introduction

COPD and asthma frequently coexist with HF and are independently associated with mortality and increased healthcare resource use[73, 210, 211]. This is partly due shared systemic inflammation, worsened by the presence of pulmonary disease and sub-optimal HF management[45, 50].

Evidence suggests that patients with HF and comorbid COPD are less likely to receive guideline recommended pharmacotherapy for their HF, particularly beta-blockers, due to reduced effectiveness of emergency beta-agonist medication or difficulty in discriminating between COPD and asthma (where beta-blockers are contraindicated[212]).

Less data exist on the relationship between asthma and HF. Some studies have shown that asthma is associated with increased occurrence of cardiovascular disease, though this may be limited to women or smokers[213] only, and depends on age of asthma-onset[214]. 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[215]. 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[82, 216], which depend on disease severity and study setting, but nevertheless worsen prognosis[211, 214].

6.2 Study aims

(1) To compare in-hospital mortality in patients with HF with and without COPD, secondarily in patients with HF with and without asthma.

(2) To compare referral to HF services at discharge (HF nurse, HF multi-disciplinary team, cardiology) in patients with HF with and without COPD; secondarily in patients with HF with and without asthma.

(3) To describe the management of HF (prescriptions of HF treatments at discharge: beta-blockers, angiotensin-converting-enzyme inhibitors [ACEi]/angiotensin receptor blockers [ARBs], mineralocorticoid receptor antagonists [MRA]) according to COPD status; secondarily according to asthma status.

(4) To investigate whether left ventricular ejection fraction (LVEF) status affects outcomes differentially in COPD patients and secondarily, in asthma patients.

6.3 Methods

6.3.1 Population

Patients older than 18 years of age admitted to hospital for HF between March 2012 to April 2018 whose data were submitted to the National Heart Failure Audit (NHFA) were included. Their first HF hospitalisation only was considered.

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 (see **Table 6.1**).

TABLE 6.1: 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

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 audit-participating NHS trusts ranged from 145 in 2012/2013 (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 clinicians, who use case ascertainment forms. Data are categorised as mandatory (main variables such as HF treatments, comorbidities, echocardiography) or non-mandatory (i.e., smoking status, pulmonary oedema, ethnicity). Non-mandatory data elements are not expected to be included, thus, there are considerable proportions of missing data across these variables. Some mandatory variables also have significant amounts of missing data (e.g., more than 70% missing data on Brain natriuretic peptide (BNP) measurements, weight, height, see **Table 6.2**).

TABLE 6.2: Variables with considerable missingness in the National Heart Failure Audit

	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]	0 [0, 0]	0 [0, 1]
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%)
ARBs	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 diuretics	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*	-	-	-	-

	HF alone (N=170297)	COPD + HF (N=32695)	Asthma + HF (N=14400)	Overall (N=217392)
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%)

ACEi= angiotensin-converting-enzyme inhibitors, ARBs=angiotensin receptor blockers; BMI= body mass index; BNP= Brain natriuretic peptide; CCB= calcium channel blocker; MRA=mineralocorticoid receptor antagonist, NT_proBNP= N-terminal proBNP
*not shown due to small numbers policy

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[217].

6.3.2 Exposures

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

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.

LVEF status was categorised as HFrEF and HFpEF. This was determined though echocardiography or another test such as MRI, nuclear scan, or angiogram. Those with an LVEF <40% were categorised as HFrEF. Due to a lack of information in the audit regarding specific diagnostic tests required to make a HFpEF diagnosis, I determined HFpEF as patients not categorised as HFrEF[16, 131].

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 (Appendix E, Table E1).

6.3.3 Outcomes

The main 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 guideline-recommended HF medications (beta-blockers, ACEis/ARBs, MRAs) at discharge, in those with HFrEF.

6.3.4 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]. Differences between groups were assessed with chi-square and Kruskall-Wallis tests. In-hospital death was analysed using multilevel logistic regression to calculate odds ratios (OR) and 95% confidence intervals (CI). To account for the hierarchical nature of the data, as patient level data was nested within hospitals, a random effect for hospital was added to the models.

Analyses assessed differences in outcomes between patients with COPD-HF compared with HF alone and between asthma-HF compared with HF-alone. This was implemented in a stepwise manner. First, an unconditional model including, COPD was considered. In a second step asthma was added. Third, an interaction term between COPD and asthma was added, to evaluate whether both diagnoses had a significant contribution to the model. In lack of statistical significance these patients were not considered in further analyses. I then evaluated effect

modification by LVEF status (HFrEF/HFpEF) by including separately an interaction term between COPD and LVEF, then asthma and LVEF.

Finally, potential confounders were adjusted for. In the main analysis, I only included variables with less than 20% missing data: age, sex, comorbidities, place of care and NYHA status.

Analyses of referrals were conducted in a similar way and excluded patients who died in-hospital. Associations between COPD or asthma and HF medication prescription rates at discharge excluded those with HFpEF (as they are not currently guideline-recommended in this subgroup of patients).

6.3.4.1 Sensitivity analyses

I aimed to assess whether COPD was independently associated with death in patients with HF, thus, adjusting for the potential association with smoking status and Body Mass Index (BMI), which are known confounders for the relationship between COPD and outcomes. I assumed data on smoking and BMI was missing at random in this study population, as the distribution of these variables across observed cases was similar to other UK cohorts of patients with HF[4, 211]. I then used a multi-level imputation approach which takes into consideration the hierarchical data structure, clustered at hospital level. These data were then adjusted for in a sensitivity analysis of the main outcome (in-hospital mortality).

Secondarily, multiple imputation was conducted for the "ethnicity" variable and then adjusted for in a sensitivity analysis of the main outcome.

To verify findings in a cohort of patients with a definitive HF diagnosis, a third sensitivity analysis involved repeating the main analysis in a cohort of patients with a "confirmed HF

diagnosis" (where ICD-10 diagnosis of HF was confirmed by imaging or BNP testing either during their index or admission or at a previous time, or was adjudicated by a clinician in the absence of echocardiography)[218].

All analyses were performed with R version 4.0.3.

6.4 Results

Baseline characteristics are presented in **Table 6.3**. 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 (see **Figure 6.1**).

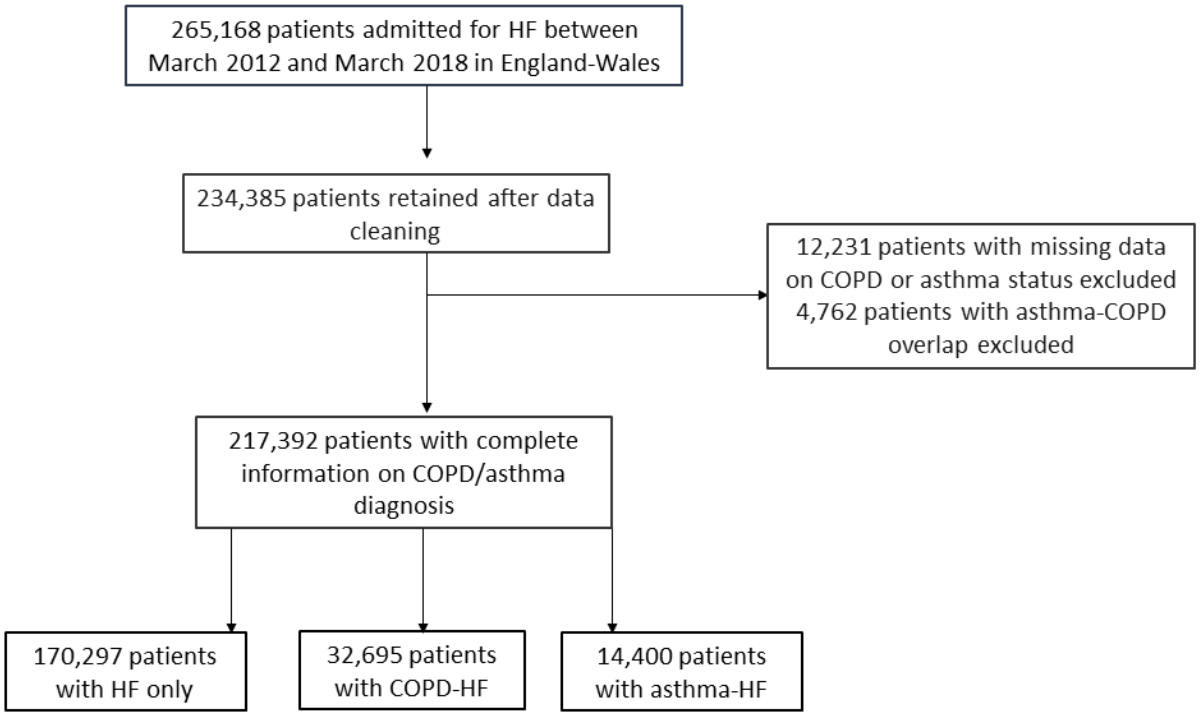

FIGURE 6.1: Study flow, patient inclusion

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 hospital 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 prevalence 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 rather than HFrEF amongst patients with comorbid asthma.

TABLE 6.3: Baseline characteristics of HF patients, according to COPD and asthma status

	HF alone (N=170,297)	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 class)				
No limitation of physical activity	12273 (7.2%)	1254 (3.8%)	768 (5.3%)	14295 (6.6%)

	HF alone (N=170,297)	COPD + HF (N=32695)	Asthma + HF (N=14400)	Overall (N=217,392)
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 in place	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%)

	HF alone (N=170,297)	COPD + HF (N=32695)	Asthma + HF (N=14400)	Overall (N=217,392)
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%)	190 (24.5%)	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%)

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.

6.4.1 In-hospital mortality

The association between COPD and in-hospital death, is presented in **Table 6.4** and **Figure 6.2.** 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 LVEF: 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).

TABLE 6.4: Association between COPD, asthma and outcomes in patients hospitalised for HF

	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<0.001)	1.05 (0.99 – 1.10, p=0.081)	-	-
Random effects (hospitals, n=216)				
Variance	0.201		-	
LR test P-value[d]	*P*-value < 0.001		-	-
Referral to cardiology follow-up (N= 166,658[c])	Interaction *P*-value < 0.001		Interaction *P*-value < 0.001	
Fixed effects	0.85 (0.81, 0.88, p<0.001)	0.73 (0.70, 0.76, p<0.001)	1.08 (1.03-1.14, p<0.01)	0.93 (0.88- 0.98, p<0.05)
Random effects (hospitals, n=216)				
Variance	0.512		0.512	
LR test p-value[d]	<0.001		<0.001	
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<0.001)	-	-
Random effects (hospitals, n=216)				
Variance	2.139		-	-
LR test p-value[d]	<0.001		-	-
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

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, see **Figure 6.2**).

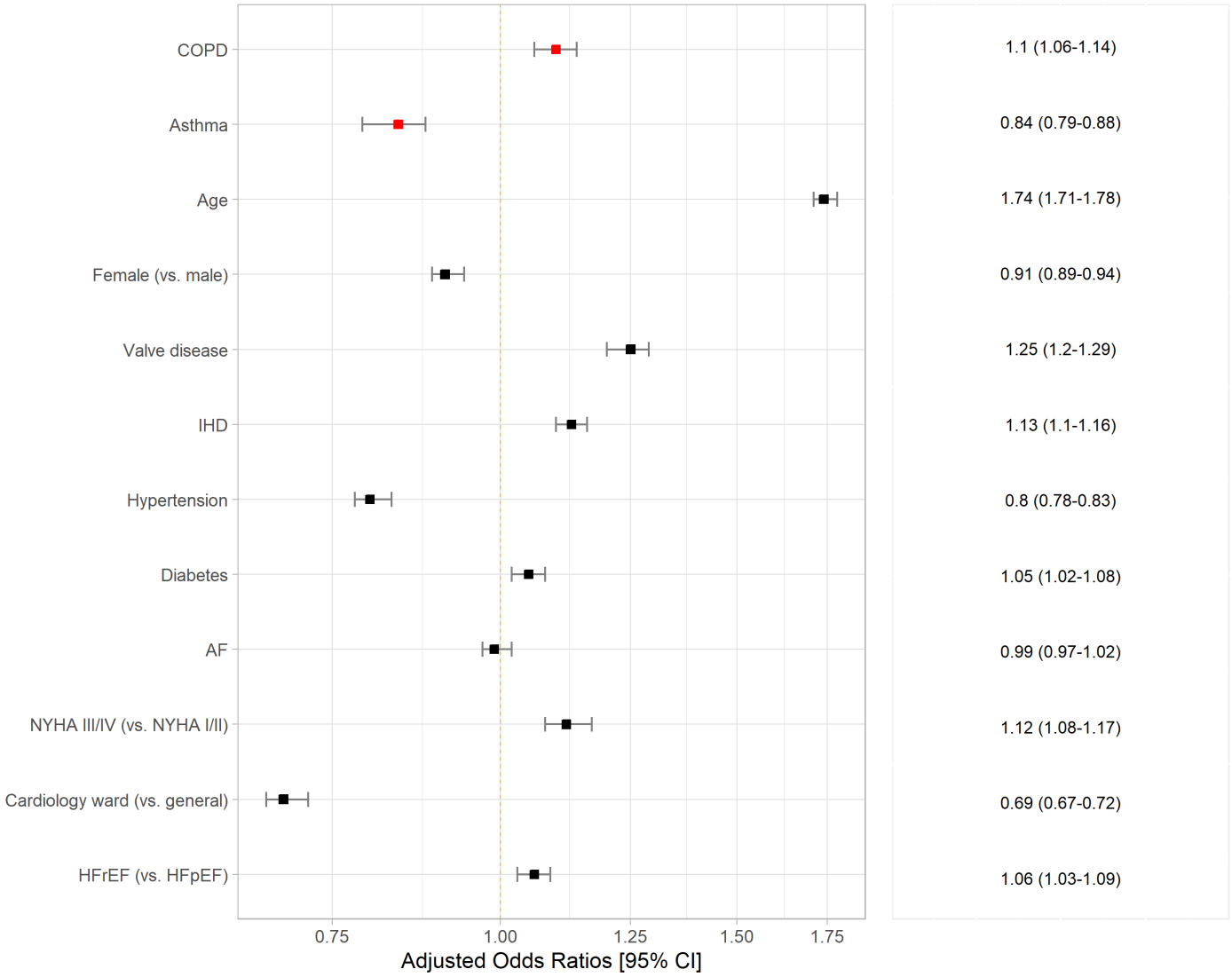

Figure 6.2: Association between COPD, asthma and in-hospital death, in patients hospitalised for HF

Odds ratio with 95% confidence intervals.

The odds of death did not vary by LVEF status for patients with asthma-HF **(**see **Table 6.4).**

Sensitivity analyses

Sensitivity analyses where smoking status, BMI and ethnicity were imputed, and where patients with a confirmed HF diagnosis only were included showed similar results to the main analysis (**Table 6.5**).

TABLE 6.5: Sensitivity analysis, association between COPD and in-hospital death in patients hospitalised for HF, imputation models

Smoking status and BMI imputed	**Adjusted model[a], OR (95% CI)**
Fixed effects (95% CI)	
COPD	1.12 (1.07 – 1.17, p<0.001)
Random effects (variance)	0.166
LR test p-value <0.001	
Smoking status, BMI and ethnicity imputed	**Adjusted model[b], OR (95% CI)**
Fixed effects (95% CI)	
COPD	1.12 (1.07 – 1.18, p<0.001)
Random effects (variance)	0.164
LR test p-value <0.001	
Confirmed HF only	**Adjusted model[c], OR (95% CI)**
Fixed effects (95% CI)	
COPD	1.11 (1.07 - 1.16, p<0.001)
Random effects (variance)	0.166
LR test p-value <0.001	

BMI= body mass index; CI= confidence intervals; COPD= chronic obstructive pulmonary disease; OR= odds ratios; 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, smoking status, Body Mass Index
[b] Adjusted for age, sex, diabetes, hypertension, ischemic heart disease, atrial fibrillation, asthma, place of care and New York Heart Association status, smoking status, Body Mass Index, ethnicity
[c] Adjusted for age, sex, diabetes, hypertension, ischemic heart disease, atrial fibrillation, asthma, place of care and New York Heart Association status.

6.4.2 Referrals to HF services

In the fully adjusted model, 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 an interaction with LVEF status, whereby 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 (see **Figure 6.3**).

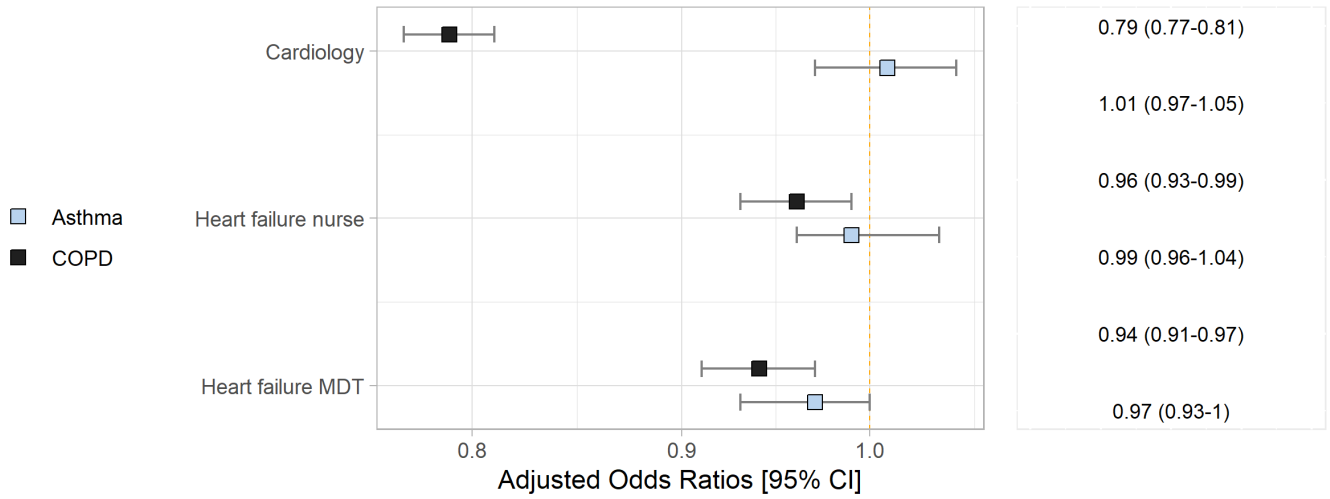

Figure 6.3: Association between COPD, asthma and referrals to HF services, in patients hospitalised for HF

Models adjusted for age, sex, valve disease, IHD, hypertension, diabetes, AF, NYHA, place of care and LVEF status.

