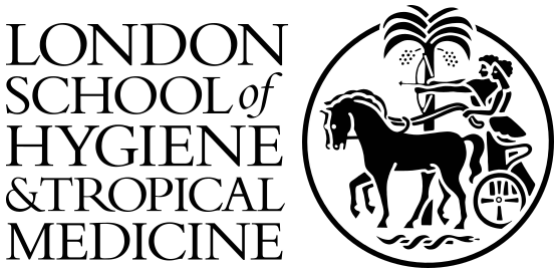

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Relationship between COPD exacerbations and cardiovascular risk

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Thesis submitted in accordance with the requirements for the degree of

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Department of Non-communicable Disease Epidemiology

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Declaration page

I, Kieran Rothnie, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Kieran Rothnie

24 May 2016

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First and foremost, I am very grateful to my supervisor, Dr Jennifer Quint, for providing me with the guidance, support and inspiration to complete this project.

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Abstract

Chronic obstructive pulmonary disease (COPD), is associated with an increased risk of myocardial infarction (MI), and additionally, cardiovascular disease is responsible for up to 1/3 of deaths in people with COPD. This may be attributable to the fact people with COPD are managed differently and have higher mortality after MI compared to people without COPD. One reason for the differences in management may be that prognostic risk scores after MI do not perform well in those with COPD. Another reason may be that acute exacerbations of COPD (AECOPD) are thought to be associated with a transiently increased risk of MI.

The aims of this thesis are to: 1)systematically review the evidence for an increased risk of MI associated with COPD and AECOPD, and increased risk of death following MI for those with COPD; 2) investigate the potential contribution of differences in management after MI on differences in mortality; 3) investigate the performance of prognostic risk scores after MI for those with COPD; 4) validate the recording of AECOPD in UK electronic healthcare records (EHR); 5) investigate the recording of hospitalisations for AECOPD in UK primary and secondary care EHR; and 6) to conduct a self-controlled case series to investigate the risk of MI associated with AECOPD.

This work showed an increased risk of MI associated with COPD independent of smoking, and evidence for an increased risk of death following hospital discharge for people with compared to those without COPD.

This work demonstrated that differences in recognition and management of MI for those with COPD may explain some of the higher risk of death for COPD patients following MI. Additionally, the GRACE score (commonly used for risk stratification following MI) does not perform as well for COPD patients and may explain some of the differences in management.

A validated algorithm was developed for identifying AECOPD both in primary care and resulting in hospital admission in electronic health records.

Finally, using a self-controlled case series analysis, data showed that AECOPD is associated with increased risk of MI for approximately four weeks following AECOPD onset, and that the risk is modified by important patient characteristics.

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Chapter 1 Introduction

This section defines chronic obstructive pulmonary disease (COPD), acute exacerbations of COPD (AECOPD), myocardial infarction (MI) and describes their epidemiology. The use of electronic healthcare records (EHR) for research is also introduced. The rationale, aims and objectives for the thesis are described. Finally, the chapter concludes with an outline of this thesis.

1.1 COPD

COPD is a heterogeneous collection of conditions characterised by progressive airflow limitation which is not fully reversible. COPD is a common disease. Worldwide, the prevalence of COPD is estimated to vary between 5-10% (Halbert et al. 2006) and is thought to be increasing (Buist et al. 2007) both due to population ageing and increased case finding of COPD. The prevalence of diagnosed COPD in the UK is estimated to be 1-2% of the general population (Simpson et al. 2010). However, there has been some suggestion that COPD is underdiagnosed, the so-called "missing millions" (British Lung Foundation). As the third leading cause of death worldwide (Lozano et al. 2012), COPD is of huge public health importance. As well as higher mortality (Shavelle et al. 2009), people with COPD have higher morbidity than the general population (Divo et al. 2012), and poorer quality of life (Garrido et al. 2006).