6.4.3 HF medication prescription at discharge

Overall, patients with COPD-HF had lower prescription proportions of ACEIs/ARBs, beta-blockers as well as double (ACEi/ARB + beta-blocker) and triple-therapy (ACEi/ARB + beta-blocker + MRA) compared to those with HF-alone. ACEIs/ARBs, MRAs and triple-therapy regimens were prescribed more frequently in the asthma-HF group compared with those with HF-alone; however, beta-blockers or double-therapy were less often prescribed for asthma-HF vs. HF-alone **(Figure 6.4).**

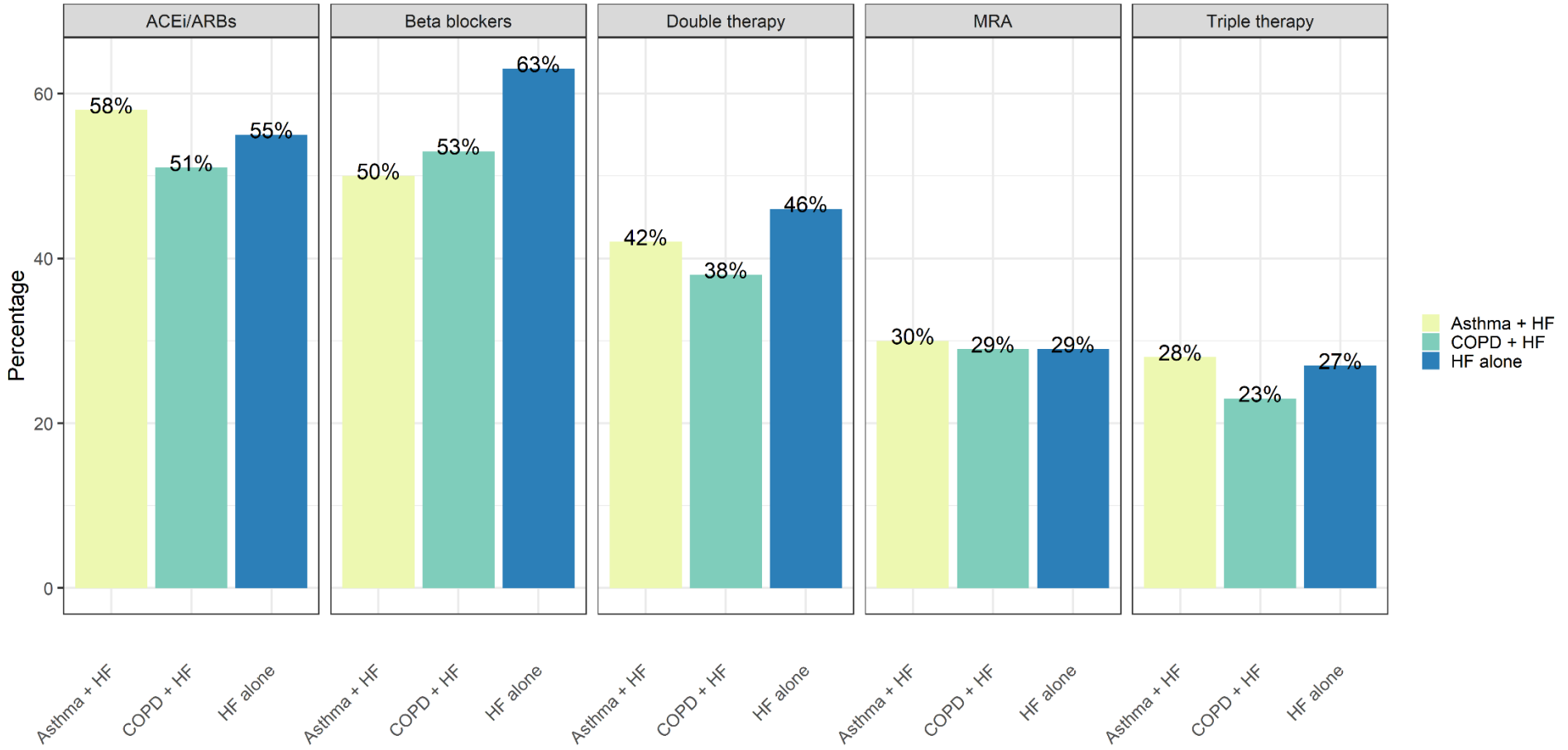

Figure 6.4: HF-medication prescription rates in patients hospitalised for HF, according to COPD and asthma status

In a subgroup of patients with HFrEF, both COPD and asthma were associated with decreased likelihood of being prescribed a beta-blocker 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 amongst HFrEF patients (see **Table 6.6**).

TABLE 6.6: Association between COPD, asthma and HF medication prescription at discharge, in patients hospitalised 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<0.001)	0.66 (0.64, 0.68, P<0.001)	0.63 (0.59, 0.67, p<0.001)	0.57 (0.54 0.60, p<0.001)
Random effects				
Variance	0.553	0.578	0.549	0.578
LR test p-value	<0.001	<0.001	<0.001	<0.001
ACEis/ARBs (N=96080 [a,b])				
Fixed effects	0.87 (0.84, 0.90, p<0.001)	0.91 (0.87-0.95, p<0.001)	1.13 (1.07, 1.19, p<0.001)	1.07 (1.01, 1.13, p<0.05)
Random effects				
Variance	0.149	0.130	0.148	0.130
LR test p-value	<0.001	<0.001	<0.001	<0.001

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)
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<0.001)	1.07 (1.02, 1.12, p<0.01)
Random effects				
Variance	0.232	0.195	0.226	0.195
LR test p-value	<0.001	<0.001	<0.001	<0.001

ACEi= angiotensin-converting-enzyme inhibitors, ARBs=angiotensin receptor blockers; CI= confidence intervals; COPD= chronic obstructive pulmonary disease; LR= likelihood ratio; MRA=mineralocorticoid receptor antagonist, OR= odd 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.

6.5 Discussion

This is the first study to provide a large assessment of contemporary HF practice, generalisable to the population of England-Wales, which evaluated the effect of COPD and asthma on clinical and management outcomes. I found that patients with COPD-HF were more likely to die during their HF admission, compared with patients with HF-alone; those with asthma-HF had a reduced probability of in-hospital death, compared with 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 disease, particularly COPD is associated with adverse events in patients with HF[45, 46, 50, 73, 210, 211], however diagnostic misclassification is often under-estimated and studies of the independent effect of asthma are lacking. I report several findings which add to the previous body of literature.

6.5.1 In-hospital mortality

The finding that COPD was associated with in-hospital mortality confirms reports from previous European data which considered longer follow-ups[127, 174]. 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[131].

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[133]. In contrast with the present report, previous studies found that risk of death is increased for those with COPD-HFpEF compared with COPD-HFrEF[114, 219], however this may be confounded by a lack of validity of LVEF status (inferred by ICD codes rather than echocardiography) or spirometry to confirm COPD, consideration of long-term rather than short term effects on mortality, or by including chronic rather than hospitalised HF. The present result therefore may be explained by poor uptake of disease-modifying treatments available for HFrEF in those with COPD[127], 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 HF 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.

Previous reports suggest asthma is associated with heightened risk of developing cardiovascular disease[213, 214, 220], however, no prior study has reported on the association between asthma and death during acute HF hospitalisation. I 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 this result. Asthma management is reliant on anti-inflammatory agents such as inhaled corticosteroids (ICS), which have been linked to cardioprotective effects[221-223] including lower all-cause mortality and decreased risk of myocardial infarction ([MI], a precursor to HF). Thus, potential long-term ICS use in the asthma-HF cohort could have diminished patients' baseline mortality risk.

The nature of inflammation is different in COPD compared with asthma, and this 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[82, 224]. While combination treatments such as ICS/Long-acting beta-agonists [LABA] may have a good cardiovascular safety profile in asthma, this differs in COPD[46, 215]. RCTs have not demonstrated mortality benefits with ICS in individuals with COPD[225], 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 this 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.

6.5.2 Referrals to HF services

The associations between COPD/asthma and referral to follow-up cardiology services have 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[226], but data suggest these timelines are not being

met[227]. The compounded effect of a COPD diagnosis has the potential to further impair the long-term prognosis of these comorbid patients.

This study also indicated LVEF status mediated the relationship with referrals, as individuals with COPD-HFpEF were less likely to have a post-discharge appointment compared with their COPD-HFrEF counterparts. This is particularly worrying as HF, irrespective of LVEF, is best monitored and managed within specialist HF teams[226].

Asthma did not adversely influence referrals to HF services, but I 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.

6.5.3 HF medication prescription at discharge

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[56, 199]. Similar to data on patients post-MI[228], 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[229, 230], 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, I expect these patients would have worse prognosis compared to their more adequately treated counterparts.

Considering these results, management needs to be optimised 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[231]. Given the contraindication of beta-blockers in asthma, these new treatments should urgently be assessed in this population, as data are currently lacking.

6.5.4 Strengths and limitations

The main strength of this study is the large sample size and representativeness to the UK (England-Wales) hospitalised population with HF. Information on duration and severity of asthma or COPD, nor lung function test results were available and thus I could not verify accuracy of these diagnoses, which are often subject to misclassification, especially in the elderly[232]. I also could not differentiate between early or late-onset asthma which may have different implications [233].

HFpEF was determined as a HF diagnosis without systolic dysfunction, which has been used in previous NHFA reports[131]. Nevertheless, there is no consensus gold standard HFpEF diagnosis[16] 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[45, 50].

There was a considerable proportion of missing data on bronchodilators/ICS 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/ethnicity were also characterised by a large percentage of missing data, however an analysis using multiple imputation indicated that even after adjusting for these confounders, the association between both COPD and asthma on in-hospital mortality remained unchanged.

I 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, I did not have access to data on concrete healthcare utilisation amongst the cohort.

Due to lack of data, I 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.

6.6 Conclusions

This analysis adds to the growing body of evidence that COPD and asthma affect outcomes in patients with acute HF. These 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 significantly lower odds of prescriptions for 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.

Chapter 7 IMPACT OF COPD ON READMISSION IN PATIENTS HOSPITALISED FOR HEART FAILURE

The issue of recurrent admission to hospital is of major importance in the management of HF. It is a major cause of poor quality of life and a significant driver of healthcare costs. However, not all readmissions are related to HF or other cardiovascular disease. The association between COPD and short-term readmission in patients withs acute HF has not been fully clarified.

The following chapter reports the findings of a study in which I assessed 30-day readmission risk in patients hospitalised for HF in the US who did and did not have COPD, as well as reasons for readmission and patient characteristics.

A portion of this work has been published in the International Journal of Cardiology (Appendix G, Paper 7). Another publication related to this work is a reply to a letter from editor (Appendix G, Paper 8).

7.1 Introduction

Patients who are hospitalised for HF remain at high risk of returning to hospital. Readmission is associated with poor prognosis[234] and represents a considerable economic burden for healthcare systems. Furthermore, 30-day readmission rates are currently used by the Centers for Medicare and Medicaid Services in the US to assess the quality of hospital care and to penalise hospitals with high readmission rates [235]. Importantly, not all readmissions are due to acute or worsening HF and in the search of more effective HF care models, there has been growing focus on the management of non-cardiovascular comorbidities in patients with this cardiac syndrome [36, 92, 236].

Few studies have specifically examined the clinical prognosis of individuals with acute HF and coexisting COPD, among which an increase in adverse outcomes, including hospitalisation and death have been demonstrated [127, 174, 211, 237]. Whether this increase in risk is directly attributed to COPD is unclear.

Furthermore, cause-specific readmission has been less well described in this population. These data are important for decisions regarding post-discharge care, resource allocation and readmission avoidance among patients with HF.

7.2 Study aims

(1) To compare the comorbidity profiles, frequency and causes of readmission among patients with hospitalised HF, with and without COPD.

(2) To assess whether COPD is independently associated with increased risk of readmission and to identify baseline comorbidities associated with risk of readmission in those with COPD and those without COPD.

7.3 Methods

7.3.1 Data source

The study cohort was identified in the National Readmissions Database (NRD) in the US. The NRD contains discharge data from 27 US states, accounting for 57.8% of the resident population and 56.6% percent of all US hospitalisations. All medical records of patients treated in community hospitals, but not rehabilitation or long-term acute care facilities, are included. Outcomes in NRD include national readmission rates, reasons for returning to the admitting hospital and discharge medical costs. In the present study, I utilised data from the calendar year 2012. Ethical approval was not required for this study as NRD is a publicly available de-identified administrative database (personal data are anonymised).

7.3.2 Study population

I used the ICD-9CM Clinical Classification Software (CCS) code 108 to identify all admission with a primary diagnosis of HF (ICD-9CM codes 428.xx), as has been used in previous studies using the NRD[238]·[239]. Admissions due to rheumatic HF were excluded as its aetiology is infectious leading to different clinical characteristics and prognosis, compared with congestive HF, considered in this analysis. COPD status was not pre-defined in the NRD. For each admission per patient, I assessed whether an ICD-9 CM code for COPD was included in the patient's record and created a diagnostic label for prevalent COPD. These ICD-9 CM codes have been used previously to identify COPD administrative databases with high accuracy [80, 240, 241] (see **Table 7.1**).

TABLE 7.1: ICD-9CM codes to identify HF and COPD

HF ICD-9CM codes	
4280	Congestive heart failure, unspecified
428.1	Left heart failure
428.20	Systolic heart failure, unspecified
428.21	Acute systolic heart failure
428.22	Chronic systolic heart failure
428.23	Acute on chronic systolic heart failure
428.30	Diastolic heart failure, unspecified
428.31	Acute diastolic heart failure
428.32	Chronic diastolic heart failure
428.33	Acute on chronic diastolic heart failure
428.40	Combined systolic and diastolic heart failure, unspecified
428.41	Acute combined systolic and diastolic heart failure
428.42	Chronic combined systolic and diastolic heart failure
428.43	Acute on chronic combined systolic and diastolic heart failure
COPD ICD-9CM codes	
491	Chronic bronchitis
491.0	Simple chronic bronchitis
491.1	Mucopurulent chronic bronchitis
491.22	Obstructive chronic bronchitis with acute bronchitis
491.20	Obstructive chronic bronchitis with acute exacerbation
4918	Other chronic bronchitis
4919	Unspecified chronic bronchitis
492	Emphysema
492.0	Emphysematous bleb
492.8	Other emphysema
496	Chronic airway obstruction, not elsewhere classified

7.3.3 Outcomes

The primary outcome was any-cause readmission, defined as the first readmission occurring within 30 days of the index (initial) HF admission for each patient, regardless of reason for admission. Time to readmission was calculated in days as the difference between time of readmission and time of discharge. If a patient had multiple readmissions within 30 days, the first one was included in the analysis.

Secondary outcomes were:

- Readmission due to any cause at 90-days.
- Cardiovascular or respiratory-related readmissions at 30- and 90- days respectively identified using ICD-9CM codes in the primary diagnosis field (**Table 7.2**).
- Causes of readmissions (identified using CCS categories based on ICD-9CM codes Appendix F, Table F1).

TABLE 7.2: Causes of 30-day readmissions in patients hospitalised with HF

Cause of readmission	CCS codes	ICD-9CM codes
All cardiovascular	98, 99, 96, 97, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121	
HF	108	4280, 428.1, 428.20, 428.21 428.22, 428.23, 428.30, 428.31, 428.32, 428.33 428.40, 428.41, 428.42, 428.43
All respiratory	122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134	
COPD		491 , 491.0 , 491.1, 491.22, 491.20, 492.2, 492.22, 491.8, 491.9, 492, 492.0, 492.8, 496

COPD= chronic obstructive pulmonary disease; CCS= Clinical Classifications Software; ICD= International Classification of Diseases; CM= clinical modification; HF= heart failure.
According to CCS and/or ICD-9CM codes in the primary diagnosis position.

For 30-day readmission analyses, patients with an index admission in December were excluded, and for 90-day readmission analyses patients with an index admission in October, November and December were excluded (to allow follow up for 30-day and 90-day readmission, see **Figure 7.1**).

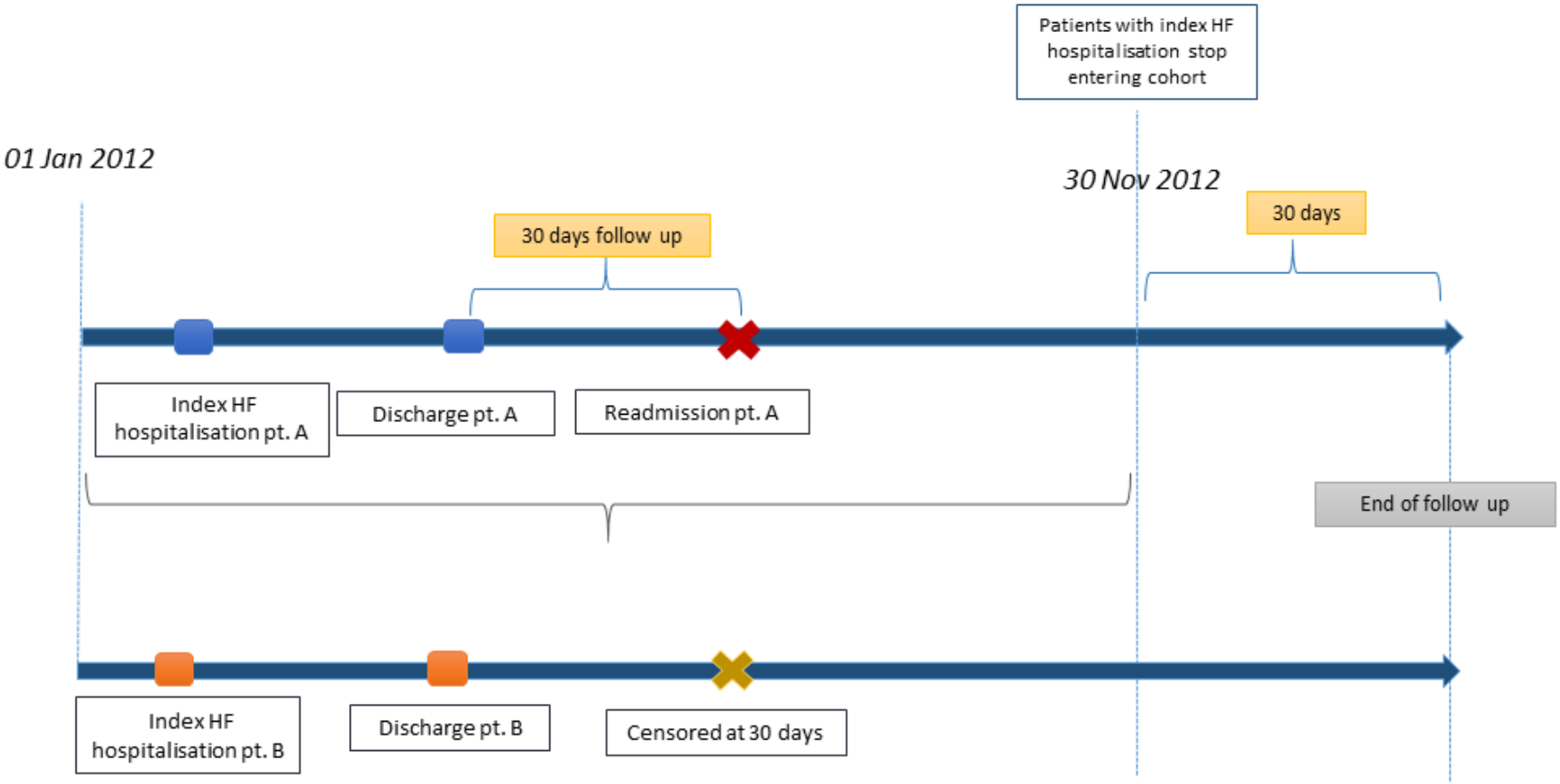

FIGURE 7.1: Study design. Example follow-up/censoring for main outcome.

Patient A – with readmission at 30 days and Patient B – without readmission and thus censoring at 30 days.

Patients with missing data on demographics, length of stay (LOS) or survival status were excluded. Those not resident in the state where the index admission had taken place were also excluded as their subsequent hospitalisations could not be linked. As COPD is generally diagnosed in older age, patients younger than 40 years were not included [39] and for all patients, only unplanned hospitalisations were included.

7.3.4 Covariates

NRD specific "cm_" variables were used to identify comorbidities, with diagnoses and the diagnosis-related group recorded on discharge date. Comorbidities were considered as diseases not directly related to the main diagnosis or the main reason for hospital stay. These methods have been used in previous studies using the NRD data source [238], [242].

Comorbidities included were:

- Atrial fibrillation (AF), coronary artery disease (CAD), diabetes, obesity (defined as Body Mass Index (BMI) > 30]), hypertension, liver disease, renal failure, cancer, anaemia, peripheral vascular disease, weight loss, coagulopathy and depression.

NRD readily available variables were used to identify patients' demographic characteristics such as age; sex, median household income category, type of insurance, discharge destination, in-hospital mortality and LOS. For the main analysis, I assumed that patients who were admitted only once and did not die in hospital were still alive at the end of 30-days, or 90-days, for respective analysis. Other studies have used a similar methodology [243, 244].

For the primary outcome of 30-day readmission risk, based on a sample of 217,979 observations (excluding patients who died during their index hospitalisation) and 0.20 probability of

readmission in the overall population, there was > 95% power to detect a HR of 1.2, assuming a type I error rate (alpha) of 0.001.

7.3.5 Statistical analysis

Data are presented as frequency (%) for categorical variables and mean and standard deviation (SD), or median interquartile range (IQR) for continuous variables. Differences in baseline characteristics between patients with and without COPD were assessed using the Chi-square test for categorical variables and Kruskall-Wallis tests for continuous variables. Outcome event rates were calculated as incidence per 1000 patient-days. Association between COPD and outcomes (30-day or 90-day all-cause, cardiovascular and respiratory-related readmission) was assessed with Cox proportional hazards regression models in presence of proportional hazards assumption being met. I adjusted for baseline characteristics such as included age, sex, comorbidities and LOS. Patients with an index hospitalisation only were censored at 30-days or 90-days, respectively. Patients who died during their index hospital admission were excluded. Time to first 30-day, or 90-day readmission was analysed for the whole cohort, and separately stratified by COPD status. No variables used in the main analyses had missing data. Statistical analyses were performed using R v3.4.4.

Sensitivity analysis

Data regarding out-of-hospital mortality were not available and this may have had a differential effect on the risk of readmission between patients with and without COPD. Since a competing risk of death with readmission could not be performed, in an attempt to address this limitation, I conducted a sensitivity analysis excluding patients without readmissions (I included only patients

with at least one readmission, as to ensure inclusion of patients for whom death status was known).

7.4 Results

7.4.1 Baseline characteristics

Among 225,160 patients hospitalised for HF, 54,953 (24.4 %) had a coexisting diagnosis of COPD (see **Figure 7.2**).