The most important risk factor for COPD, in the developed world at least, is tobacco smoking (Mannino and Buist, 2007). However, genetics and environmental factors appear to play a role in influencing which smokers develop COPD, as only around 25% of smokers develop COPD (Løkke et al. 2006). As with many diseases associated with smoking, COPD is over-represented in those of lower socioeconomic status (SES) (Gershon et al. 2012). In addition, SES may contribute to the development of COPD, perhaps through both early life factors and occupational exposures. COPD is associated very strongly with age, with around half of those with COPD being 70 years or older (Afonso et al. 2011).

COPD is a diagnosis which may be considered in patients over the age of 35 who have a risk factor (in the UK, this is normally a history of tobacco smoking), and one or more of cough, breathlessness, sputum production, wheeze, or frequent winter bronchitis (NICE 2010). A diagnosis of COPD should be based on clinical symptoms and then confirmed by post-bronchodilator obstructive spirometry. Spirometric obstruction is defined as a ratio of 0.7 of FEV_1 (forced expiratory volume in one second) to FVC (forced vital capacity), or as FEV_1/FVC <lower limit of normal. There is no single diagnostic test for COPD, as such, diagnosis is to an

extent a clinical judgement. In many epidemiological studies, COPD has been defined using spirometry only, with many studies using pre-bronchodilator spirometry (Buist et al. 2007, Petty 2000, Tilert et al. 2013). Without information on symptoms or clinical judgement, this may result in misclassification of COPD. Recent evidence from NHANES has suggested that using pre-bronchodilator spirometry in the general population setting results in over-estimation of the prevalence of fixed airflow obstruction by 50% (Tilert et al. 2013). Misclassification of COPD in research studies is likely to be minimised if information on symptoms or physician diagnosis COPD is available. However, even when such clinical information is available, COPD may still be misclassified with, for example, asthma with fixed airflow obstruction in an older person, or bronchiectasis.

Irritants, such as tobacco smoke, cause inflammation in the lung, and although inflammation is present in the lungs of all smokers, this is exaggerated in people with COPD. Chronic airway inflammation in people with COPD results in destruction of the alveoli (emphysema), and mucus hypersecretion (chronic bronchitis), which contribute to airway obstruction (Figure 1).

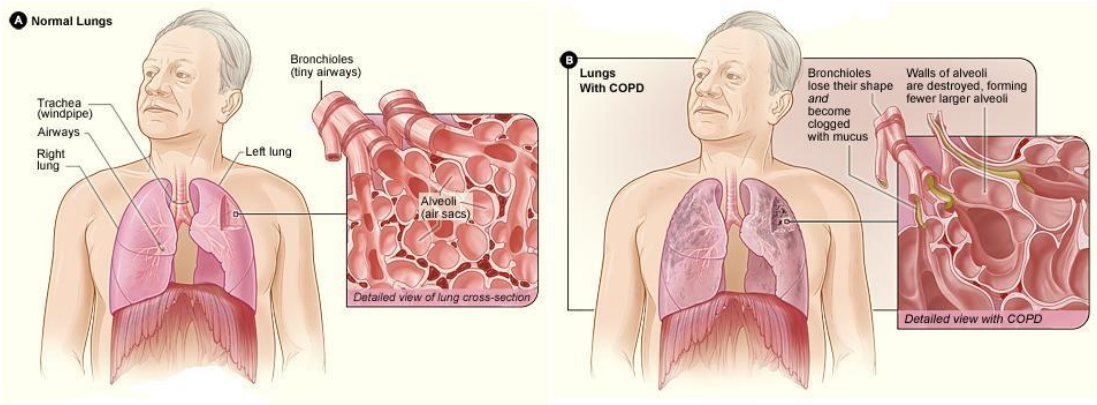

Figure 1. Diagram of A normal lungs and B changes associated with COPD.Image source: www.nhlbi.nih.gov/health//dci/Diseases/Copd/Copd_WhatIs; work of the US Federal Government and free from copyright restriction.

The mainstay of treatment of COPD includes smoking cessation; inhaled bronchodilators and corticosteroids; and pulmonary rehabilitation therapy. The aims of treatment are to improve functional status and quality of life, reduce morbidity and mortality, and to prevent exacerbations. Smoking cessation improves survival in those with COPD (Anthonisen, Skeans et al. 2005, Godtfredsen et al. 2008). However, there is no definitive evidence that pharmacological therapy or pulmonary rehabilitation reduces mortality (Mannino and Kiri 2006).

The severity of COPD varies widely between individuals. Traditionally, COPD severity the severity of COPD was graded according to FEV1 %predicted only (Table 1). More recently, presence of co-morbidities, frequency of exacerbations, degree of dyspnoea, and functional status have been recognised to contribute to COPD severity. (GOLD 2016).

Table 1. GOLD 2010 criteria for grading severity of COPD.

Grade	**FEV_1**
GOLD 1 Mild	FEV_1 ≥80% predicted
GOLD 2 Moderate	50% ≤ FEV_1 <80% predicted
GOLD 3 Severe	30% ≤ FEV_1 <50% predicted
GOLD 4 Very severe	FEV_1 < 30% predicted

1.2 Acute exacerbations of COPD

AECOPD are acute worsening of symptoms of cough, breathlessness and sputum volume and purulence that goes beyond day-to-day variation, and may require a change in treatment (Seemungal et al. 1998).

AECOPD are typically caused by infections, both bacterial and viral (Sethi 2004, Wedzicha 2004). However, for some exacerbations an infective cause cannot be found. Some health care professionals believe that these exacerbations may be attributable to environmental factors, such as air pollution (Sunyer et al. 1993). However they are triggered, the stimulus seems to result in an increase in airway inflammation and mucus secretion, resulting in the symptoms of AECOPD.

AECOPD are important events in the natural history of COPD. AECOPD drive mortality (Suissa et al. 2012), FEV_1 decline (Donaldson et al. 2002), and reduced quality of life (Miravitlles et al. 2004). In addition, as the second most common reason for emergency admission to hospital in the UK, they are of great public health importance (Healthcare Commission 2006).

There are numerous reasons for breathlessness and other symptoms of AECOPD in people with COPD: cardiovascular diseases, such as heart failure (Hawkins et al. 2009); other lung problems, such as pneumonia (MacIntyre and Huang 2008); or psychological issues such as anxiety (Maurer et al. 2008). Again, like COPD itself, as there is no single diagnostic test for AECOPD, in epidemiological studies, AECOPD may be misclassified with other problems such as these.

AECOPD can be graded by severity according to healthcare utilisation, with mild events managed by patients themselves, moderate events being treated in primary care (or by use of

previously prescribed "rescue packs"), and severe events requiring admission to hospital. Typically, COPD patients may experience around two AECOPD per year (including mild events) (Donaldson et al. 2002). In primary care, treatment for moderate AECOPD may involve the use of antibiotics and/or oral corticosteroids.

In relation to AECOPD, people with COPD can be characterised as frequent or infrequent exacerbators. The frequent exacerbator phenotype is based on moderate and severe AECOPD and has been defined as two or more of these events per year (Wedzicha et al. 2013). Infrequent exacerbators have fewer than two moderate or severe AECOPD per year. The exacerbator phenotypes appear to be stable over the course of several years (Hurst et al. 2010).

Frequent exacerbators have higher levels of inflammation during stable periods, compared to infrequent exacerbators (Bhowmik et al. 2000). Additionally, following an AECOPD, levels of inflammation take longer to return to baseline levels in frequent exacerbators compared to infrequent exacerbators (Perera et al. 2007).

1.3 Myocardial infarction

Worldwide, cardiovascular disease (CVD) is the leading cause of death (Lozano et al. 2012). However, in developed countries such as the UK, the incidence, and mortality due to cardiovascular disease is declining (Bhatnagar et al. 2015). One of the largest contributors to CVD is myocardial infarction (MI).