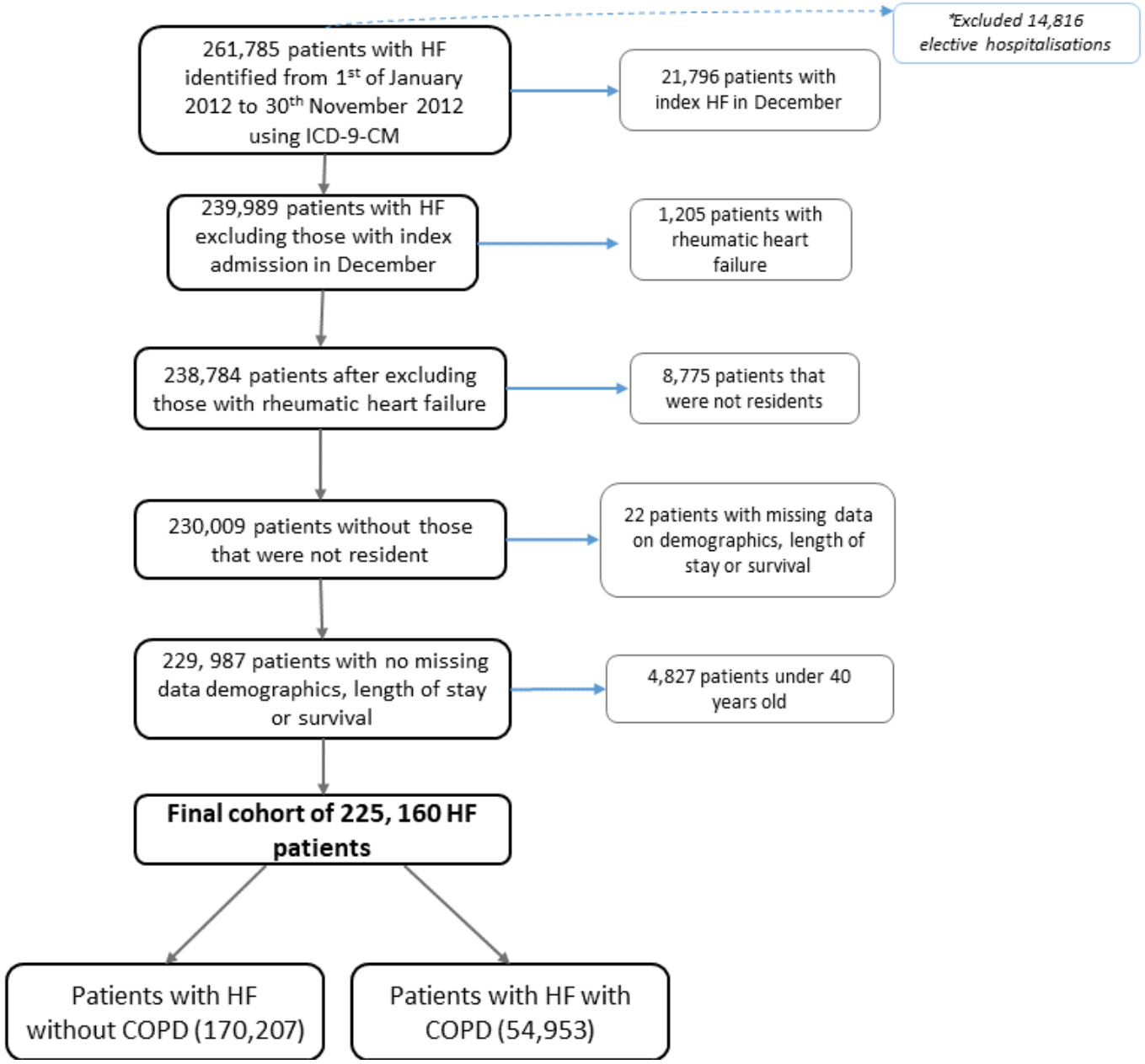

FIGURE 7.2: Study flow, patient inclusion

Baseline characteristics of the study population are presented in **Table 7.3**. Compared with patients with HF alone, those with HF and COPD were, on average, younger, less frequently female and had higher rates of other chronic conditions such as CAD, AF, renal failure, diabetes and obesity. Data regarding income were available for 222,002 (98.6%) patients. Approximately half of the total study cohort were in middle income brackets (26^{th}-75^{th} percentiles), with equal percentages of patients with and without COPD. There were more patients with COPD insured by Medicare, compared to those without (81% vs. 76%) with private insurance (7% vs. 11%) or self-payers (4% vs. 6%).

TABLE 7.3: Baseline characteristics of patients hospitalised for HF

	Overall (N = 225,160)	**HF alone (N = 170,207)**	**HF + COPD (N = 54,953)**
Sex			
Male	111,753 (50%)	82,751 (49%)	29,002 (53%)
Female	113,407 (50%)	87,456 (51%)	25,951 (47%)
Age (years)			
Median (IQR)	76 (65, 85)	77 (64, 86)	76 (66, 84)
Atrial fibrillation	92,653 (41%)	68,968 (41%)	23,685 (43%)
Coronary artery disease	122,372 (54%)	89,545 (53%)	32,827 (60%)
Obesity**	39,514 (18%)	28,848 (17%)	10,666 (19%)
Weight loss	10,410 (5%)	7,750 (5%)	2,660 (5%)
Peripheral vascular disorders	27,884 (12%)	19,259 (11%)	8,625 (16%)
Coagulopathy	13,374 (6%)	10,115 (6%)	3,259 (6%)
Renal failure	90,764 (40%)	67,715 (40%)	23,049 (42%)
Liver disease	6,642 (3%)	4,882 (3%)	1,760 (3%)
Diabetes	75,966 (34%)	56,632 (33%)	19,334 (35%)
Cancer	6,603 (3%)	4,835 (3%)	1,768 (3%)
Anaemia	69,719 (31%)	51,806 (30%)	17,913 (33%)
Hypertension	173,646 (77%)	131,565 (77%)	42,081 (77%)
Depression	20,634 (9%)	14,619 (9%)	6,015 (11%)
LOS (days)			
Median (IQR)	4 (2, 6)	4 (2 6.)	4 (3, 7)
In-hospital mortality	7,181 (3.19%)	5,655 (3.3%)	1,526 (2.8%)
Income			
0-25th percentile	70,703/222,002* (32%)	52,489/167,861* (31%)	18,214/54,141* (34%)

	Overall (N = 225,160)	HF alone (N = 170,207)	HF + COPD (N = 54,953)
26th to 50th percentile (median)	52,716/222,002* (24%)	39,178/167,861* (23%)	13,538/54,141* (25%)
51st to 75th percentile	51,811/222,002* (23%)	39,477/167,861* (24%)	12,334/54,141* (23%)
76th to 100th percentile	46,772/222,002* (21%)	36,717/167,861* (22%)	10,055/54,141* (19%)
Unknown	3,158 (1%)	2,346 (1%)	812 (1%)
Insurance type			
Medicare	173,412/224,399* (77%)	129,111/169,587* (76%)	44,301/54,812* (81%)
Medicaid	16,904/224,399* (8%)	12,854/169,587* (8%)	4,050/54,812* (7%)
Private insurance	22,052/224,399* (10%)	17,964/169,587* (11%)	4,088/54,812* (7%)
Self-pay/No charge/Other	12,031/224,399* (5%)	9,658/169,587* (6%)	2,373/54,812* (4%)
Unknown	761 (0) †	620 (0) †	141 (0) †
Discharge destination			
Home	116,170 (52%)	89,345 (52%)	26,825 (49%)
Home health care	54,452 (24%)	40,162 (24%)	14,290 (26%)
Transfer to a skilled nursing facility	42,523 (19%)	31,479 (18%)	11,044 (20%)
Transfer to short-term hospital	2,326 (1%)	1,761 (1%)	565 (1%)
Other	9,689 (4%)	7,460 (4%)	2,229 (4%)
Total charges ($)			
Median (IQR)	218,464*; 25,297.00 (14,650.00, 46,057.25)	164,588*; 25,000.00 (14,467.00, 45,477.00)	53,876*; 26,269.00 (15,218.75, 47,750.25)
Unknown	6,696 (3%)	5,619 (3%)	1,077 (2%)

COPD= chronic obstructive pulmonary disease; IQR= interquartile range; HF= heart failure; LOS= length of stay
* Denotes number of patients for which data was available (non-missing)
† Approximated
**Obesity was defined as Body Mass Index (BMI) > 30

7.4.2 Index admission to hospital

Overall, 7,181 (3.19%) patients died during their index HF hospitalisation. Fewer patients with concomitant COPD died, compared with those without COPD (2.8% HF with COPD vs. 3.3% HF alone). However, patients with COPD had a comparable LOS (median [IQR] 4 [3-7] days with COPD and 4 [2-6] days without COPD) and greater cost of hospitalisation (median cost $26,269 with COPD vs. $25,000 for patients without COPD). Discharge destination also differed by COPD status. Those with COPD were more frequently discharged to home with additional health care (26% COPD vs. 24% no COPD) or transferred to a skilled nursing facility (20% HF with COPD vs. 18% HF alone), rather than discharged home (see **Table 7.3**).

7.4.3 Readmission risk

In total, 65,237 (29%) patients were readmitted to hospital. 24,646 (45 %) patients had an additional COPD diagnosis and 40,591 (24 %) did not have COPD. Median (IQR) time to first readmission was shorter in patients with COPD (47 days [18-106]) compared with those without (51 days [19 - 115], p<0.001). A diagnosis of COPD was also correlated with a higher frequency of 30-day (17% COPD vs. 8% no COPD, p<0.001) and 90-day readmission (31% COPD vs. 16% no COPD, p<0.001). Compared with patients without COPD, those with COPD had a double risk of readmission within 30 days of discharge from their index HF admission, after adjusting for baseline factors such as age, sex, comorbidities and LOS (HR_{adj} 2.02, 95% CI 1.97 - 2.08). At 90 days, the risk increased marginally (adjusted HR_{adj}: 2.08, 95% CI 2.04 - 2.12) (see **Table 7.4**).

TABLE 7.4: Association between COPD and readmission risk, in patients hospitalised with HF

	COPD Number of events (%)*	No COPD Number of events (%)*	Unadjusted HR† (95% CI)	Adjusted HR† (95% CI)
		All-cause readmission		
30-day	9,238 (16.8%)	14,430 (8.4%)	2.06 (2, 2.11)	2.02 (1.97, 2.08)
90-day	15,535 (33.7%)	23,982 (17.5%)	2.07 (2.02, 2.11)	2.12 (2.07, 2.16)
		Cardiovascular readmission		
30-day	4,586 (8.3%)	7,458 (4.3%)	1.98 (1.90, 2.05)	1.92 (1.85, 1.99)
90-day	7,747 (16.8%)	12,479 (9.1%)	2.03 (1.97, 2.08)	1.97 (1.91, 2.03)
		HF readmission		
30-day	3,025 (5.5%)	4,664 (2.7%)	2.08 (2, 2.18)	2.05 (1.96, 2.15)
90-day	5,135 (11%)	7,786 (5.7%)	2.15 (2.08, 2.23)	2.12 (2.05, 2.20)
		Respiratory readmission		
30-day	1,170 (2.1%)	1,258 (0.73%)	2.99 (2.76, 3.24)	2.90 (2.68, 3.15)
90-day	1,940 (4.2%)	2,000 (14.6%)	3.16 (2.97, 3.37)	3.08 (2.90, 3.29)
		COPD readmission		
30-day	82 (0.14%)	55 (0.03%)	4.80 (3.14, 6.76)	4.76 (3.37, 6.72)
90-day	139 (0.3%)	92 9 (0.07%)	4.95 (3.8, 6.44)	4.82 (3.7, 6.03)

CI= confidence intervals; COPD= chronic obstructive pulmonary disease; HR= hazard ratio

† COPD vs. no COPD

HR adjusted for age, sex, diabetes, hypertension, obesity, renal failure, liver disease, cancer, weight loss, peripheral vascular disease, coagulopathy, anaemia, depression, length of stay.

*Calculated as number of events/total number of patients (30-day denominator COPD: 53,427; no COPD: 164,552; 90-day denominator COPD: 46,090; no COPD: 136,608). Note: the denominator used for 90-day readmission did not include patients with an index HF hospitalization in the months of October, November and December – see Methods

When 30-day readmission data were stratified by COPD status, female sex, diabetes, renal failure, anaemia, and index admission LOS were associated with an increased risk of readmission, regardless of COPD status. On the other hand, AF, CAD, liver disease, cancer and peripheral vascular disease were associated with increased risk of readmission in patients with HF only. There was a trend in the direction of diminished readmission risk in patients above 70 years old, which was statistically significant in patients with concomitant COPD (and in patients without the lung disease, between 70-79 years old) (see **Table 7.5**).

TABLE 7.5: Association between baseline characteristics and any-cause 30-day readmission in patients hospitalised with HF, stratified by COPD status

	HF + COPD		HF alone	
	Unadjusted HR (95%CI)	**Adjusted HR (95%CI)**	**Unadjusted HR (95%CI)**	**Adjusted HR (95%CI)**
Age, years (reference group: 40 -49)				
50-59	1.04 (0.93, 1.16)	1.01 (0.90, 1.12)	0.97 (0.88, 1.06)	0.91 (0.83, 1.00)
60-69	0.99 (0.90, 1.10)	0.92 (0.83, 1.02)	1.06 (0.98, 1.16)	0.95 (0.87, 1.04)
70-79	0.96 (0.86, 1.06)	0.87** (0.78, 0.96)	1.06 (0.97, 1.15)	0.91* (0.83, 0.99)
80-90	0.93 (0.84, 1.03)	0.83*** (0.75, 0.92)	1.12** (1.03, 1.21)	0.95 (0.87, 1.03)
Sex (female vs. male)	1.00 (0.97, 1.04)	1.03 (0.99, 1.07)	1.02 (0.99, 1.06)	1.06** (1.02, 1.10)
Comorbidities at baseline				
Atrial Fibrillation	1.07*** (1.03, 1.11)	1.08*** (1.04, 1.12)	1.09*** (1.05, 1.13)	1.08*** (1.04, 1.12)
Coronary Artery Disease	1.01 (0.97, 1.05)	0.96 (0.92, 1.01)	1.13*** (1.09, 1.17)	1.10*** (1.06, 1.14)
Diabetes	0.93** (0.89, 0.98)	0.87*** (0.83, 0.92)	1.04 (1.00, 1.08)	1.06** (1.02, 1.10)
Hypertension	1.26*** (1.22, 1.31)	1.23*** (1.18, 1.27)	0.99 (0.95, 1.04)	0.94** (0.90, 0.98)
Obesity	1.17** (1.06, 1.29)	1.08 (0.98, 1.20)	0.84*** (0.80, 0.89)	0.84*** (0.80, 0.89)
Renal failure	1.08 (0.98, 1.20)	1.07 (0.96, 1.19)	1.38*** (1.33, 1.43)	1.30*** (1.25, 1.35)
Liver disease	1.23*** (1.13, 1.33)	1.13** (1.04, 1.23)	1.29*** (1.18, 1.42)	1.24*** (1.13, 1.37)
Cancer	1.01 (0.96, 1.07)	0.98 (0.93, 1.03)	1.29*** (1.17, 1.43)	1.26*** (1.14, 1.39)
Weight loss	1.11** (1.03, 1.20)	1.01 (0.94, 1.09)	1.21*** (1.11, 1.31)	1.05 (0.97, 1.15)
Peripheral vascular disease	1.22*** (1.17, 1.26)	1.13*** (1.09, 1.18)	1.18*** (1.12, 1.25)	1.09** (1.03, 1.15)
Coagulopathy	1.05 (0.99, 1.11)	1.04 (0.99, 1.11)	1.18*** (1.10, 1.27)	1.04 (0.96, 1.11)
Anaemia	1.08** (1.03, 1.14)	1.07** (1.02, 1.13)	1.29*** (1.25, 1.34)	1.16*** (1.11, 1.20)
Depression	1.25*** (1.19, 1.32)	1.22*** (1.16, 1.29)	1.07* (1.01, 1.14)	1.06 (1.00, 1.13)
LOS, days (reference group: 0-2)				
3-5	1.42*** (1.33, 1.51)	1.35*** (1.27, 1.44)	1.13*** (1.08, 1.18)	1.10*** (1.05, 1.15)
6-9	1.02 (0.98, 1.06)	1.04 (1.00, 1.08)	1.35*** (1.28, 1.42)	1.27*** (1.20, 1.33)
≥10	1.02 (0.98, 1.06)	1.01 (0.97, 1.05)	1.56*** (1.47, 1.66)	1.42*** (1.33, 1.51)

COPD= chronic obstructive pulmonary disease; HR, hazard ratio; CI, confidence interval; LOS, length of stay.
*p<0.05; **p<0.01; ***p<0.001

7.4.4 Reasons for readmission

The most common reason for readmission within 30-days was a disease of the circulatory system (50.9% of all admissions). The second most frequent cause of readmission was respiratory disease (13.3% of all admissions, 26% of non-circulatory admissions) (see **Figure 7.3**).

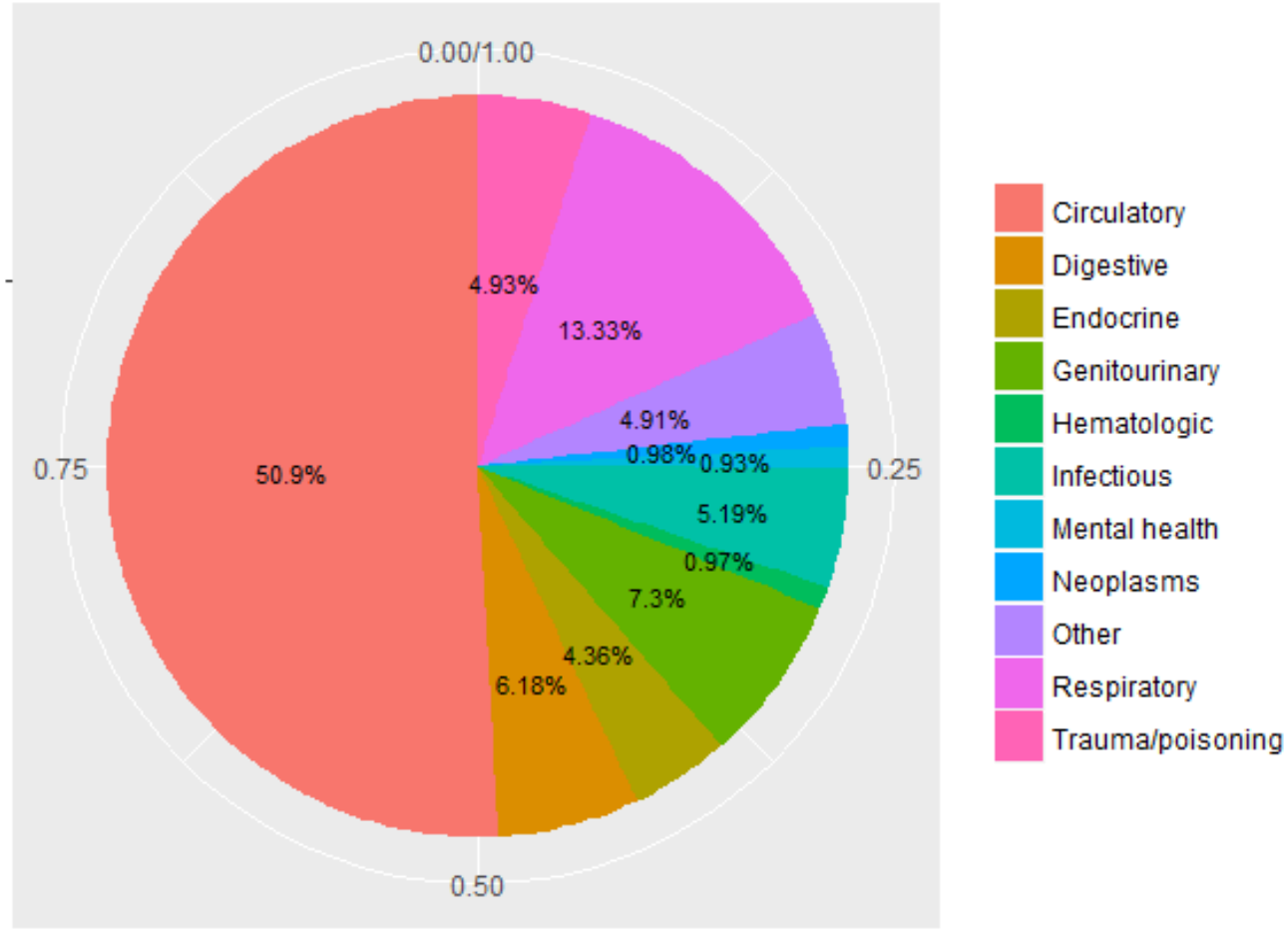

FIGURE 7.3: Aetiologies of 30-day readmission for patients hospitalised with HF

Slightly less patients with COPD had a primary cardiovascular readmission within 30-days, compared with patients without COPD (49% vs. 51%, p-value <0.001). A significantly higher percentage of HF patients with COPD were readmitted for respiratory-related reasons vs. HF patients without COPD (16% vs. 11%, p<0.001) (see **Figure 7.4**).