A MI occurs when the blood supply to the heart is interrupted resulting in myocardial injury and myocardial cell death due to prolonged lack of oxygen supply (Figure 2). Typically, this is a result of the blockage of a coronary artery. Most MIs are due to the rupture or erosion of an atherosclerotic plaque, which results in activation and aggregation of platelets to form a thrombus and local endothelial vasoconstriction, thus blocking blood supply to the myocardium. Atherosclerosis itself is hardening of arteries due to the build-up of fatty plaque and other material. Atherosclerosis is a complex and dynamic process, and lipid does not just passively accumulate in the arteries. Inflammation has been implicated in all stages of the atherosclerotic process, and seems to accompany atherogenesis, progression to unstable plaques, and thrombosis (Libby et al. 2002).

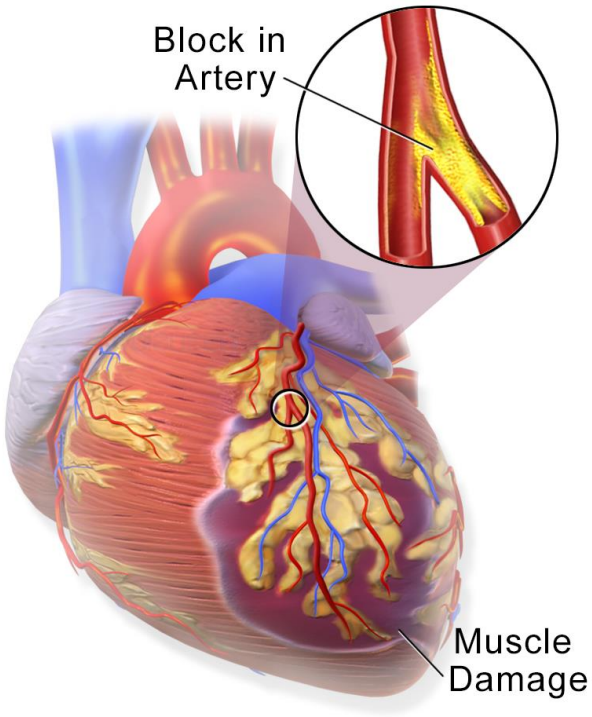

Figure 2. Myocardial infarction. Image source: Blausen Medical Communications, Inc. Image licensed under CC BY 3.0, and can be freely copied and distributed.

Major risk factors for MI including age (Lloyd-Jones et al. 2006), sex (Lerner and Kannel 1986), smoking (Kannel et al. 1987), hypertension (Castelli 1984), obesity (Hubert et al. 1983), raised cholesterol (Ridker et al. 2005), inactivity (Hamilton et al. 2007), low SES (Winkleby et al. 1992), and several other diseases such as diabetes mellitus (Kannel and McGee 1979) and chronic kidney disease (Muntner et al. 2002). Recently, other diseases which results in increased systemic inflammation have also been recognised as risk factors for MI (Wallberg-Jonsson et al. 1997, Meune et al. 2009, Ahlehoff et al. 2011, Kristensen et al. 2013).

Diagnosis of MI is made through distinctive changes to the electrocardiogram (ECG) and raised blood levels of biomarkers of cardiac necrosis such as troponin fragments (troponin I or T) or the MB fraction of creatine kinase, which are components of the contractile architecture of cardiac myocytes. Major symptoms of MI include chest pain and breathlessness, but a significant proportion of those with acute MI have atypical presentation which may involve atypical pain, or even no pain at all (Culic et al. 2002). In addition, many MIs may go undetected, so called "silent MIs" (de Torbal et al. 2006).

MIs are classified as either ST-segment elevation MIs (STEMIs) or non-ST-elevation MIs (non-STEMIs). ST-elevation relates to an increase in the trace between the S and T segments of the ECG. ST-elevation indicates that the full thickness of the myocardium has been damaged and

generally results from complete and persistent blockage of a coronary artery. Non-STEMIs are events in which partial thickness damage to the myocardium occurs and are generally the result of partial or transient blockage of a coronary artery.

Recently, the cardiology community has also recognised so called "type 2" MIs which do not result from coronary artery plaque rupture. Instead, type 2 MIs may result from a mismatch in myocardial supply and demand for oxygen due to, for example, tachyarrhythmia, bleeding, or exacerbations of COPD or asthma (Baron et al. 2015).

Treatment of MI depends on whether the event was a STEMI or non-STEMI. Initial treatment of STEMI is directed towards restoring blood flow to the myocardium. Until recently, this was mostly achieved using pharmacological means, however the predominant method for reperfusion is now primary percutaneous coronary intervention (pPCI). This procedure involves inflating a balloon in the infarct-related coronary artery to open the artery and restore blood flow. Reducing time to reperfusion improves prognosis and hospitals have been targeted to initiate reperfusion therapy within 90 minutes of arrival at hospital (O'Gara et al. 2013). Pharmacological secondary prevention is used for both STEMIs and non-STEMIs. Current guidance suggests that, unless contraindicated, the following drugs are initiated: β-blockers; angiotensin converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB); statins; and dual anti-platelet therapy (aspirin and a thienopyridine) (NICE 2013).

Following an MI, patients are often stratified into categories of risk of death, commonly expressed as risk of death at 6 months following MI. Several risk scores are available, including the TIMI, PURSUIT, and GRACE score. Accurate prediction of risk of death after MI is not only important for prognostication, but is also used for decision making about treatment. Those at higher risk of death benefit most from early aggressive treatment. This is of most relevance to non-STEMI, and current guidelines recommend that those at moderate risk or higher (>3%) GRACE score predicted risk of death at 6 months should have angiography, and subsequent treatment if necessary, within 72 hours of admission to hospital (NICE 2010, Roffi et al. 2015). Previous work has investigated whether other diseases affect the utility of the GRACE score, but this has not been investigated in those with COPD (Eagle et al. 2004).

Recent years have seen vast improvements in mortality associated with MI in the general population (Yeh et al. 2010). The case fatality rate (risk of death in the 30 days) for MI in the UK has fallen from 12.4% in 2003-2004 to 8.1% in 2011-2014 (MINAP 2014). This change is thought to be due to introduction of certain technologies such as pPCI and newer secondary prevention drugs, and improvement in the quality of care following acute MI such as reduction in time to pPCI after STEMI, and targeting early aggressive treatment for those with non-STEMI and unstable angina. In the UK, it has been estimated that around 50% of the reduction

in mortality attributable to MI has been due to primary prevention, and 50% to improved care after acute MI (Smolina et al. 2012). For this reason, cardiovascular epidemiologists have been interested in both primary prevention of MI and in improving the quality of care following acute MI.

1.4 COPD, AECOPD and myocardial infarction

MI is a common co-morbidity in those with COPD (Müllerova et al. 2013). In addition, cardiovascular disease is the cause of death for up to one third of those with COPD (Sin et al. 2006). Several studies have found that as well as being a risk factor for prevalent MI, COPD also seems to be a risk factor for incident MI (Sidney et al. 2005, Schneider et al. 2010, Sode et al. 2011, Yin et al. 2014), and this may be independent of smoking status (Feary et al. 2010). Cardiovascular disease, and MI in particular, are therefore an important target for reducing the mortality associated with COPD.