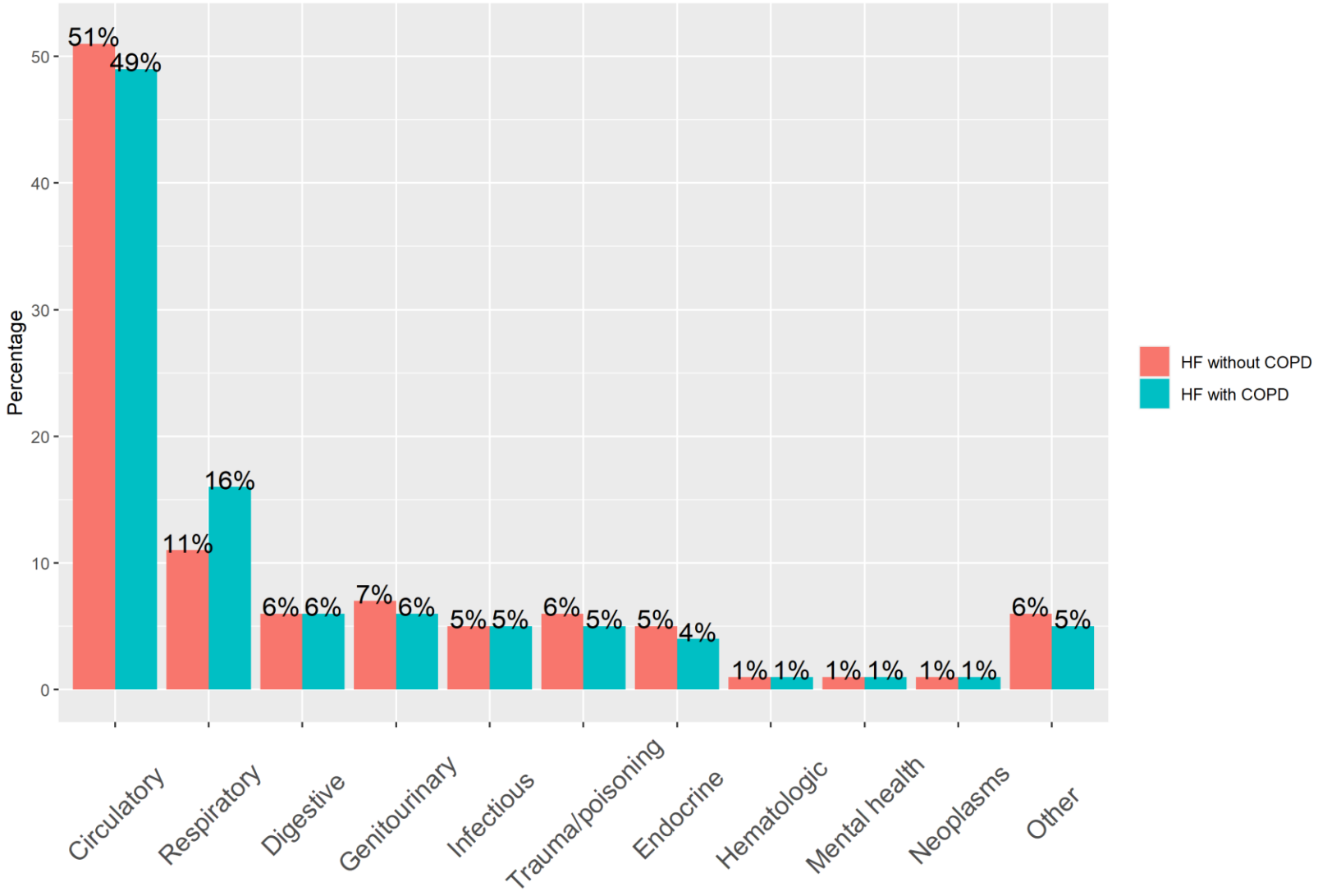

FIGURE 7.4: Causes of readmission in patients hospitalised with HF, with and without COPD.

7.4.5 Sensitivity analysis results – inclusion of patients with at least one readmission

The results from the sensitivity analysis are presented in **Table 7.6**. Risk of readmission associated with COPD was attenuated across all outcomes, with the exception of risk of cardiovascular readmission, which was no longer significant.

TABLE 7.6: Association between COPD and 30-day readmission in patients hospitalised with HF (sensitivity analysis including only patients with a readmission).

Readmission outcome	Unadjusted HR (95% CI)	Adjusted[a] HR (95% CI)
Any-cause	1.06***(1.03, 1.09)	1.06***(1.04, 1.09)
Cardiovascular	1.02 (0.98, 1.06)	1.02 (0.98, 1.06)
Respiratory	1.54***(1.43, 1.67)	1.51***(1.40, 1.64)
HF	1.08**(1.03, 1.13)	1.51***(1.40, 1.64)
COPD	2.47*** (1.76, 3.48)	1.51*** (1.40, 1.64)

CI= confidence interval; COPD= chronic obstructive pulmonary disease, HF= heart failure; HR= hazard ratio.
*p<0.05; **p<0.01; ***p<0.001
[a] HR adjusted for age, gender, diabetes, hypertension, obesity, renal failure, liver disease, cancer, weight loss, peripheral vascular disease, coagulopathy, anaemia, depression, length of stay.
Patients that were admitted only once were excluded.

7.5 Discussion

7.5.1 Main findings

In this nationally representative cohort of patients with an index admission for HF in the US, comorbid COPD was present in a quarter of patients. When compared to HF patients without COPD, those with COPD had an increased risk of all-cause readmission. This included more

frequent HF-specific and respiratory-related readmissions. Although the most frequent reason for readmission was due to a cardiovascular cause, the risk of a respiratory-related readmission was two-fold higher, and COPD-specific readmission three-fold greater, in patients with COPD vs. those without. These results indicate there is a significant difference in the short-term clinical trajectory of patients admitted to hospital due to HF for individuals with COPD compared to those without COPD, particularly due to increased risk of respiratory disease-exacerbation.

7.5.2 Comparison with other studies

This analysis is one of the largest reports to date of patients with hospitalised HF (n=225,160). The reported prevalence of COPD amongst a HF population was similar to contemporary studies using routine databases, as well as clinical studies where COPD diagnosis was clinician-adjudicated [245], [246]. Patients with HF and COPD had a greater overall burden of comorbidity and shorter time to readmission, but were less likely to die in-hospital, compared to those without COPD. This is in contrast with two European studies which reported higher in-hospital mortality among patients with HF and coexisting COPD compared to those with HF alone [127, 211]. Several reasons may explain this discrepancy: First, in the present sample, patients with COPD were younger than those with HF alone, which may have contributed to a lower baseline in-hospital mortality. Second, specific therapeutic strategies, such as oral steroids, which may unintentionally treat other conditions besides COPD, or other unrecorded differences in management that may not be completely captured by routinely collected electronic health record data could have contributed to this lower mortality rate. Alternatively, and more plausibly, this may be a chance finding, as can frequently happen in analyses of big data.

That HF patients with COPD are younger than their HF-alone counterparts has been reported in a previous European study [127], whilst other authors found the opposite [237]. This may be due to differences in study design, such as distinct inclusion criteria which ranged from requirements to be over 18 years old [237], to over 40 [211] or 65 years old [247]. Nevertheless, in this study, patients' greater comorbidity burden cannot exclusively be attributed to older age and highlight a high-risk subgroup.

7.5.3 Readmission in patients hospitalised for HF, according to COPD status

As expected, and similar to previous reports, patients with HF and COPD were more likely to be readmitted as compared with those without COPD [127, 248]. Importantly, however, whilst previous studies [127, 174, 211] showed an increased risk of cardiovascular or HF readmission in the long term (at one-year, or longer follow-up), my analysis highlights an increased risk within the immediate post-discharge period, at 30- and 90-days post-discharge. Likely factors associated with this "early" risk include a greater burden of comorbidity and sustained low-grade inflammation associated with COPD, which may increase in time. The plausibility of this assumption is suggested by the increasing trend in risk of cardiovascular readmission 90-days post first discharge (an increase of 5% compared to the 30-day results, respectively 7% for HF-specific rehospitalisation). Further, under-recognition or suboptimal treatment of HF symptoms in this group of patients may also affect cardiovascular risk.

Since the most common reason for readmission was still due to a cardiovascular cause, including HF, early identification of post-discharge HF decompensation in this population remains paramount.

This study has also highlighted an independent association between comorbid COPD and the risk of respiratory-related readmission, particularly due to COPD, in patients admitted for HF. While this may be expected, if true, it suggests a potential opportunity for COPD-targeted therapy to improve outcomes in this subgroup. An alternative concern is that, due to overlapping symptoms and signs similar to HF, a proportion of cardiovascular or HF-related readmissions may be (mis)attributed (or coded) as being due to COPD in patients with this additional diagnosis. The existence of financial incentives, created by the national hospital penalty program [249] has encouraged documentation of comorbid conditions and may have led to more sensitive of COPD (containing possible false positive diagnoses). Ibrahim et al [250] reported that more than half of the reduction in the risk-adjusted readmission risk for three targeted conditions, including HF, may be attributed to an increase in up-coding of severity of illness based on comorbid diseases. Differentiation of these hypotheses will need prospective evaluation and confirmation and would be important to ensure suitable care pathways were followed for patients with HF and COPD.

The present study also detected different baseline comorbidities were associated with risk of readmission in the two stratified groups considered (HF with vs. without COPD). The finding that recognised risk factors for readmission in the HF alone cohort (AF, CAD and renal failure) were not found to be associated with readmission in patients with HF and COPD, may suggest a greater prognostic impact of COPD in this timeframe.

Finally, these results support a need for early recognition and optimisation of COPD management in patients who present to hospital with acute HF.

There are several limitations to the present analysis. Firstly, data regarding out-of-hospital mortality were not available and this may have had a differential effect on the risk of readmission between patients with and without COPD. Interestingly, previous studies report conflicting

findings regarding the competing risk of post-discharge death [251, 252], and these data are not currently included in the assessment of US hospital performance. The sensitivity analysis results were not significantly different from the main analysis, with the exception of cardiovascular readmission risk. Whilst this analysis does not completely circumvent the lack of post-discharge death data, it suggests that the difference in risk of all-cause, HF, and respiratory-related readmission between the two groups cannot be entirely explained by a competing risk of death. Therefore, the present data support a detrimental effect of COPD in patients admitted for HF.

Secondly, this is a retrospective analysis of routinely-collected administrative data, subject to known limitations of large data sources, such as possible coding errors resulting in diagnosis inaccuracy. However, ICD-9CM diagnostic codes were used to identify COPD, a strategy that has been used in studies using large administrative databases, in the US and elsewhere. Studies where the codes were validated report an accuracy of identifying COPD of 85%, considered acceptable for epidemiological investigations [80, 241]. The gold standard for diagnosing COPD remains spirometry, but this was not documented for this sample. However, spirometric-diagnosis of COPD has only been used few studies of HF as its interpretation may be problematic during acute HF decompensation leading to misclassification [127]. Data on potential confounders such as clinical stage of HF (New York Heart Association class), left ventricular ejection fraction, and treatment were unavailable.

Lastly, the NRD tracks readmissions within a single calendar year only, thus our numbers are only representative of this time period and may be underestimated.

7.6 Conclusions

In this large, nationally representative, US cohort, I demonstrated that COPD is associated with increased short-term risk of readmission in patients with acute decompensation of HF. While the majority of readmission were due to a cardiovascular disease, patients with COPD were at a significantly increased risk of respiratory, in addition to cardiovascular readmission.

These data suggest that having a COPD diagnosis carries a considerable burden and is an important factor in the management of patients hospitalised for HF. There is a need for clinicians and policy makers to design clinical care strategies aimed at reducing both respiratory and cardiovascular readmissions in this population.

Future studies should evaluate whether concurrent evaluation and optimisation of COPD therapeutic management, would reduce readmission risk, among patients with acute decompensated HF.

Chapter 8 GENERAL DISCUSSION

This chapter includes an overview of the findings from the work comprising this thesis, potential implications for clinical practice and future research. Specific discussion points for each of the chapters are provided in their respective discussion sections.

8.1 Aim 1 (Chronic heart failure): Comorbidity patterns in patients with heart failure

In the first study presented in Chapter 3 of this thesis (Paper 1), I aimed to evaluate comorbidity patterns in patients with chronic HF and to establish whether COPD is a key discriminating factor. Secondarily, I examined differences in clinical outcomes amongst the comorbidity clusters identified.

I identified five comorbidity clusters amongst HF patients with different clinical trajectories: the risk of hospital admission after HF diagnosis was lowest in the low-burden and metabolic groups, intermediate in the anaemic and ischemic groups and highest in the metabolic-vascular group. Mortality rates and healthcare utilisation also differed between clusters.

The main strength of this study was the large sample size, largely representative of the US insured population in terms of age and sex. The identification of comorbidities prior to HF limited the inclusion of cases where precursors of HF may have been incorrectly entered into the cohort. The use of model-based clustering, rather than methods such as hierarchical clustering techniques is also deemed an advantage as the fit of the model can be evaluated using statistics.

8.1.1 Clinical implications

Clinicians need to consider a holistic approach when caring for HF patients, which should go beyond tackling individual comorbidities separately. The recognition that specific patterns of additional diagnoses incur greater burden than others (with respect to hospitalisation or mortality), could help clinicians prioritise therapeutic goals in the management of very complex patients. Further, this could aid personalisation of clinical risk assessment and subsequent, tailored resource allocation.

8.1.2 Future research recommendations

Most pharmacological therapies are approved for use in HF based on randomised controlled trials (RCT) which exclude the elderly, typically affected by additional and significant comorbidities. The assumption of efficacy in this group is based on extrapolations of data and thus, the true benefit is not clear. In the context of increasing prevalence of HF due to aging and other factors, such as increase in number of comorbidities over time[4], it is important that RCTs include representative HF samples, including those with additional diseases. The identification of combinations of comorbidities, which affect clinical outcomes to differing degrees, suggests a tailored approach in managing these comorbidity clusters should be evaluated in future RCTs, to identify strategies aimed at reducing mortality, hospitalisation, as well as healthcare use in these patients.

More comprehensive approaches to HF phenotyping are needed which may include, in addition to assessing comorbidities, integration of genetic, behavioural and biomarker data. It is known that comorbidities are associated with cardiac and structural changes in HF[253], therefore establishing causal pathways between these interactions would be valuable in devising prevention and treatment strategies.

Polypharmacy is an issue in the management of HF patients with additional diagnoses. Since this can lead to poor medication adherence and drug-drug interactions may worsen prognosis, it is important to address these issues in future studies.

8.2 Aim 2 (Chronic heart failure): assessing outcomes in COPD-HF LVEF phenotypes

Following the findings of the study presented in Chapter 3 (Paper 1), indicating COPD did not play a major role in determining the formation of any of the comorbidity clusters, in the study presented in Chapter 4 I aimed to isolate a subgroup of patients with HF and concomitant COPD and to compare clinical, healthcare utilisation outcomes and management across left ventricular ejection fraction (LVEF) groups. Results indicated COPD-HF with preserved EF (HFpEF) was the most common phenotype amongst those with HF and COPD. Outcomes differed across EF groups.

8.2.1 Clinical implications

I showed that COPD is the main driver of outcomes in those with HFpEF. Patients with COPD and HFpEF were at heightened risk of exacerbations due to COPD, compared to those with COPD and HF with reduced LVEF (HFrEF), who experienced more HF-specific admissions.

The main recommendation resulting from this analysis is that separating respiratory versus cardiac causes of symptoms is valuable in patients with HF and COPD. This may help to prevent admission to hospital and to identify treatment needs specific to each patient, which would subsequently avoid use of unnecessary medications.

It is recognised that differentiating between HF and COPD in clinical practice, particularly primary care, is difficult. In the presence of common symptoms such as dyspnoea, and/or unclear diagnostic tests, clinicians are faced with a dilemma: “does the patient have HF or COPD?”. This can be further complicated if the patient has in fact HF/pEF and COPD. Therefore, before considering long-term bronchodilators in patients with HF and suspected COPD, it would be

preferrable to conduct comprehensive pulmonary function testing to confirm the COPD diagnosis. This could include body plethysmography as determining the ratio of residual volume and total lung capacity is useful, since air-trapping and hyperinflation is often occurring in COPD[139]. This method can identify COPD accurately in patients with HF, even in the recently post-acute phase[44].

Further, levels of HF prescriptions, particularly beta-blockers were low in the HFrEF group, signalling HF under-treatment. Clinicians should aim to maximise use of guideline-recommended treatments in these patients, which may result in diminished risk of mortality and hospitalisation.

8.2.2 Recommendations for future research

While this study identified differing clinical trajectories across those with COPD-HFrEF versus COPD-HFpEF, the use of ICD codes only to ascertain COPD, in the particular context of HF, was a limitation. A more sensitive classification of COPD based on spirometric assessment performed on euvolemic patients or body plethysmography should be incorporated in future studies.

Though case identification for HF was more robust, as data on LVEF was available, HFpEF remains a difficult diagnosis to make, more so in the presence of COPD. Beyond EF measurement, the current "gold-standard"[16] in adjudicating HFpEF includes assessment of natriuretic peptides, specific comorbidities (atrial fibrillation [AF], obesity, diabetes), an electrocardiogram and detailed echocardiography. In "borderline" cases, additional functional testing is required including invasive haemodynamic exercise stress tests. Incorporating a more sensitive definition of HFpEF and excluding pulmonary causes for breathlessness in patients

with cardiac disease should be done in future prospective studies aimed at disentangling the association between HF LVEF phenotypes and clinical outcomes, in those with concomitant COPD.

Further, if current understanding of HFpEF is correct in assuming multiple sub-phenotypes exist with different underlying pathophysiology and prognosis[25, 27], it would be valuable to investigate whether there is a potential causal relationship with COPD.

8.3 Aim 3 (Management of heart failure in COPD): Effect of beta-blockers

The aim of the systematic literature review and network meta-analysis presented in Chapter 5 (Paper 4), was to evaluate the effect of beta-blocker therapy on patient centric outcomes of individuals with COPD. Clinical trial data indicated that propranolol only was associated with a clinically significant decrease in lung function out of seven agents included in the analysis, whereas observational data suggested no detrimental effect of any beta-blocker on mortality, hospitalisation or quality of life outcomes.

8.3.1 Clinical implications

Based on the results of this study, the use of beta-blockers (except propranolol) should not be withheld in patients with COPD, particularly cardioselective beta-blockers celiprolol and labetalol which ranked highest in the hierarchy of treatments least likely to affect FEV_1. The concern regarding decrease in lung function as a result from administration of beta-blockers (apart from propranolol) is not being supported by evidence presented in this thesis. However, the effect of these medications on mortality and hospitalisation was inferred from observational

data, deemed of lower quality according to the GRADE system, suggesting interpretation of results needs to be done with caution.

8.3.2 Recommendations for research

Markers of COPD such as breathlessness and fatigue severely affect quality of life by preventing those affected to exercise or socialise, which may subsequently trigger increase in anxiety or depression. Since there are no disease-modifying treatments, improving patient centric outcomes is paramount amongst those with COPD.

While the qualitative interpretation of results amongst studies presented in Chapter 5 did not indicate that beta-blockers were associated with decreases in quality of life, there were insufficient data to allow a formal quantitative analysis, thus no definitive consensus can be drawn. Further, previous studies suggested beta-blockers improve functional status in cardiovascular disease, thus whether these benefits extend to those with COPD as well needs to be evaluated, ideally in the RCT settings, using validated COPD-specific instruments such as the CRQ, CAT or SGRQ[254].

The results on mortality and hospitalisation were based on data of low quality (i.e., observational studies) according to the GRADE system. In order to establish the true effect of beta-blockers, clinical trial data with longer follow-up times are needed to validate results presented in this thesis. It is important to mention one trial evaluating metoprolol in patients with COPD did not have conclusive results on mortality and all-cause hospitalisation, therefore more beta-blockers need to be assessed in order to construct a comprehensive foundation of evidence needed for clinical decision making.