There are several possible reasons for the increased risk of MI associated with COPD. Firstly, irreversible airflow limitation is characteristic of COPD, and it is known that airflow limitation is associated with increased risk of MI in the general population (Sin et al. 2005). Several COPD medicines have been implicated in increased risk of MI, however findings differ between RCT and observational studies (Singh et al. 2008, Wise et al. 2013). Another possible reason for the increased risk of MI is the increased systemic inflammation associated with COPD. Increased inflammation in those with COPD is thought to "spill over" from the lungs, and influence the risk of other diseases (Figure 3). Increased inflammation is known to be a factor in atherogenesis (Libby et al. 2002), progression to plaque instability (Lombardo et al. 2004) and is associated with increased coaguability (Esmon 2004) in the general population. In COPD patients, acute and chronic inflammation is thought to contribute to arterial stiffness (Maclay et al. 2009), and to increased platelet activation and an increased prothrombotic and hypercoaguable state (Davi et al. 1997, Ashitani et al. 2002, Maclay et al. 2011). One possibility which has received particular attention is the role of acute systematic inflammatory response to AECOPD and chest infections in those with COPD.

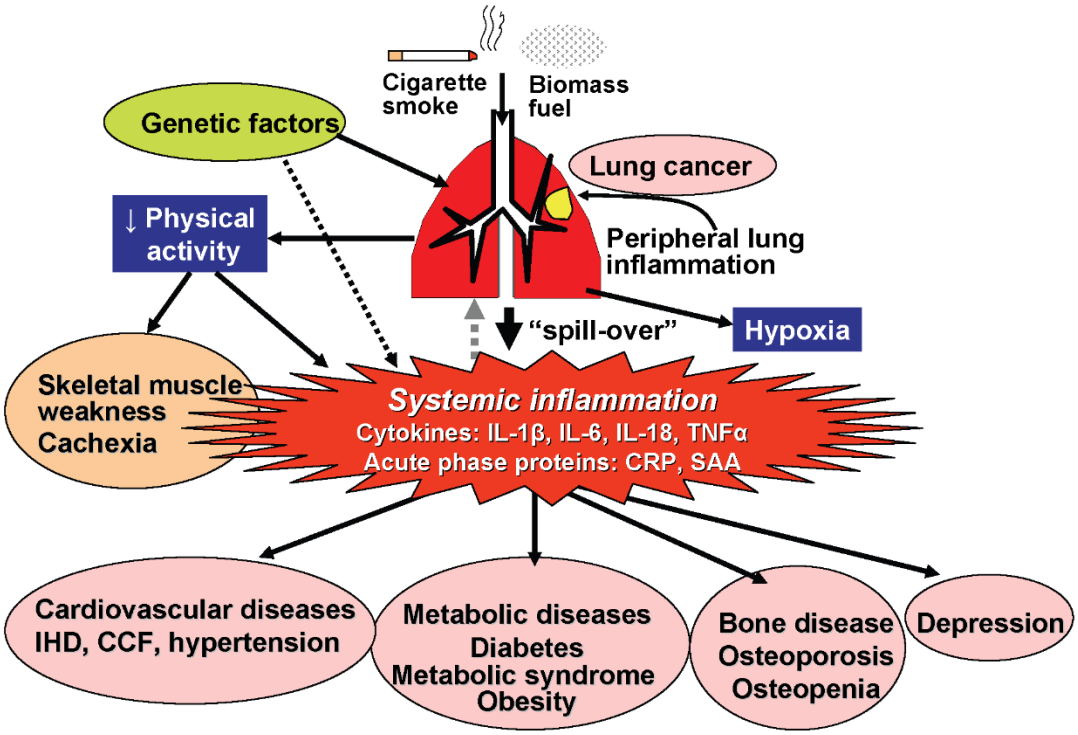

Figure 3. The effects of "spill over" of systematic inflammation in those with COPD. Original image from Barnes 2010 (Barnes 2010). Licensed under CC BY and can be freely copied and distributed.

In the general population, it is known that the period of time following certain infections is associated with an increased risk of MI. Of particular relevance, lower respiratory tract infections (LRTI) are associated with an almost 5-fold increased risk of MI in the first 3 days following onset of infection (Smeeth et al. 2004). This increased risk then gradually falls back down to baseline levels.

Two studies have investigated whether AECOPD are associated with increased risk of MI. In a study using CPRD data, Dolandson et al. demonstrated a 2 fold increased risk of MI in the 5 days following AECOPD onset (Donaldson et al. 2010). However, this finding was only apparent when AECOPD were defined using prescription of antibiotics and steroids in a person with COPD, but not when either prescription of antibiotics or steroids alone were used. The validity of using prescription of both antibiotics and steroids to define AECOPD in EHR is unclear. Halpin et al. (Halpin et al. 2011), used data from the UPLIFT trial in a post hoc analysis and compared the risk of MI in the 30 days following AECOPD to the 30 days before AECOPD, and found a 13-fold increased risk of MI in the 30 day period following AECOPD.

However, due to a small number of events, uncertainty in this estimate was high, and the confidence interval ranged from 1.71-99.7.

Another study (McAllister et al. 2012) demonstrated that one in 12 patients without chest pain who were admitted to hospital with a diagnosis of AECOPD met the universal definition of MI (rise and fall in serial troponin plus evidence of myocardial ischaemia). There are two possibilities for this finding: 1) those patients who met the criteria for MI may have initially been misdiagnosed with AECOPD; or 2) those patients who met the criteria for MI had both AECOPD and MI. Given that potential for misclassification of MI as AECOPD in those with COPD, and the small amount of evidence that AECOPD are associated with MI, it is possible both of these situations occurred.

As well as the risk of MI associated with COPD and AECOPD, researchers have also investigated the risk of death following MI in COPD patients compared to those without COPD. Several investigators have found that people with COPD have a higher risk of death after MI compared to those who do not have COPD (Salisbury et al. 2007, Bursi et al. 2010, Andell et al. 2014). Others have focussed on differences in treatment after MI, and found that those with COPD are significantly less likely to receive certain treatments, such as pPCI after a STEMI, or to be discharged on β-blockers (Stefan et al. 2012). Further work has also suggested that COPD patients tend to present atypically, with fewer having chest pain than compared to people without COPD (Hadi et al. 2010). As much of the fall in MI case fatality has been attributed to improvements in management, it is possible that some of the increased risk of death following MI for those with COPD can be explained by differences in recognition and management of MI.

Taken together with the evidence that many of those hospitalised with AECOPD meet the diagnostic criteria for MI, the fact that many of those with COPD present atypically after MI, suggests that there could be significant misdiagnosis of MI as AECOPD. This is important for epidemiologists as it suggests that for COPD patients, MI and AECOPD may be misclassified. This is also important clinically as it suggests that there is potential for delayed, or entirely missed, diagnosis of MI in those with COPD.

1.5 Electronic healthcare records

EHRs are digital collections of patient health related information, and may be used to aid clinical management, for audit, or for administrative purposes. Clinical records are used as an accessible record of information for individual patients as well as a tool to increase workflow efficiency for tasks such as the generation of prescriptions and requesting tests. Administrative

EHR records maybe contain clinical information, but are used for non-clinical purposes. One common example of administrative EHR are healthcare insurance databases, where information is held on claims for consultations, procedures and tests. In the UK, administrative EHR are often used to determine remuneration to hospitals for individual episodes of patient care.

EHRs have great potential to be used for research. Their strengths include massive size allowing high statistical power and representativeness. In addition, linkages with other datasets allow information collected from multiple sources to be used for research. Unlike RCTs and most bespoke cohort studies, EHRs allow epidemiology in "real life" to be examined. In this sense, the external validity of research conducted using EHRs is high. EHRs also contain detailed health care information, which is not only useful when health care itself is being studied, but is also useful for the reliable identification of certain diseases, such as COPD.