8.4 Aim 4 (Acute heart failure): Impact of COPD on in-hospital mortality and management of patients hospitalised for heart failure

The study presented in Chapter 6 of this thesis (Paper 6, submitted) evaluated the association between COPD, asthma and in-hospital death, referral to follow-up cardiology services as well as medication prescriptions amongst hospitalised HF patients. The main findings supported the consideration that COPD is associated with increased likelihood of in-hospital death - particularly in those with HFrEF – and with reduced chances of post-discharge referrals to HF services, whereas asthma did not negatively impact on these outcomes. Decreases in HF recommended medication prescription were observed across both pulmonary disease conditions, in comparison with the HF-only diagnosed group of patients.

8.4.1 Clinical implications

Misclassification of COPD versus asthma is a major issue, therefore clinicians should prioritise evaluation and correct classification of pulmonary disease history for those with acute HF. This is relevant in ensuring adequate management and appropriate treatment plans, i.e., balancing use of bronchodilators in COPD in the context of associated increased risk of cardiovascular events and leveraging use of steroids in asthma which have a better safety profile than in COPD.

COPD was associated with a decrease in probability of referral to follow-up to cardiology services, in contrast with asthma, which did not have a significant effect on this outcome. Since careful clinical monitoring post-acute HF has been identified as an important factor in improving long-term prognosis, these results are worrying for HF-COPD comorbid patients. Efforts should be taken to guarantee this subgroup of patients receives the same high-quality care as their HF-alone or asthma-HF counterparts.

Furthermore, both COPD and asthma negatively impacted prescription of post-discharge HF medications and specifically beta-blockers in the HFrEF subgroup. This suggests clinicians may still limit access to life-saving treatment based on fears of bronchoconstriction, which is not based on evidence as demonstrated in the study presented in Chapter 5.

8.4.2 Recommendations for research

A major limitation of this study was lack of data on medications received for COPD and asthma labelled individuals, therefore it was not possible to verify the relationship with outcomes in patients with acute HF. It was also not possible to evaluate healthcare resource used after hospitalisation. Variables such as smoking, BMI and ethnicity had considerable proportions of missing data, and while multiple multi-level imputation was used to mitigate this limitation, future studies should aim to collect these data, in order to confirm results and establish whether the effects of COPD/asthma are truly independent.

8.5 Aim 5 (Acute heart failure): Impact of COPD on readmission in patients hospitalised with heart failure

The immediate post-hospitalisation period has been identified as one where risk for readmission is higher for patients with HF and concomitant COPD, versus those diagnosed with HF alone. The purpose of the study presented in Chapter 7 (Paper 7) was to investigate outcomes relevant in the acute setting, beyond mortality, which was assessed in Chapter 6. I thus evaluated the risk and reasons for short-term readmission associated with COPD in patients hospitalised for HF. COPD was associated with a doubled risk of readmission in the principally HF diagnosed cohort and with increased risk of acute exacerbation due to COPD; however, reasons for readmissions were primarily due to cardiovascular disease.

8.5.1 Clinical implications

Based on these findings, it may be beneficial for clinicians to employ a greater focus on identifying individuals with a diagnosis of COPD who present to hospital with acute HF. While there are no demonstrated integrated treatments for this specific subgroup of patients, it is important that both their cardiac and pulmonary conditions are treated according to the guidelines specific to each disease, in order to prevent short-term readmission to hospital.

As those with HF and COPD are less likely to be managed with prognostically beneficial beta-blockers as showed in the study presented in Chapter 6, it is crucial to ensure discharge medication is aligned with guideline recommendations and that up titration of treatment is achieved, as this may be a particular issue in those with comorbid disease. Conversely, an increased risk of acute exacerbation of COPD in those with HF and comorbid COPD signals under-treatment of the pulmonary disease in the acute HF cohort.

8.5.2 Recommendations for research

While the use of ICD-10 codes has been validated previously in database studies of both HF and COPD, there may still be misclassification in the selected cohort, due to variability in coding practices or financial incentives to up-code severity of comorbidities. A more robust diagnostic assessment should be carried out in future studies.

Reasons for cause-specific admission were defined by the diagnoses recorded in the primary fields during the first 30-day readmission, for each patient. The issue of misattributing COPD exacerbation for HF decompensation (due to similar presentations) has not been completely eliminated and remains an unresolved issue in understanding of the relationship between HF and

COPD, as indicated in the study presented in Chapter 4. One way of attempting to clarify this in future database studies, would be consideration of secondary diagnoses available per patient, per first 30-day readmission as well as using validated algorithms to identify acute exacerbations due to COPD. Based on this, strategies to categorise respiratory respectively cardiac reasons for readmission with greater confidence could be devised, however prospective validation in trials would be needed.

8.6 Overall conclusions

My research focused on assessing to what extent COPD impacts prognosis and management of HF patients and what can be done to improve their outcomes, by using multiple big data sources. In the era of personalised medicine and value-based healthcare, the HF-COPD comorbidity is a key challenge for health care systems, and it is only by considering presentations across the whole spectrum of acute and chronic care that the full burden of disease can be understood and tackled.

I found that COPD is important in HF for two major reasons: first, patients with HF and concomitant COPD have worse outcomes, including mortality and hospitalisation, as well as poorer access to health services compared to those with HF alone. Second, coexisting COPD impacts on the use of specific, prognostically beneficial medication, particularly for those with HFrEF and may partly explain the aforementioned increased risks in adverse clinical events.

Devising new HF phenotypes, beyond the currently accepted systems is a relatively new research endeavour, with algorithms increasing in quantity and sophistication. My results suggested COPD is not a main determinant of comorbidity clusters (phenotypes) in HF; however it appears to determine long-term outcomes in those with HFpEF particularly, in the chronic setting. In the

acute setting, a COPD diagnosis affects mortality of those with HFrEF to a greater degree compared to HFpEF, while readmissions risk is identified as higher amongst individuals with the pulmonary disease, regardless of LVEF status. The relationship between COPD and HF phenotypes, and sub-phenotypes, whether established or emerging, should be investigated further.

One other major overall finding of the work presented in this thesis is the significance of accurately distinguishing between COPD and HFrEF versus HFpEF. Longitudinal studies should identify the ideal diagnostic algorithms needed to accurately separate cardiovascular from respiratory causes of symptoms and the treatments strategies that best treat them should be evaluated in controlled settings, in the context of single versus multiple comorbidities.

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APPENDIX

APPENDIX A: Supplementary material for Chapter 2 *(Data sources)*

APPENDIX B: Supplementary material for Chapter 3 *(Comorbidities in heart failure)*

APPENDIX C: Supplementary material for Chapter 4 *(Differences in outcomes in COPD patients with HF and preserved versus reduced ejection fraction)*

APPENDIX D: Supplementary material for Chapter *5 (Impact of beta-blocker therapy on outcomes in patients with COPD)*

APPENDIX E: Supplementary material for Chapter 6 *(Impact of COPD on in-hospital mortality and management of patients hospitalised for heart failure)*

APPENDIX F: Supplementary material for Chapter 7 *(Impact of COPD on readmission in patients hospitalised for heart failure)*

APPENDIX G: Published and submitted papers

Appendix A: Supplementary material for Chapter 2

DATA USE AGREEMENT for the Nationwide Databases from the Healthcare Cost and Utilization Project Agency for Healthcare Research and Quality

This Data Use Agreement ("Agreement") governs the disclosure and use of data in the HCUP Nationwide Databases from the Healthcare Cost and Utilization Project (HCUP) which are maintained by the Center for Delivery, Organization, and Markets (CDOM) within the Agency for Healthcare Research and Quality (AHRQ). The HCUP Nationwide databases include the National (Nationwide) Inpatient Sample (NIS), Kids' Inpatient Database (KID), Nationwide Emergency Department Sample (NEDS), and Nationwide Readmissions Database (NRD). Any person ("the data recipient") seeking permission from AHRQ to access HCUP Nationwide Databases must sign and submit this Agreement to AHRQ or its agent, and complete the online Data Use Agreement Training Course at www.hcup-us.ahrq.gov, as a precondition to the granting of such permission.

Section 944(c) of the Public Health Service Act (42 U.S.C. 299c-3(c)) ("the AHRQ Confidentiality Statute"), requires that data collected by AHRQ that identify individuals or establishments be used only for the purpose for which they were supplied. Pursuant to this Agreement, data released to AHRQ for the HCUP Databases are subject to the data standards and protections established by the Health Insurance Portability and Accountability Act of 1996 (HIPAA) (P.L. 104-191) and implementing regulations ("the Privacy Rule"). Accordingly, HCUP Databases may only be released in "limited data set" form, as that term is defined by the Privacy Rule, 45 C.F.R. § 164.514(e). HCUP data may only be used by the data recipient for research which may include analysis and aggregate statistical reporting. AHRQ classifies HCUP data as protected health information under the HIPAA Privacy Rule, 45 C.F.R. § 160.103. By executing this Agreement, the data recipient understands and affirms that HCUP data may only be used for the prescribed purposes, and consistent with the following standards:

No Identification of Persons–The AHRQ Confidentiality Statute prohibits the use of HCUP data to identify any person (including but not limited to patients, physicians, and other health care providers). The use of HCUP Databases to identify any person constitutes a violation of this Agreement and may constitute a violation of the AHRQ Confidentiality Statute and the HIPAA Privacy Rule. This Agreement prohibits data recipients from releasing, disclosing, publishing, or presenting any individually identifying information obtained under its terms. AHRQ omits from the data set all direct identifiers that are required to be excluded from limited data sets as consistent with the HIPAA Privacy Rule. AHRQ and the data recipient(s) acknowledge that it may be possible for a data recipient, through deliberate technical analysis of the data sets and with outside information, to attempt to ascertain the identity of particular persons. Risk of individual identification of persons is increased when observations (i.e., individual discharge records) in any given cell of tabulated data is ≤10. This Agreement expressly prohibits any attempt to identify individuals, including by the use of vulnerability analysis or penetration testing. In addition, methods that could be used to identify individuals directly or indirectly shall not be disclosed, released, or published. Data recipients shall not attempt to contact individuals for any purpose whatsoever, including verifying information supplied in the data set. Any questions about the data must be referred exclusively to AHRQ. By executing this Agreement, the data recipient understands and agrees that actual and considerable harm will ensue if he or she attempts to identify individuals. The data recipient also understands and agrees that actual and considerable harm will ensue if he or she intentionally or negligently discloses, releases, or publishes information that identifies individuals or can be used to identify individuals.

Use of Establishment Identifiers–The AHRQ Confidentiality Statute prohibits the use of HCUP data to identify establishments unless the individual establishment has consented. Permission is obtained from the HCUP data sources (i.e., state data organizations, hospital associations, and data consortia) to use the identification of hospital establishments (when such identification appears in the data sets) for research, analysis, and aggregate statistical reporting. This may include linking institutional information from outside data sets for these purposes. Such purpose does *not* include the use of information in the data sets concerning individual establishments for commercial or competitive purposes involving those individual establishments, or to determine the rights, benefits, or privileges of establishments. Data recipients are prohibited from identifying

establishments directly or by inference in disseminated material. In addition, users of the data are prohibited from contacting establishments for the purpose of verifying information supplied in the data set. Any questions about the data must be referred exclusively to AHRQ. Misuse of identifiable HCUP data about hospitals or any other establishment constitutes a violation of this Agreement and may constitute a violation of the AHRQ Confidentiality Statute.

The undersigned data recipients provide the following affirmations concerning HCUP data:

Protection of Individuals

- I will not release or disclose, and will take all necessary and reasonable precautions to prohibit others from releasing or disclosing, any information that directly or indirectly identifies persons. This includes attempts to identify individuals through the use of vulnerability analysis or penetration testing.

- I acknowledge that the release or disclosure of information where the number of observations (i.e., individual discharge records) in any given cell of tabulated data is ≤10 can increase the risk for identification of persons. I will consider this risk and avoid publication of a cell containing a value of 1 to 10.

- I will not attempt to link, and will prohibit others from attempting to link, the discharge records of persons in the data set with individually identifiable records from any other source.

- I will not attempt to use and will take all necessary and reasonable precautions to prohibit others from using the data set to contact any persons in the data for any purpose.

Protection of Establishments

- I will not publish or report, through any medium, data that could identify individual establishments directly or by inference.

- When the identities of establishments are not provided in the data sets, I will not attempt to use and will take all necessary and reasonable precautions to prohibit others from using the data set to learn the identity of any establishment.

- I will not use and will take all necessary and reasonable precautions to prohibit others from using the data set concerning individual establishments: (1) for commercial or competitive purposes involving those individual establishments; or (2) to determine the rights, benefits, or privileges of individual establishments.

- I will not contact and will take all necessary and reasonable precautions to prohibit others from contacting establishments identified in the data set to question, verify, or discuss data in the HCUP databases.

- I acknowledge that the HCUP NIS, KID, and NRD may contain data elements from proprietary restricted computer software (e.g., 3M™ APR DRGs) supplied by private vendors to AHRQ for the sole purpose of supporting research and analysis with the HCUP NIS, KID, and NRD. While I may freely use these data elements in my research work using the HCUP NIS, KID, and NRD I agree that I will not use and will prohibit others from using these proprietary data elements for any commercial purpose. In addition, I will enter into a separate agreement with the appropriate organization or firm for the right to use such proprietary data elements for commercial purposes. In particular, I agree not to disassemble, decompile, or otherwise reverse-engineer the proprietary software, and I will prohibit others from doing so.

Limitations on the Disclosure of Data and Safeguards

- I acknowledge and affirm that I am personally responsible for compliance with the terms of this Agreement, to the exclusion of any other party, regardless of such party's role in sponsoring or funding the research that is the subject of this Agreement.

- I will only allow access to HCUP Nationwide data to those who have become authorized users of the HCUP data by signing a copy of this Data Use Agreement and completing the online Data Use Agreement Training Course at www.hcup-us.ahrq.gov. Before granting any individual access to the data set, I will submit the signed data use agreements to the address at the end of this Agreement.

- I will not use or disclose and I will prohibit others from using or disclosing the data set, or any part thereof, except for research, analysis, and aggregate statistical reporting, and only as permitted by this Agreement.

- I will not redistribute HCUP data by posting on any Website or other publicly-accessible online repository.

- I will ensure that the data are kept in a secured environment and that only authorized users will have access to the data.

- I acknowledge and affirm that interpretations, conclusions, and/or opinions that I reach as a result of my analyses of the data sets are my interpretations, conclusions, and/or opinions, and do not constitute the findings, policies, or recommendations of the U.S. Government, the U.S. Department of Health and Human Services, or AHRQ.

- I agree to acknowledge in all reports based on these data that the source of the data is the "National Inpatient Sample (NIS), Healthcare Cost and Utilization Project (HCUP), Agency for Healthcare Research and Quality." Substitute "Nationwide Inpatient Sample (NIS)" (if using data prior to 2012), "Kids' Inpatient Database (KID)," "Nationwide Emergency Department Sample (NEDS)," or "Nationwide Readmissions Database (NRD)" as appropriate.

- I will indemnify, defend, and hold harmless AHRQ and the data organizations that provide data to AHRQ for HCUP from any or all claims and losses accruing to any person, organizations, or other legal entity as a result of violation of this Agreement. This provision applies only to the extent permitted by Federal and State law.

- I agree to report the violation or apparent violation of any term of this Agreement to AHRQ without unreasonable delay and in no case later than 30 calendar days of becoming aware of the violation or apparent violation.

Terms, Breach, and Compliance

Any violation of the terms of this Agreement shall be grounds for immediate termination of this Agreement. AHRQ shall determine whether a data recipient has violated any term of the Agreement. AHRQ shall determine what actions, if any, are necessary to remedy a violation of this Agreement, and the data recipient(s) shall comply with pertinent instructions from AHRQ. Actions taken by AHRQ may include but not be limited to providing notice of the termination or violation to affected parties and prohibiting data recipient(s) from accessing HCUP data in the future.

In the event AHRQ terminates this Agreement due to a violation, or finds the data recipient(s) to be in violation of this Agreement, AHRQ may direct that the undersigned data recipient(s) immediately return all copies of the HCUP Nationwide Databases to AHRQ or its designee without refund of purchase fees.

Acknowledgment

I understand that this Agreement is requested by the United States Agency for Healthcare Research and Quality to ensure compliance with the AHRQ Confidentiality Statute. My signature indicates that I understand the terms of this Agreement and that I agree to comply with its terms. I understand that a violation of the AHRQ Confidentiality Statute may be subject to a civil penalty of up to $14,140 under 42 U.S.C. 299c-3(d), and that deliberately making a false statement about this or any matter within the jurisdiction of any department or agency of the Federal Government violates 18 U.S.C. § 1001 and is punishable by a fine, up to five years in prison, or both. Violators of this Agreement may also be subject to penalties under state confidentiality statutes that apply to these data for particular states.

Signed: _____ Date: 8 Nov 2018

Print or Type Name: CLAUDIA GULEA

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The information above is maintained by AHRQ only for the purpose of enforcement of this Agreement and for notification in the event data errors occur.

Note to Purchaser: Shipment of the requested data product will only be made to the person who signs this Agreement, unless special arrangements that safeguard the data are made with AHRQ or its agent.

Submission Information

Please send signed HCUP Data Use Agreements and proof of online training to:

HCUP Central Distributor
Social & Scientific Systems, Inc.
8757 Georgia Avenue, 12th Floor
Silver Spring, MD 20910
E-mail: HCUPDistributor@AHRQ.gov
Fax: (866) 792-5313

According to the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number. The valid OMB control number for this information collection is 0935-0206. The time required to complete this information collection is estimated to average 30 minutes per response, including the time to review instructions, search existing data resources, gather the data needed, and complete and review the information collection. If you have any comments concerning the accuracy of the time estimate(s) or suggestions for improving this form, please write to: Agency for Healthcare Research and Quality, Attn: Reports Clearance Officer, 5600 Fishers Lane, Rockville, Maryland 20857.

OMB Control No. 0935-0206 expires 01/31/2019.

FIGURE A 1: HCUP Data User Agreement

Go straight to content.

MRC Medical Research Council

NHS Health Research Authority

Do I need NHS REC approval?

To print your result with title and IRAS Project ID please enter your details below:

Title of your research:

Impact of chronic obstructive pulmonary disease (COPD) on management and outcomes of patients hospitalised with heart failure

IRAS Project ID (if available):

Your answers to the following questions indicate that **you do not need NHS REC approval for sites in England.** However, **you may need other approvals.**

You have answered ***'YES'*** to: Is your study research?

You answered ***'NO'*** to all of these questions:

Question Set 1

- Is your study a clinical trial of an investigational medicinal product?
- Is your study one or more of the following: A non-CE marked medical device, or a device which has been modified or is being used outside of its CE mark intended purpose, and the study is conducted by or with the support of the manufacturer or another commercial company (including university spin-out company) to provide data for CE marking purposes?
- Does your study involve exposure to any ionising radiation?
- Does your study involve the processing of disclosable protected information on the Register of the Human Fertilisation and Embryology Authority by researchers, without consent?

Question Set 2

- Will your study involve potential research participants identified in the context of, or in connection with, their past or present use of services (adult and children's healthcare within the NHS and adult social care), including participants recruited through these services as healthy controls?

FIGURE A 2: Health Research Authority Decision Tool

Appendix B: Supplementary material for Chapter 3

TABLE B 1: ICD codes used to identify comorbidities of patients with heart failure

Comorbidity	ICD-9/10 Codes
Atrial fibrillation	I48, I480, I481, I482, I483, I484, I489, I4891 I4892, 42731, 42732
Alcohol misuse disorder	2910, 2911, 2912, 2913, 2915, 29181, 29182 29189, 2919, 30300, 30301, 30302, 30303, 30390, 30391, 30392, 30393, 30500, 30501 30502, 30503, V113, F10231, F1096, F1027 F10951, F10950, F10239, F10182, F10282 F10982, F10159, F10180, F10181, F10188 F10259, F10280, F10281, F10288, F10959 F10980, F1099, F10229, F10229, F10229 F10229, F1020, F1020, F1020, F1021, F1010 F1010, F1010, F1011, Z658
Anaemia	D500, D508, D501, D508, D509, D510, D511, D513, D518, D520 D521, D528, D529, D531, D530, D532, D538, D539, D631, D630 D638, D649, O99019, O99011, O99012, O99013, O9902, O9903 O99011, O99012, O99013, O9081, O9903, 2800, 64820, 64821, 64822, 64823, 64824, 2801, 2808, 2809, 2800, 280, 28521, 28522 28529, 2859, 2858
CAD	4110, 4111, 41181, 41189, 412, 4130, 4131, 4139, 41400, 41401-06, 4142-4, 4148-9, V4581, V4582, I25- I2542, I255-57, I2570, I25700, I25701, I25708, I25709, I2571, I25710, I25711, I25718, I25719, I2572, I25720, I25721, I25728, I25729, I2573, I25730, I25731, I25738, I25739, I2575, I25750, I25751, I25758, I25759, I2576, I25760, I25761, I25768, I25769, I2579, I25790, I25791, I25798, I25799, I258, I25810-12, I2582-4, I2589, I259, I200, I241, I201, I1248, I208, I209, Z951, Z9861
Cancer	C codes; D00 – D48, 1400-20892; 1960-1991; 19881-2; 19889
COPD	491, 491, 4911, 49122, 4912, 4918, 4919, 492, 492, 4928, 496, J43 J448, J449, J430, J431, J432, J438, J439, J440, J44
CVA	G450-G462; I61-63; I6781-2, I67841-8; I691-I693, Z8673, 430-438
Dementia	F00-F03, F051, F107, G30-G318, 290x
Depression	F32-F224; F920, F412; ICD9: 3004, 30112, 3090-1, 311
Diabetes	E10-E149, G590, G632, H280, H360, M142, N083, O240, O241, O243, 2500-09
Hypertension	401-405, 642, I10-I15, O10, O11, O16
Liver disease	B18, I85, K70-K76; Z944, 702-5, 456, 671, V427
Obesity	27800, 27801, E669, E6601, E661
PAD	I70-I73, I771, K551, K559, Z95828, 442, 443, 447, 5571-9
Peptic ulcer	531, 532, 533, 534, K25, K26
Renal failure	N18, I12, I13, E082, E092, E102, E112, E132Z940, 403, 404585, V420, V4511, V560, V561, V562, V568, V451

CAD= coronary artery disease; COPD= chronic obstructive pulmonary disease; CVA= cerebrovascular accident; PAD = peripheral arterial disease

TABLE B 2: Medication classes captured from pharmacy claims

Cardioselective beta-blockers	Noncardioselective beta-blockers	ACEi/ARBs	MRA	Loop diuretics	Thiazide diuretics	Potassium-sparing diuretics
acebutolol, atenolol, betaxolol, bisoprolol, betoprolol, nebivolol	carvedilol, nadolol, labetalol, penbutolol, pindolol propranolol	captopril, enalapril, lisinopril, ramipril, trandolapril, fosinopril, perindopril or candesartan, valsartan, losartan, telmisartan, irbesartan, quinapril	eplerenone, spironolactone	furosemide, bumetanide, torasemide	bendroflumethiazide, hydrochlorothiazide, metolazone, indapamide	amiloride, triamterene,

ACEi= angiotensin-converting-enzyme inhibitors; ARBs= angiotensin II receptor blockers; MRA= mineralocorticoid receptor

TABLE B 3: AMA, revenue and CPT codes used to identify hospitalisations, ER and outpatient visits

AMA Code	Description
11	Ambulatory care facility
21	Inpatient hospital
22	Outpatient hospital
23	Emergency room
31	Skilled nursing facility
32	Nursing facility
33	Custodial care facility
34	Hospice
24	Ambulatory surgical centre
51	Inpatient psychiatric facility
53	Community mental health centre
54	Intermediate care facility for mentally retarded
55	Residential substance abuse treatment facility
56	Psychiatric residential treatment facility
61	Comprehensive inpatient rehabilitation facility
62	Comprehensive outpatient rehabilitation facility
65	End-stage renal disease treatment facility
71	State or local public health clinic
72	Rural health clinic
Revenue code	
0450 – 0455	Emergency room
0457-0457	Emergency room
0981	Emergency room
0456	Urgent care
CPT code	
99281	Emergency department visit, minor problems

AMA Code	Description
99282	Emergency department visit, low to moderate severity of problems
99283	Emergency department visit, moderate severity of problems
99284	Emergency department visit, immediate high severity but no threat to life or physiologic function
99285	Emergency department visit, immediate high severity with significant threat to life or physiologic function
99288	Physician direction of emergency medical systems

AMA= American Medical Association; CPT= Current Procedural Terminology; ER= emergency room

TABLE B 4: Costs associated with healthcare resource use, per comorbidity cluster, within one-year follow-up (currency United States dollars $)

Cost (median, IQR)	Low-burden	Metabolic-vascular	Ischemic	Anaemia	Metabolic	Overall	P-Value[a]
N	24753	37011	42484	6459	21208	131915	
Inpatient admissions	10400 [3350, 25700]	15600 [6710, 37200]	12800 [4910, 31100]	12800 [4730, 30400]	12800 [5360, 28800]	13200 [5250, 31600]	<0.001
N	30382	45134	47694	7289	27836	158335	
ER visits	821 [299, 1950]	1030 [369, 2540]	798 [267, 1950]	915 [335, 2200]	1040 [396, 2520]	912 [332, 2240]	<0.001
N	66025	64773	73067	12742	52529	269136	
Outpatient visits	1710 [441, 5070]	3080 [934, 8160]	2270 [625, 6250]	2770 [735, 9180]	2290 [637, 6430]	2320 [632, 6520]	<0.001
N	78958	69040	78523	13560	60222)	300303	
Office visits	1310 [633, 2440]	1720 [808, 3210]	1650 [781, 3090]	1490 [651, 3170]	1460 [711, 2740]	1520 [720, 2880]	<0.001
N	6123	13109	16323	2293	4618	42466	
Long-term stays	423 [191, 894]	589 [251, 1350]	531 [229, 1180]	499 [198, 1100]	495 [226, 1090]	523 [227, 1170]	<0.001[b]
N	72729	82259	82460	14753	62725	314926	
All medical claims	5580 [2040, 17200]	15100 [4940, 41400]	12700 [4390, 35500]	11400 [3710, 36500]	7870 [2780, 22700]	9700 [3230, 29100]	
N	72729	82259	82460	14753	62725	314926	
Overall cost	7150 [2750, 19300]	16900 [6000, 43200]	14400 [5670, 36800]	13200 [4340, 40000]	9940 [3630, 25800]	11500 [4160, 31200]	<0.001

IQR, inter-quartile range; ER, emergency room

[a] Bonferroni adjusted Kruskall-Wallis test was used to compare proportions between clusters (and Dunn post-hoc test to identify significant paired comparisons).

[b] Low-burden vs. metabolic not significant.

TABLE B 5: Competing risk analysis (death as competing risk to hospitalisation)

	Adjusted HR (95%CI)
Age (years)	0.99 (0.99 – 0.99)
Sex (male vs. female)	0.98 (0.97 – 0.99)
Race (ref: White)	
Black	1 (0.99 – 1.02)
Hispanic	0.90 (0.89 - 93)
Asian	0.86 (0.82 – 0.90)
Comorbidities	
Hypertension	1.58 (1.51 – 1.64)
Peptic ulcer	1.42 (1.40 – 1.46)
Dementia	1.15 (1.13 – 1.77)
Alcohol misuse disorder	1.22 (1.18 – 1.27)
Education (ref: Bachelor Degree +)	
High School Diploma	1.04 (1.02 – 1.06)
Less than 12 grade	1.04 (0.94 – 1.15)
Less than Bachelor Degree	1.01 (0.99 – 1.03)
Commercial vs. Medicare Advantage	0.88 (0.86 – 0.89)
Inpatient vs. outpatient diagnosis	1.26 (1.25 – 1.27)
Medications at baseline	
Cardioselective beta-blockers	0.97 (0.96 – 0.98)
Nonselective beta-blockers	0.99 (0.98 – 1.01)
ACEIs/ARBs	0.98 (0.97 – 0.99)
MRA	0.98 (0.96 – 1.01)
Thiazide diuretics	1.03 (1.01 – 1.05)
Potassium-sparing diuretics	1.22 (1.03 – 1.44)
Loop diuretics	1.17 (1.16 – 1.19)
Comorbidity cluster (ref: Low-burden)	
Metabolic-vascular	2.21 (2.17 - 2.25)
Ischemic	2.07 (2.04 – 2.11)
Anaemia	1.5 (1.44 – 1.54)
Metabolic	1.16 (1.14 – 1.19)

ACEi: angiotensin-converting-enzyme inhibitors; ARB: angiotensin receptor blocker; CI: confidence intervals; HR: hazard ratio; ref= reference; MRA: mineralocorticoid receptor antagonist

TABLE B 6: Association between mortality and comorbidity cluster with interaction between ejection fraction and cluster, including coefficients and standard errors for interaction terms

	Unadjusted model			Adjusted model[a]		
Term	Coefficient	SE	P Value	Coefficient	SE	P Value
LVEF	0.00066	0.0007	0.379	-0.0012	0.002	0.613
Anaemia	-0.0932	0.3812	=0.806	-0.1456	0.423	0.730
Ischemic	0.7996	0.1082	<0.001	0.541	0.164	<0.01
Metabolic-vascular	0.6699	0.1414	<0.001	0.573	0.189	<0.01
Metabolic	-0.6898	0.2050	<0.001	-0.433	0.252	0.08
Interactions						
Anaemia * LVEF	0.01366	0.0064	0.035	0.011	0.007	0.132
Ischemic * LVEF	-0.00012	0.0018	0.945	-0.001	0.003	0.709
Metabolic-vascular * LVEF	0.0001	0.0024	0.967	-0.0018	0.003	0.606
Metabolic * LVEF	0.00934	0.0036	0.010	0.007	0.004	0.113

SE= standard error; LVEF= left ventricular ejection fraction.

[a] Adjusted for age, sex, race, education, medical insurance status, whether diagnosis was gained in-patient or in out-patient, heart failure medications (angiotensin-converting-enzyme inhibitors, angiotensin receptor blockers, mineralocorticoid receptor antagonists) and smoking status

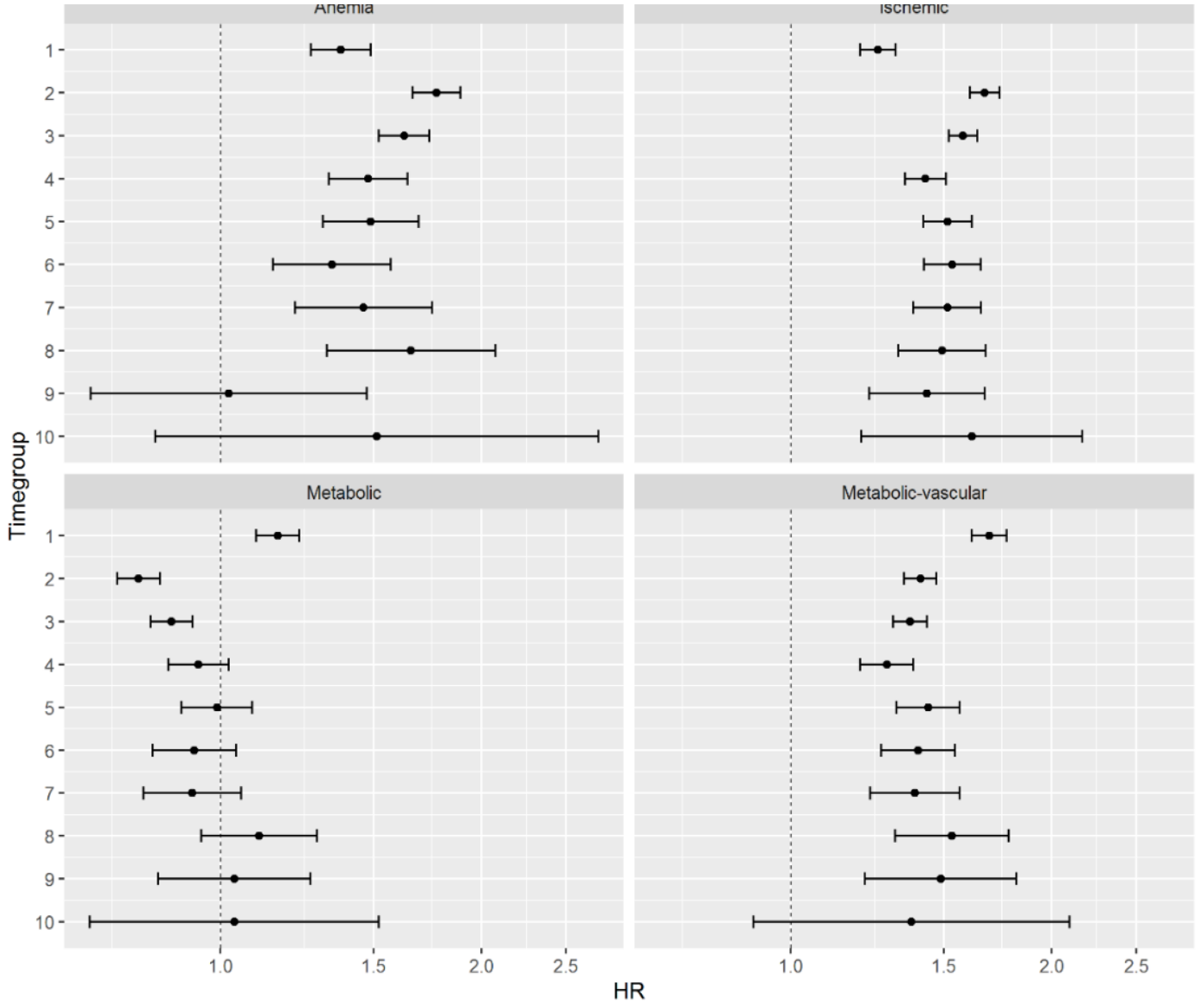

FIGURE B 1: Hazard ratios (95%CI) for mortality per time group, denoting comparison with reference group low-burden.

In the first 12 months of follow up (time group 1), the risk of death associated with all clusters was higher compared to the low-burden group. The association between the anaemic, ischemic and metabolic-vascular clusters with risk of death, remained positive though lost significance in the last two periods for the anaemic cluster, respectively last period for the metabolic vascular cluster. Notably, the metabolic group was the only cluster that was associated with a decrease in risk of death – but only during time groups 2 and 3 (from 24 to 54 months).

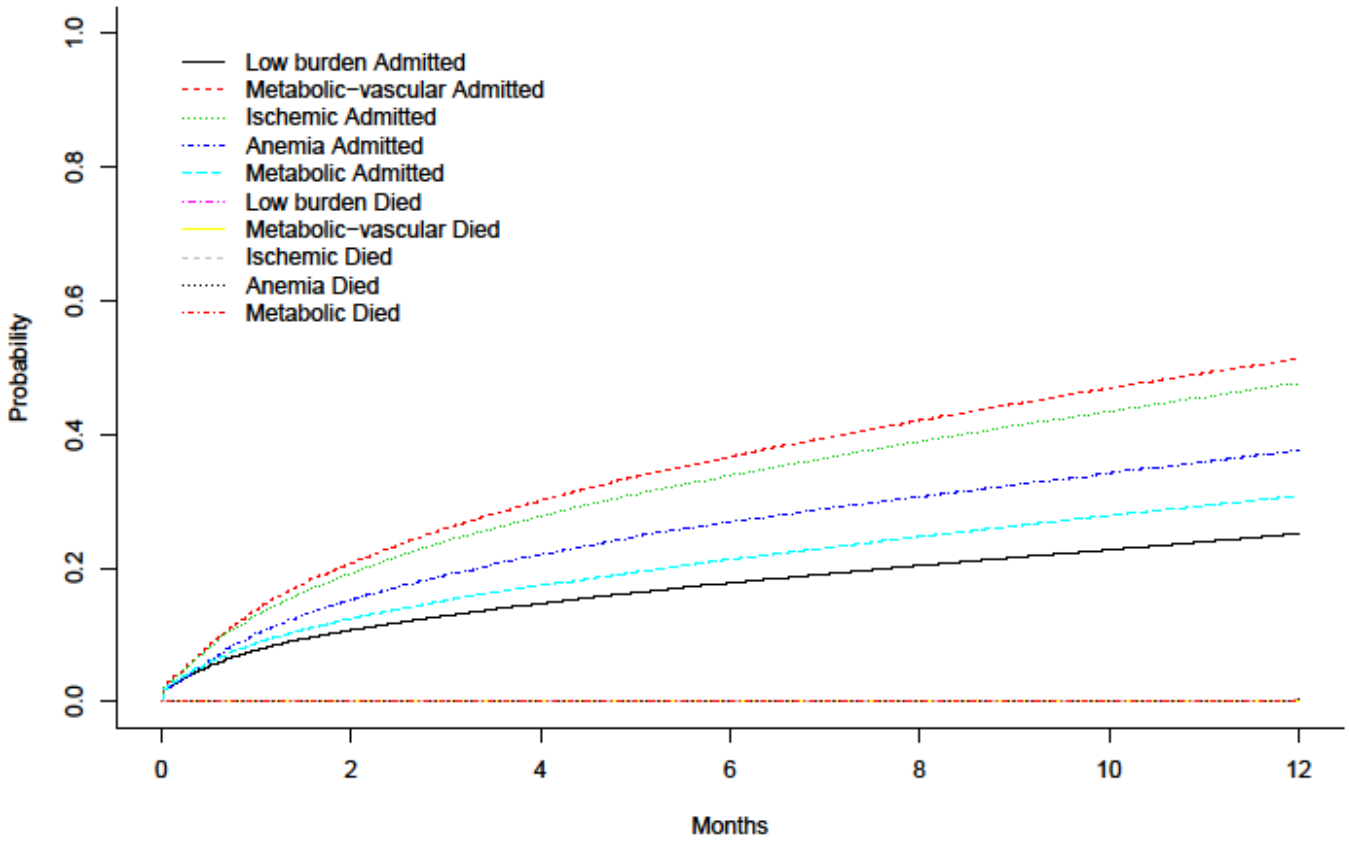

FIGURE B 2: Cumulative incidence of admission to hospital and death as competing risk in patients with HF, per comorbidity cluster within one year follow-up (Gray's test for equality, p <0.001, admission, death)

Appendix C: Supplementary material for Chapter 4

TABLE C 1: COPD medication categories

COPD medication regimens							
Short acting bronchodilator			Long-acting bronchodilator		ICS containing regimen		
SABA only	SAMA only	SAMA or SAMA	LAMA or LABA	LAMA and LABA	ICS + LAMA +LABA	ICS + LAMA	ICS only

SABA= short-acting beta-agonist; SAMA= Short-acting muscarinic antagonist; LAMA= long-acting muscarinic antagonist; LABA= long-acting beta-agonist; ICS= inhaled corticosteroids.
NDC codes used available here: https://www.ncqa.org/hedis/measures/hedis-2019-ndc-license/hedis-2019-final-ndc-lists/

TABLE C 2: Codes used to identify administration of steroids or antibiotics

Code	Type	Description	Class
C9034	HCPCS	Injection dexamethasone 9% intraocular 1 mcg	Steroid
C9048	HCPCS	Dexamethasone lacrimal ophthalmic insert 01 mg	Steroid
C9469	HCPCS	Injection triamcinolone acetonide preservative-free extended-release microsphere formulation 1 mg	Steroid
G2112	HCPCS	Patient receiving ≤5 mg daily prednisone (or equivalent) or ra activity is worsening or glucocorticoid use is for less than 6 months	Steroid
G2113	HCPCS	Patient receiving >5 mg daily prednisone (or equivalent) for longer than 6 months and improvement or no change in disease activity	Steroid
G9467	HCPCS	Patient who have received or are receiving corticosteroids greater than or equal to 10 mg/day of prednisone equivalents for 60 or greater consecutive days or a single prescription equating to 600 mg prednisone or greater for all fills within the last twelve months	Steroid
G9468	HCPCS	Patient not receiving corticosteroids greater than or equal to 10 mg/day of prednisone equivalents for 60 or greater consecutive days or a single prescription equating to 600 mg prednisone or greater for all fills	Steroid
G9469	HCPCS	Patients who have received or are receiving corticosteroids greater than or equal to 10 mg/day of prednisone equivalents for 90 or greater consecutive days or a single prescription equating to 900 mg prednisone or greater for all fills	Steroid
G9470	HCPCS	Patients not receiving corticosteroids greater than or equal to 10 mg/day of prednisone equivalents for 60 or greater consecutive days or a single prescription equating to 600 mg prednisone or greater for all fills	Steroid
J0702	HCPCS	Injection betamethasone acetate 3 mg and betamethasone sodium phosphate 3 mg	Steroid
J1020	HCPCS	Injection methylprednisolone acetate 20 mg	Steroid
J1030	HCPCS	Injection methylprednisolone acetate 40 mg	Steroid
J1040	HCPCS	Injection methylprednisolone acetate 80 mg	Steroid
J1094	HCPCS	Injection dexamethasone acetate 1 mg	Steroid
J1095	HCPCS	Injection dexamethasone 9 percent intraocular 1 microgram	Steroid
J1096	HCPCS	Dexamethasone lacrimal ophthalmic insert 01 mg	Steroid
J1100	HCPCS	Injection dexamethasone sodium phosphate 1 mg	Steroid
J1700	HCPCS	Injection hydrocortisone acetate up to 25 mg	Steroid
J1710	HCPCS	Injection hydrocortisone sodium phosphate up to 50 mg	Steroid
J1720	HCPCS	Injection hydrocortisone sodium succinate up to 100 mg	Steroid
J2650	HCPCS	Injection prednisolone acetate up to 1 ml	Steroid
J2920	HCPCS	Injection methylprednisolone sodium succinate up to 40 mg	Steroid
J2930	HCPCS	Injection methylprednisolone sodium succinate up to 125 mg	Steroid

Code	Type	Description	Class
J3300	HCPCS	Injection triamcinolone acetonide preservative free 1 mg	Steroid
J3301	HCPCS	Injection triamcinolone acetonide not otherwise specified 10 mg	Steroid
J3302	HCPCS	Injection triamcinolone diacetate per 5 mg	Steroid
J3303	HCPCS	Injection triamcinolone hexacetonide per 5 mg	Steroid
J3304	HCPCS	Injection triamcinolone acetonide preservative-free extended-release microsphere formulation 1 mg	Steroid
J7312	HCPCS	Injection dexamethasone intravitreal implant 01 mg	Steroid
J7506	HCPCS	Prednisone oral per 5 mg	Steroid
J7509	HCPCS	Methylprednisolone oral per 4 mg	Steroid
J7510	HCPCS	Prednisolone oral per 5 mg	Steroid
J7512	HCPCS	Prednisone immediate release or delayed release oral 1 mg	Steroid
J7624	HCPCS	Betamethasone inhalation solution compounded product administered through dme unit dose form per milligram	Steroid
J7637	HCPCS	Dexamethasone inhalation solution compounded product administered through dme concentrated form per milligram	Steroid
J7638	HCPCS	Dexamethasone inhalation solution compounded product administered through dme unit dose form per milligram	Steroid
J7683	HCPCS	Triamcinolone inhalation solution compounded product administered through dme concentrated form per milligram	Steroid
J7684	HCPCS	Triamcinolone inhalation solution compounded product administered through dme unit dose form per milligram	Steroid
J8540	HCPCS	Dexamethasone oral 025 mg	Steroid
Q9993	HCPCS	Injection triamcinolone acetonide preservative-free extended-release microsphere formulation 1 mg	Steroid
C9479	HCPCS	Instillation ciprofloxacin otic suspension 6 mg	Antibiotic
G9313	HCPCS	Amoxicillin with or without clavulanate not prescribed as first line antibiotic at the time of diagnosis for documented reason	Antibiotic
G9314	HCPCS	Amoxicillin with or without clavulanate not prescribed as first line antibiotic at the time of diagnosis reason not given	Antibiotic
G9315	HCPCS	Documentation amoxicillin with or without clavulanate prescribed as a first line antibiotic at the time of diagnosis	Antibiotic
J0120	HCPCS	Injection tetracycline up to 250 mg	Antibiotic
J0200	HCPCS	Injection alatrofloxacin mesylate 100 mg	Antibiotic
J0290	HCPCS	Injection ampicillin sodium 500 mg	Antibiotic
J0295	HCPCS	Injection ampicillin sodium/sulbactam sodium per 15 gm	Antibiotic
J0456	HCPCS	Injection azithromycin 500 mg	Antibiotic
J0558	HCPCS	Injection penicillin g benzathine and penicillin g procaine 100000 units	Antibiotic
J0561	HCPCS	Injection penicillin g benzathine 100000 units	Antibiotic
J0690	HCPCS	Injection cefazolin sodium 500 mg	Antibiotic
J0692	HCPCS	Injection cefepime hydrochloride 500 mg	Antibiotic
J0694	HCPCS	Injection cefoxitin sodium 1 gm	Antibiotic

Code	Type	Description	Class
J0696	HCPCS	Injection ceftriaxone sodium per 250 mg	Antibiotic
J0697	HCPCS	Injection sterile cefuroxime sodium per 750 mg	Antibiotic
J0698	HCPCS	Injection cefotaxime sodium per gm	Antibiotic
J0713	HCPCS	Injection ceftazidime per 500 mg	Antibiotic
J0714	HCPCS	Injection ceftazidime and avibactam 05 g/0125 g	Antibiotic
J0744	HCPCS	Injection ciprofloxacin for intravenous infusion 200 mg	Antibiotic
J1364	HCPCS	Injection erythromycin lactobionate per 500 mg	Antibiotic
J1956	HCPCS	Injection levofloxacin 250 mg	Antibiotic
J2010	HCPCS	Injection lincomycin hcl up to 300 mg	Antibiotic
J2265	HCPCS	Injection minocycline hydrochloride 1 mg	Antibiotic
J2280	HCPCS	Injection moxifloxacin 100 mg	Antibiotic
J2400	HCPCS	Injection chloroprocaine hydrochloride per 30 ml	Antibiotic
J2460	HCPCS	Injection oxytetracycline hcl up to 50 mg	Antibiotic
J2510	HCPCS	Injection penicillin g procaine aqueous up to 600000 units	Antibiotic
J2540	HCPCS	Injection penicillin g potassium up to 600000 units	Antibiotic
J2543	HCPCS	Injection piperacillin sodium/tazobactam sodium 1 gram/0125 grams (1125 grams)	Antibiotic
J2700	HCPCS	Injection oxacillin sodium up to 250 mg	Antibiotic
J7342	HCPCS	Instillation ciprofloxacin otic suspension 6 mg	Antibiotic
Q0144	HCPCS	Azithromycin dihydrate oral capsules/powder 1 gram	Antibiotic
S0032	HCPCS	Injection nafcillin sodium 2 grams	Antibiotic
S0034	HCPCS	Injection ofloxacin 400 mg	Antibiotic
S0074	HCPCS	Injection cefotetan disodium 500 mg	Antibiotic
S0077	HCPCS	Injection clindamycin phosphate 300 mg	Antibiotic
S0081	HCPCS	Injection piperacillin sodium 500 mg	Antibiotic
4041F	CPT-4	DOC ORDER CEFAZOLIN/CEFUROXIME ANTIMICRB PROPHYL	Antibiotic

CPT= Current Procedural Terminology; HCPCS= Healthcare Common Procedure Coding System

TABLE C 3: Comparison of patient characteristics between patients with HF, with and without LVEF recording available in OLDW

	HF with EF data (N=13,560)	HF without EF data (N=304,824)	Overall (N=318,384)
Age, median [IQR]	73.0 [64, 80]	73 [63, 80]	73.0 [63, 80]
Sex (male vs. female)	7167 (52.9%)	147697 (48.5%)	154864 (48.6%)
Comorbidities			
COPD	5419 (40.0%)	120969 (39.7%)	126388 (39.7%)
AF	6385 (47.1%)	117781 (38.6%)	124166 (39.0%)
Alcohol misuse disorder	466 (3.4%)	8922 (2.9%)	9388 (2.9%)
Anemia	3922 (28.9%)	92304 (30.3%)	96226 (30.2%)
CAD	10231 (75.4%)	205463 (67.4%)	215694 (67.7%)
CVA	5751 (42.4%)	123664 (40.6%)	129415 (40.6%)
Liver disease	1798 (13.3%)	36581 (12.0%)	38379 (12.1%)
Cancer	2983 (22.0%)	64669 (21.2%)	67652 (21.2%)
Dementia	756 (5.6%)	24234 (8.0%)	24990 (7.8%)
Depression	2380 (17.6%)	48906 (16.0%)	51286 (16.1%)
Diabetes	6343 (46.8%)	132879 (43.6%)	139222 (43.7%)
PAD	6685 (49.3%)	134962 (44.3%)	141647 (44.5%)
Hypertension	12942 (95.4%)	290284 (95.2%)	303226 (95.2%)
Renal failure	3494 (25.8%)	63574 (20.9%)	67068 (21.1%)
Peptic ulcer	850 (6.3%)	15173 (5.0%)	16023 (5.0%)
Obesity	5969 (44%)	60967 (20%)	66936 (21.0%)
In-patient diagnosis	7618 (56.2%)	155826 (51.1%)	163444 (51.3%)
Insurance status			
Medicare	10021 (73.9%)	210458 (69.0%)	220479 (69.2%)
Commercial	3539 (26.1%)	94366 (31.0%)	97905 (30.8%)
Education			
Bachelor Degree Plus	1850 (13.6%) *>1500 (>12%)	35185 (11.5%)	37035 (11.6%)
High School Diploma	3931 (29%)	106566 (35%)	110497 (34.7%)
Less than 12 grade	*<11 (<0.2%)	1039 (0.3%)	1047 (0.3%)
Less than Bachelor Degree	7707 (56.8%)	159997 (52.5%)	167704 (52.7%)
Missing	64 (0.5%)	2037 (0.7%)	2101 (0.7%)
Income			
<$40,000	4022 (29.7%)	97495 (32.0%)	101517 (31.9%)
$40,000-$74,000	3792 (28.0%)	79501 (26.1%)	83293 (26.2%)
$75,000-$124,999	2895 (21.3%)	56195 (18.4%)	59090 (18.6%)
$125,000-$199,999	929 (6.9%)	18640 (6.1%)	19569 (6.1%)
$200,000+	434 (3.2%)	8550 (2.8%)	8984 (2.8%)
Missing	1488 (11.0%)	44443 (14.6%)	45931 (14.4%)

	HF with EF data (N=13,560)	HF without EF data (N=304,824)	Overall (N=318,384)
Race			
White	10596 (78.1%)	210824 (69.2%)	221420 (69.5%)
Asian	147 (1.1%)	6213 (2.0%)	6360 (2.0%)
Black	1566 (11.5%)	44676 (14.7%)	46242 (14.5%)
Hispanic	444 (3.3%)	22331 (7.3%)	22775 (7.2%)
Missing	807 (6.0%)	20780 (6.8%)	21587 (6.8%)

AF= atrial fibrillation; CAD=coronary artery disease; COPD= chronic obstructive pulmonary disease; CVA= cerebrovascular disease; HFmEF= heart failure with mid-range ejection fraction; HFpEF= heart failure with preserved ejection fraction HFrEF= heart failure with reduced ejection fraction; IQR= inter-quartile range; PAD= peripheral artery disease; OLDW= OptumLabs Data Warehouse; U.S= United States;
* Exact numbers not presented in order to comply with OptumLabs cell size suppression policy

TABLE C 4: Costs associated with healthcare resource use, according to LVEF phenotype, in a cohort of patients with COPD-HF, within one-year of HF diagnosis (currency United States dollars, $)

Cost ($)	HFpEF (n=2025)	HFmEF (n=272)	HFrEF (n=493)	Overall (n=2790)	P- Value
Inpatient admissions					NS
Median [IQR]	13900 [5800, 33000]	18400 [6300, 34600]	16500 [7220, 36800]	14400 [5980, 34100]	
ER	HFpEF (n=2452)	HFmEF (n=331)	HFrEF (n=565)	Overall (n=3348)	NS
Median [IQR]	1070 [364, 2630]	997 [369, 2360]	963 [340, 2310]	1040 [361, 2530]	
Outpatient	HFpEF (n=3515)	HFmEF (n=507)	HFrEF (n=927)	Overall (n=4949)	<0.01
Median [IQR]	2900 [900, 7490]	2550 [857, 6560]	3510 [1100, 8960]	2960 [938, 7630]	
Office visits	HFpEF (n=3652)	HFmEF (n=541)	HFrEF (n=977)	Overall (n=5170)	NS
Median [IQR]	1610 [816, 2910]	1480 [808, 2850]	1650 [877, 2890]	1610 [829, 2900]	
Long-term care	HFpEF (n=773)	HFmEF (n=81)	HFrEF (n=131)	Overall (n=985)	NS
Median [IQR]	576 [242, 1190]	505 [207, 972]	512 [266, 1130]	559 [242, 1170]	
Medical claims					
Median [IQR]	15500 [5130, 38800]	13600 [4660, 35300]	17100 [5690, 41900]	15400 [5150, 39100]	=0.05
Other	HFpEF (n=3805)	HFmEF (n=560)	HFrEF (n=1000)	Overall (n=5365)	<0.001
Median [IQR]	1640 [300, 6360]	925 [143, 3580]	1140 [161, 5290]	1450 [247, 5860]	
Overall	HFpEF (n=3798)	HFmEF (n=558)	HFrEF (n=998)	Overall (n=5354)	p=0.06
Median [IQR]	17100 [6170, 40500]	15000 [5550, 37100]	19100 [7040, 42300]	17100 [6310, 40500]	

HFpEF= heart failure with preserved ejection fraction; HFmEF= heart failure with mid-range ejection fraction; HFrEF= heart failure with reduced ejection fraction; IQR, inter-quartile range; ER, emergency room; NS= not significant

Appendix D: Supplementary material for Chapter 5

TABLE D 1: Search strategy

Embase and Medline (via Ovid)

1.	**Lung Diseases, Obstructive/**
2.	exp Pulmonary Disease, Chronic Obstructive/
3.	emphysema$.mp.
4.	(chronic$ adj3 bronchiti$).mp.
5.	(obstruct$ adj3 (pulmonary or lung$ or airway$ or airflow$ or bronch$ or respirat$)).mp.
6.	COAD.mp
7.	COBD.mp
8.	AECB.mp
9.	COPD.mp
10.	Or/1-9
11.	(beta blocker$ or BB or acebutolol or atenolol or betaxolol or bisoprolol or carvedilol or labetalol or metoprolol or nadolol or nebivolol or penbutolol or pindolol or propranolol or sotalol or celiprolol or esmolol or levobunolol or oxprenolol).mp.
12.	adrenergic beta-antagonists.mp. or exp Adrenergic beta-Antagonists/
13.	((adrenergic* and antagonist*) or (adrenergic* and block*) or (adrenergic* and beta-receptor*) or (beta-adrenergic* and block*) or beta-blocker*andadrenergic*).mp.
14.	or/11-13
15.	(random$ or placebo$ or single blind$ or double blind$ or triple blind$).ti,ab.
16.	10 and 14 and 15
17.	exp cohort studies/
18.	exp longitudinal study/
19.	exp prospective study/
20.	cohort$.tw.
21.	controlled clinical trial.pt.
22.	Or/17-21
23.	(conference review or conference abstract or comment or editorial or meta-analysis or practice-guideline or guideline$ or review or letter or journal or correspondence or short-survey or note).pt.
24.	RCTs: 10 and 14 and 15 not 23 – limit to humans
25.	Observational studies and non-randomized trials: 10 and 14 and 22 not 23 – limit to humans

Central database

1.	**(Pulmonary Disease, Chronic Obstructive).ti.ab.**
2.	MeSH descriptor: [Pulmonary Disease, Chronic Obstructive] explode all trees
3.	emphysema$.mp.
4.	(chronic$ adj3 bronchiti$) .mp.
5.	(obstruct$ adj3 (pulmonary or lung$ or airway$ or airflow$ or bronch$ or respirat$)) .mp.

6.	COPD.mp.
7.	COAD.mp.
8.	COBD.mp.
9.	AECB.mp.
10.	MeSH descriptor: [Adrenergic beta-Antagonists] explode all trees
11.	(beta blocker$ or BB or acebutolol or atenolol or betaxolol or bisoprolol or carvedilol or labetalol or metoprolol or nadolol or nebivolol or penbutolol or pindolol or propranolol or sotalol or celiprolol or esmolol or levobunolol or oxprenolol):ti,ab (adrenergic* and antagonist*) or (adrenergic* and block*) or (adrenergic* and beta-receptor*) or (beta-adrenergic* and block*) or (beta-blocker* and adrenergic*)
12.	(adrenergic* and antagonist*) or (adrenergic* and block*) or (adrenergic* and beta-receptor*) or (beta-adrenergic* and block*) or (beta-blocker* and adrenergic*)
13.	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9
14.	#10 or #11 or #12
15.	#13 and #14 – limit to Humans

TABLE D 2: Baseline characteristics (RCTs)

Author	Treatment arm	Dose	No. patients	Age mean (SD)	Males %	Race	Comorbidities	BMI mean (SD)	Smoking status
Adam 1982	Placebo	-	10	-	-	-	HTN: 100%	-	-
Adam 1982	Labetalol	200	10	-	-	-	HTN: 100%	-	-
Adam 1982	Metoprolol	100	10	-	-	-	HTN: 100%	-	-
Adam 1982	Atenolol	100	10	-	-	-	HTN: 100%	-	-
Adam 1982	Propranolol	80	10	-	-	-	HTN: 100%	-	-
Hawkins 2009	Placebo	-	13	68.7	77	-	HF 100%, Angina: 31% MI: 46% AF: 23%	26.9 (4.4)	Former smokers: 100%
Hawkins 2009	Bisoprolol	Started at 1.25mg, increased to 10mg	14	72.8	64	-	HF: 100%, Angina: 29% MI: 36% AF: 29%	29.2 (5.6)	
McGavin 1979	Propranolol	80 mg	9	63 (4)	100	-	-	-	-
McGavin 1979	Metoprolol	100 mg	9	63 (4)	100	-	-	-	-
Van Der Woude 2005	Placebo	-	15	60.5 (7.3)	87	-	-	-	-
Van Der Woude 2005	Celiprolol	200 mg	15	60.5 (7.3)	87	-	-	-	-

Author	Treatment arm	Dose	No. patients	Age mean (SD)	Males %	Race	Comorbidities	BMI mean (SD)	Smoking status
Van Der Woude 2005	Metoprolol	100 mg	15	60.5 (7.3)	87	-	-	-	-
Van Der Woude 2005	Propranolol	80 mg	15	60.5 (7.3)	87	-	-	-	-
Lainscak 2011	Bisoprolol	Mean 6.4 g daily	32	72 (8)	78	-	HF:100%; IHD:72%; HTN:81%; DM: 31%	27.8 (3.9)	
Lainscak 2011	Carvedilol	Mean 47 mg daily	31	73 (9)	84	-	HF: 100% IHD: 65% HTN: 74% DM: 35%	26.8 (5.4)	
Mainguy 2012	Bisoprolol	2.5 mg/day for 2 days; up titrated to 5 mg/day for 2 days.	27	65 (8)	63	-	-	27 (5)	-
Mainguy 2012	Placebo	-	27	65 (8)	63	-	-	27 (5)	-
Chang 2010	Placebo	-	11	65	73	-	-	-	
Chang 2010	Propranolol	80 mg daily	11	65	73	-	-	-	Current smokers: 45 % Former smokers: 55%
Chang 2010	Metoprolol 190 mg open label	190 mg daily	11	65	73	-	-	-	
Jabbal 2017	Bisoprolol	5mg qd	18	65	83	Caucasian : 100%	-	-	Former smokers: 100%
Jabbal 2017	Carvedilol	12.5mg bid	18	65	83	Caucasian: 100%	-	-	

Author	Treatment arm	Dose	No. patients	Age mean (SD)	Males %	Race	Comorbidities	BMI mean (SD)	Smoking status
Sinclair 1979	Placebo	0.9 % saline	10	63	-	-	-	-	Current smokers: 100%
Sinclair 1979	Propranolol	mean 3-8 mg	10	63	-	-	-	-	
Sinclair 1979	Metoprolol	mean 7-6 mg	10	63	-	-	-	-	
Chester 1981	Placebo		13	53.7 (5.3)	100	-	-	-	-
Chester 1981	Propranolol	40mg	13	53.7 (5.3)	100	-	-	-	-
Dorow 1986	Placebo		12	45.8 (6.4)	92	-	CHD: 100%	-	-
Dorow 1986	Atenolol	100mg	12	45.8 (6.4)	92	-	CHD: 100%	-	-
Dorow 1986	Bisoprolol	20mg	12	45.8 (6.4)	-	-	-	-	-
Ranchod 1982	Placebo		15	39	-	-	-	-	Current smokers: 100%
Ranchod 1982	Propranolol	140 mg per day	15	39	-	-	-	-	
Ranchod 1982	Aatenolol	100 mg per day	15	39	-	-	-	-	
Excluded from NMA									
Butland 1980	Placebo	-	10	61 (11)	60	-	-	-	-
Butland 1980	Atenolol	100 mg daily for 4 weeks	10	62 (11)	60	-	-	-	-

Author	Treatment arm	Dose	No. patients	Age mean (SD)	Males %	Race	Comorbidities	BMI mean (SD)	Smoking status
Butland 1980	Metoprolol	100 mg daily for 4 weeks	10	63 (11)	60	-	-	-	-
Dransfield 2019	Metoprolol	After adjustment: 25 mg, 50 mg, or 100 mg	268	65.2 (7.5)	53.7	White: 66.4 % Black: 31 % Other: 2.6 %	CAD,: 14.9%, DM:16.4%, HTN: 44.0%	26.9 (6.9)	Current smokers: 35.4%
Dransfield 2019	Placebo		264	64.8 (7.9)	53.4	White: 73.5 % Black: 22.7% Other: 3.8 %	CAD:14.8%, DM: 15.2%, HTN: 48.9%	27.4 (6.1)	Current smokers: 26.9%

AF= atrial fibrillation; bid= twice a day; CAD= coronary artery disease; CHD= coronary heart disease; DM= diabetes mellitus; HF= heart failure; HTN= hypertension; IHD= ischemic heart disease; MI= myocardial infarction; Mg= milligram; qd= once a day.

TABLE D 3: GRADE assessment from each pair-wise comparison within the NMA network (FEV_1 analysis)

Comparison	Direct evidence		Indirect evidence		NMA estimate	
	MD (95% CrI)	**Quality of evidence**	**MD (95% CrI)**	**Quality of evidence**	**MD (95% CrI)**	**Quality of evidence**
Bisoprolol vs Atenolol	0.19 (-0.15, 0.56)	Moderate (2)	-0.048 (-0.32, 0.25)	Moderate (2)	0.039 (-0.17, 0.25)	Moderate
Atenolol vs. Labetalol	-0.185 (-0.338, -0.0404)	Moderate (2)	-	-	-0.185 (-0.338, -0.0404)	Moderate
Metoprolol vs Atenolol	0.060 (-0.12, 0.26)	Moderate (2)	0.14 (-0.15, 0.42)	Moderate (2)	0.083 (-0.067, 0.24)	Moderate
Atenolol vs. Placebo	-0.0986 (-0.224, 0.0151)	Moderate (2)	-	-	-0.098 (-0.22, 0.014)	Moderate
Propranolol vs. Atenolol	-0.059 (-0.24, 0.12)	Moderate (2)	0.070 (-0.28, 0.42)	Moderate (2)	-0.050 (-0.19, 0.098)	Moderate
Bisoprolol vs. Carvedilol	-0.0984 (-0.207, 0.402)	Low (1, 2)	-	-	-0.0984 (-0.207, 0.402)	Low
Bisoprolol vs. Placebo	-0.057 (-0.256, 0.144)	Low (1, 2)	-	-	-0.057 (-0.256, 0.144)	Low
Celiprolol vs. Metoprolol	0.123 (-0.178, 0.423)	Very low (1, 2)	-	-	0.123 (-0.178, 0.423)	Very low
Celiprolol vs. Placebo	0.105 (-0.196, 0.403)	Very low (1, 2)	-	-	0.105 (-0.196, 0.403)	Very low
Celiprolol vs. Propranolol	0.248 (-0.0519, 0.549)	Very low (1, 2)	-	-	0.248 (-0.0519, 0.549)	Very
Labetalol vs. Metoprolol	0.105 (-0.0485, 0.258)	Very low (1, 2)	-	-	0.105 (-0.0485, 0.258)	Very low
Labetalol vs. Placebo	0.0872 (-0.0565, 0.22)	Very low (1, 2)	-	-	0.0872 (-0.0565, 0.22)	Very low
Labetalol vs. Propranolol	0.231 (0.074, 0.383)	Very low (1, 2)	-	-		Very low

Comparison	Direct evidence		Indirect evidence		NMA estimate	
Placebo vs. Metoprolol	0.017 (-0.13, 0.17)	Moderate (2)	0.0094 (-0.66, 0.66)	Moderate (2)	0.017 (-0.11, 0.15)	Moderate
Metoprolol vs. Propranolol	0.126 (-0.0183, 0.267)	Moderate (2)	-	-	0.126 (-0.0183, 0.267)	Moderate
Placebo vs. Propranolol	0.143 (0.0175, 0.275)	Moderate (2)	-	-	0.143 (0.0175, 0.275)	Moderate
Atenolol vs Carvedilol	-	-	-0.205 (-0.517, 0.104)	Very low(1, 2)	-0.205 (-0.517, 0.104)	Very low
Bisoprolol vs Celiprolol	-	-	-0.162 (-0.518, 0.198)	Very low(1, 2)	-0.162 (-0.518, 0.198)	Very low
Bisoprolol vs Labetalol	-	-	-0.143 (-0.377, 0.0964)	Very low(1, 2)	-0.143 (-0.377, 0.0964)	Very low
Bisoprolol vs Metoprolol	-	-	-0.0392 (-0.271, 0.198)	Very low(1, 2)	-0.0392 (-0.271, 0.198)	Very low
Carvedilol vs placebo	-	-	-0.155 (-0.517, 0.212)	Very low(1, 2)	-0.155 (-0.517, 0.212)	Very low
Celiprolol vs atenolol	-	-	0.205 (-0.104, 0.517)	Moderate (2)	0.205 (-0.104, 0.517)	Moderate
Celiprolol vs labetalol	-	-	-0.242 (-0.623, 0.15)	Moderate (2)	-0.242 (-0.623, 0.15)	Moderate
Celiprolol vs Propranolol			0.248 (-0.0519, 0.549)		0.248 (-0.0519, 0.549)	
Labetalol vs. carvedilol	-	-	-0.0186 (-0.333, 0.297)	Very low (1, 2)	-0.0186 (-0.333, 0.297)	Very low
Metoprolol vs atenolol			0.0809 (-0.0635, 0.231)		0.0809 (-0.0635, 0.231)	
Metoprolol vs Bisoprolol	-	-	0.0867 (-0.145, 0.322)	Moderate (2)	0.0867 (-0.145, 0.322)	Moderate
Metoprolol vs Placebo	-0.0178 (-0.152, 0.11)	Moderate (2)	-	-	-0.0178 (-0.152, 0.11)	Moderate

Comparison	Direct evidence		Indirect evidence		NMA estimate	
Propranolol vs Bisoprolol	-	-	-0.0867 (-0.322, 0.145)	Moderate (2)	-0.0867 (-0.322, 0.145)	Moderate
Propranolol vs carvedilol	-	-	0.0111 (-0.376, 0.391)	Very low (1, 2)	0.0111 (-0.376, 0.391)	Very low
Propranolol vs placebo	-0.143 (-0.275, -0.0175)	High	-	-	-0.143 (-0.275, -0.0175)	High

GRADE judgments refer not to individual studies but to a body of evidence, and quality, as used in GRADE, means more than risk of bias. A body of evidence (for instance, a number of well-designed and executed trials) may be associated with a low risk of bias, but our confidence in effect estimates may be compromised by a number of other factors (imprecision, inconsistency, indirectness, and publication bias).

GRADE for FEV1 (network meta-analysis)

Reasons for downgrading:

(1) Study limitations: We downgraded by one level when comparisons were made from at least one study which was rated as a serious or very serious risk of bias

(2) Imprecision: We downgraded one level if the estimate in mean change included the null effect. We downgraded one further level if the effect size comes from one study only or there are few events.

(3) Inconsistency: We planned to downgrade comparisons with important inconsistency ($p<0.01$), however all comparisons were consistent (direct and indirect estimates were in agreement), thus we did not downgrade any studies based on this.

(4) Indirectness: We ensured there were no treatment modifiers in our analyses by conducting meta-regression, which indicate no implication of covariates assessed. We thus did not downgrade any studies based on this.

(5) Publication bias: The comparison-adjusted funnel plot (Figure S3) did not suggest presence of overall publication bias, therefore we did not downgrade for this item.

TABLE D 4: Mortality estimates of beta-blocker versus no beta-blocker use, from individual studies

Author	Comparison	Mean (SD)/median [IQR] follow-up (months)	All-cause mortality HR [95% CI]	Covariates adjusted for in analysis
Rutten, 2010	BB vs. no BB	86.4 (NR)	0.68 [0.56 -0.83]	Age, sex, smoker, diabetes, HTN, CVD, pulmonary drugs, referral to pulmonologist
Rutten, 2010	Cardioselective BB vs. no BB	86.4 (NR)	0.67 [0.55 - 0.83]	Age, sex, smoker, diabetes, HTN, CVD, pulmonary drugs, referral to pulmonologist
Rutten, 2010	Non-cardioselective vs. no BB	86.4 (NR)	0.82 [0.61-1.1]	Age, sex, smoker, diabetes, HTN, CVD, pulmonary drugs, referral to pulmonologist
Short, 2011	BB vs. no BB	52 (27)	0.78 [0.67 – 0.92]	Age, sex, cardiovascular and respiratory hospital admissions, DM, smoking, cardiac drug use (aspirin, statins, CCBs, ACEis), FEV1, resting arterial oxygen saturation, deprivation index
Quint, 2013	BB vs. no BB	34.8 [1.07 – 86.4]	0.5 [0.36 – 0.69]	Age, sex, smoking history, angina, HTN, dyslipidaemia, PAD, CVD, HF, DM, MI, frequent exacerbations, diuretics before MI, anti-arrhythmia drugs, ACEi, nitrates and CCBs, anti-platelets and statins
Zeng, 2013	BB vs. no BB	22.2 [NR]	0.96 [0.40 – 2.29]	Age, BMI, blood pressure, HR, biochemical markers, echocardiographic parameters, COPD severity, NYHA classification, current smoking status, comorbidities, prescribed drug use
Bhatt 2016	BB vs. no BB	25.2 [NR]	0.85 [0.54 – 1.32]	Age, sex, race, smoking burden in pack-years, BMI, CAD, HF, CAC, FEV1, %emphysema on CT, respiratory medications
Mentz, 2013	Cardioselective BB vs. no BB	2 (NR)	0.53 [0.25 – 1.13]	Age, sex, cause of admission, depression, liver disease, weight, systolic blood pressure, lower extremity edema, serum sodium, serum creatinine, statin use, arrhythmias, HTN, hyperlipidemia, CAD, ICD or pacemaker, DBP
Mentz, 2013	Non-cardioselective BB vs. no BB	2 (NR)	0.47 [0.25 - 0.89]	Age, sex, depression, liver disease, weight, SBP, lower extremity edema, serum sodium, serum creatinine, statin use, cause of

Author	Comparison	Mean (SD)/median [IQR] follow-up (months)	All-cause mortality HR [95% CI]	Covariates adjusted for in analysis
				admission, arrhythmias, HTN, hyperlipidemia, CAD, ICD or pacemaker, DBP
Gottlieb, 1998	BB vs. no BB	24 (NR)	0.6 [0.57 - 0.63]	Unadjusted
Sin, 2002	BB vs. no BB	21 (NR)	0.78 [0.63 - 0.95]	Age, sex, CCI, HTN, IDH, propensity scores for BB, use of other medications for HF
Ekstrom, 2013	BB vs. no BB	13 [NR]	1.19 [1.04 - 1.37]	Age, sex, BMI, WHO performance status, resting blood gas tensions breathing air, comorbidities, concomitant medication
Coiro, 2016	BB vs. no BB	20 [NR]	0.73 [0.6 - 0.9]	Age, sex, smoking habit, Killip class ≥3, MI, HF, HTN, renal failure, AF, PAD, DM, CVD, SBP, DBP, HR, eGFR, LVEF, digoxin, ACE/ARB, diuretics, aspirin, CCB, statins
Staszewsky, 2016	BB vs. no BB	48 [NR]	0.74 [0.64 - 0.84]	Age, sex, comorbidities
Su, 2016	Carvedilol, high dose (nonselective) vs. no BB	52 (NR)	0.81 [0.56 - 1.18]	Age, sex, severity of COPD and HF, DM, dysrhythmia, ischemic stroke, intracranial hemorrhage, HTN, IHD, CKD, liver cirrhosis
Su, 2016	Bisoprolol, high dose (cardioselective) vs. no BB	52 (NR)	0.4 [0.26 - 0.63]	Age, sex, severity of COPD and HF, DM, dysrhythmia, ischemic stroke, intracranial hemorrhage, hypertension, IHD, CKD, liver cirrhosis
Su, 2016	Metoprolol, high dose (cardioselective) vs. no BB	52 (NR)	0.36 [0.09 - 1.43]	Age, sex, severity of COPD and HF, DM, dysrhythmia, ischemic stroke, intracranial hemorrhage, HTN, IHD, CKD, liver cirrhosis

Author	Comparison	Mean (SD)/median [IQR] follow-up (months)	All-cause mortality HR [95% CI]	Covariates adjusted for in analysis
Kubota, 2015	BB vs. no BB	33.9 (NR)	0.46 [0.19 - 1.11]	Age, sex, BMI, HTN, AF, BB, BNP, LVEF, ACEI or ARB, GOLD stage 3-4, history of COPD exacerbation, inhaled tiotropium
Hawkins, 2009	BB vs. no BB	24.7 (NR)	0.74 [0.68 - 0.8]	Unadjusted
Ellingsen, 2020	BB vs. no BB	study period 10 years (follow up 64,306 person-years, no other details)	0.86 [0.76 - 0.97]	Age, sex, education, marital status, income, pneumonia, HF, MI, IHD, stroke, HTN, DM, osteoporosis, depression, asthma, exacerbations
Rodriguez-Manero, 2019	BB vs. no BB	23 (3.3)	0.62 [0.38 - 0.99]	Age, sex, HF, HTN, thromboemoblic event, vascuopathy, DM, AF, dementia, oral anticoagulants, antiplatelet, ACEi/ARBs, digoxin
Su 2019b	cardioselective BB vs. no BB	112 (NR)	0.72 [0.71 - 0.72]	Age, sex, income level, comorbidities, exacerbation frequency of COPD and HF, CCI, urbanization level, SABD, LABA, ICS, ICS/LABA, LAMA, ACEi, ARB, aldosterone, digoxin, statins
Su 2019b	nonselective BB vs. no BB	112 (NR)	0.92 [0.92 - 0.93]	Age, sex, income level, comorbidities, exacerbation frequency of COPD and HF, CCI, urbanization level, SABD, LABA, ICS, ICS/LABA, LAMA, ACEi, ARB, aldosterone, digoxin, statins
Su 2019	BB vs. no BB (patients receiving PCI/CABG)	Overall survival	0.87 [0.82 -0.92]	Adjusted with IPTW on covariates: age, sex, socioeconomic status, length of stay for the index acute MI, comorbidities, previous outpatient treatment for COPD, inpatient treatments,

Author	Comparison	Mean (SD)/median [IQR] follow-up (months)	All-cause mortality HR [95% CI]	Covariates adjusted for in analysis
				complications of acute MI during hospitalization, other outpatient prescriptions
Su 2019	BB vs. no BB (not receiving PCI/CABG)	Overall survival	0.94 [0.85 – 1.04]	Adjusted with IPTW on covariates: age, sex, socioeconomic status, length of stay for the index acute MI, comorbidities, previous outpatient treatment for COPD, inpatient treatments, complications of acute MI during hospitalization, other outpatient prescriptions
Wang 2019	Cardioselective vs. no BB	96 (NR)	0.93 [0.89 – 0.98]	Age, sex, HTN, DM, PVD, HF, previous CVA, ESRF, AF, MI, PCI, antiplatelet, ACEi, ARB, statin, CCB, xanthins, corticosteroids, SAMA, LAMA
Wang 2019	Non-cardioselective vs. no BB	96 (NR)	0.98 [0.94 – 1.02]	Age, sex, HTN, DM, PVD, HF, previous CVA, ESRF, AF, MI, PCI, antiplatelet, ACEi, ARB, Statin, CCB, xanthins, corticosteroids, SAMA, LAMA
Wang 2019	BB vs. no BB	96 (NR)	0.97 [0.93 - 1]	Age, sex, HTN, DM, PVD, HF, previous CVA, ESRF, AF, MI, PCI, antiplatelet, ACEi, ARB, Statin, CCB, xanthins, corticosteroids, SAMA, LAMA
Scrutinio, 2019	BB vs. no BB	24 (NR)	0.66 [0.53 – 0.83]	Age, sex, DM, HF-related hospitalizations in the 6 months preceding the index event, symptoms severity at admission, admission SBP, use of inotropes during hospitalization, LVEF, eGFR, NT-proBNP, hemoglobin, sodium levels
Van Gestel, 2008	BB vs. no BB	120 (NR)	0.73 (0.6 – 0.88)	Age, sex, HTM, hypercholesterolemia, DM, renal dysfunction, smoking status, BMI, type of surgery, year of surgery, CVD history, a composite variable of statins, aspirin and ACEi

ACEis= angiotensin-converting-enzyme inhibitors; ARB= angiotensin receptor blockers; AF= atrial fibrillation; BB= beta-blockers; BMI= body mass index; CAC= coronary artery calcification; CCB= calcium channel blocker; CCI,= Charlson Comorbidy Index; CT= computed tomography; CVA= cerebrovascular accident; CVD= cardiovascular disease; DBP= diastolic blood pressure; DM= diabetes mellitus; eGFR= estimated glomerular filtration rate; ESRF= end stage renal failure; FEV_1= forced expiratory volume in 1 second; GOLD= Global Initiative for Chronic Obstructive Lung Disease; HF= heart failure; HR= heart rate; HTN= hypertension; ICD= implantable cardioverter-defibrillator; IDH= intradialytic hypotension; IPTW= inverse probability treatment weighting; LVEF= left ventricular ejection fraction; LAMA= long-acting

Author	Comparison	Mean (SD)/median [IQR] follow-up (months)	All-cause mortality HR [95% CI]	Covariates adjusted for in analysis
muscarinic antagonist; MI= myocardial infarction; NT-proBNP=N-terminal pro-brain natriuretic peptide; NYHA= New York Heart Association; PAD= peripheral artery disease; PCI= percutaneous coronary intervention; PVD= peripheral vascular disease; SABD= short acting bronchodilator; SAMA= short-acting muscarinic antagonist; SBP= systolic blood pressure; WHO= World Health Organization				

Appendix E: Supplementary material for Chapter 6

TABLE E 1: Comorbidity definitions, according to NHFA dataset, variables recorded from patient history

TABLE E 1: Comorbidity definitions, according to NHFA dataset, variables recorded from patient history

COPD	History of COPD - chronic bronchitis, emphysema or their cooccurrence. Must be indicated by pulmonary function testing evidence (i.e., FEV_1<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

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

COPD= chronic obstructive pulmonary disease; FEV1= forced expiratory volume in the 1st second; ECG = electrocardiogram; MI= myocardial infarction; CABG= coronary artery bypass graft;

Appendix F: Supplementary material for Chapter 7

TABLE F 1: Diagnostic codes used to identify cause of readmission

TABLE F 1: Diagnostic codes used to identify cause of readmission

Cause	CCS category	ICD-9CM chapters
Circulatory	96-121	7
Digestive	135-155	9
Endocrine	48-58	3
Genitourinary	156-175	10
Hematologic	59-64	4
Infectious	1-10	1
Mental health	650-663,670	5
Neoplasms	11-47	2
Other	245-260	17
Respiratory	122-134	8
Trauma/poisoning	225-244	16

Appendix G: Published and submitted papers

Paper 1: Gulea, C., Zakeri, R. and Quint, J.K., 2021. Model-based comorbidity clusters in patients with heart failure: association with clinical outcomes and healthcare utilization. *BMC medicine*, *19*(1), pp.1-13. **[Chapter 3].**

Paper 2: Gulea, C., Zakeri, R. and Quint, J.K., 2021, Differences in outcomes between heart failure phenotypes in patients with coexistent COPD, *Under review.* **[Chapter 4]**

Paper 3: Gulea, C., Zakeri, R. and Quint, J.K., 2018. Effect of beta-blocker therapy on clinical outcomes, safety, health-related quality of life and functional capacity in patients with chronic obstructive pulmonary disease (COPD): a protocol for a systematic literature review and meta-analysis with multiple treatment comparison. *BMJ open*, *8*(11), p.e024736. **[Chapter 5]**

Paper 4: Gulea, C., Zakeri, R., Alderman, V., Morgan, A., Ross, J. and Quint, J.K., 2021. Beta-blocker therapy in patients with COPD: a systematic literature review and meta-analysis with multiple treatment comparison. *Respiratory research*, *22*(1), pp.1-14. **[Chapter 5]**

Paper 5 [letter to editor]: Gulea, C., Quint, J.K. and Zakeri, R., 2021. Clinical and methodological considerations when interpreting meta-analyses of beta-blocker use in patients with chronic obstructive pulmonary disease. *European Heart Journal*. **[Chapter 5]**

Paper 6: Gulea, C., Zakeri, R., Kallis C. and Quint, J.K., 2021. Impact of COPD and asthma on in-hospital mortality and management of patients with heart failure. *Under review.* **[Chapter 6]**

Paper 7: Gulea, C., Zakeri, R. and Quint, J.K., 2019. Impact of chronic obstructive pulmonary disease on readmission after hospitalization for acute heart failure: a nationally representative US cohort study. *International journal of cardiology*, *290*, pp.113-118. **[Chapter 7]**

Paper 8: [reply to letter to editor] Gulea, C., Zakeri, R. and Quint, J.K., 2019. Reply to letter to the editor by Dr. Jolobe. *International journal of cardiology*, *292*, p.161. **[Chapter 7]**