There are some limitations to the secondary use of EHR, however. The data contained in EHR are generally not collected for research. They tend to be clinical, administrative or audit records. The major problem that this causes is that sometimes important data can be missing or misclassified. In epidemiological studies where data are collected for the purposes of research, strict definitions of population, exposures, comparators, and outcomes are created at the outset. In general, there may also be opportunities for research staff to clarify issues with participants or their treating clinicians. In epidemiological studies using EHR, definitions are developed based on data which are already collected and complicated algorithms may be used to create disease definitions. A more detailed discussion and examples of these algorithms are presented in the next chapter. In addition, further contact with participants, or their treating clinicians, is not generally possible. EHR studies are therefore ultimately limited by the accuracy and coding behaviour of the clinicians who originally record the data.

At the international level, there are several EHR datasets available which have been used widely for research. In the USA, two common sources of EHR data are the Medicare and Medicaid datasets, which are administrative claims data from national social insurance programmes for the elderly and those with disabilities, and those with low incomes respectively. Another widely used North American database in the Saskatchewan health database in Canada, which is another administrative database. Although these databases are large, and contained detailed information on medicine usage, they do not contain information on lifestyle factors (such as smoking status), which make them limited for studying diseases such as COPD and MI due to lack of information on important confounders.

There are also several large EHR databases in Europe which can be used for research. The Danish National Patient Registry (Schmidt et al. 2015) is a database of all contact with secondary care (inpatient, outpatient and A&E attendance) for all patients in Denmark.

Although this is an excellent source of information on serious events which might lead to hospitalisation (for example, an MI), the database is limited by lack of information on issues which are commonly treated in primary care, for example COPD and smoking. The construction of a COPD definition using this database would mean defining only patients severe enough to be admitted to hospital or referred to secondary care as COPD patients, resulting in potential selection bias. The Dutch Integrated Primary Care Information (IPCI) database (Erasmus MC) was set up with the purpose of conducting pharmacoepidemiology studies, and therefore contains detailed information on primary care diagnoses, medical therapy, important lifestyle factors, and events which resulted in hospitalisation.

In the UK, there are several sources of clinical primary care EHR data including: The Health Improvement Network (THIN), ResearchOne, QResearch, and the Clinical Practice Research Datalink (CPRD). These databases are broadly similar in terms of the data they contain, but do differ in terms of size and linkage with other datasets. Data from secondary care in the UK are also available separately within each constituent nation. The largest source of secondary care data in the UK is the Hospital Episodes Statistics (HES), and is an administrative database which contains information on all episodes of admitted patient care, as well as limited information on outpatient and A&E attendances.

This thesis uses CPRD data linked with HES (where necessary). The advantages of using CPRD are the availability of information on lifestyle factors, such as smoking status, which is important when investigating diseases such as COPD and MI; and the availability of linked data between primary and secondary care. These databases are described in detail in the next chapter.

1.6 Aims and objectives

1.6.1 Aims

The ultimate question that this thesis aims to address is that of the relationship between AECOPD and risk of MI. However, in reaching this aim, it will also be necessary to investigate both some aspects of the relationship between COPD and MI and consequences of MI; and to develop methods to identify, as accurately as possible, AECOPD in EHR.

The thesis has three broad aims:

1. Improve the understanding of the risk of MI in people with COPD; and differences between people with COPD and people without COPD in the presentation, management, and outcomes after MI
2. Improve the identification of AECOPD in EHR
3. Improve the understanding of the relationship between AECOPD and risk of MI

1.6.2 Objectives

The specific objectives of this thesis are to:

1. **Conduct a systematic review and meta-analysis of the risk of MI associated with COPD and AECOPD and risk of death in those with COPD following MI**. Although several studies have investigated the risk of MI associated with COPD and AECOPD and risk of death following MI for those with COPD, these studies have not been systematically reviewed, assessed or meta-analysed. Previous systematic reviews in this area have not focussed on risk of MI associated with COPD, and have instead investigated prevalent disease (Chen et al. 2015 , Müllerova et al. 2013).
2. **Investigate the possible contribution of differences in recognition and management of MI in those with COPD to differences in mortality in the UK.** Although many studies have investigated both the risk of death following MI associated with COPD (Salisbury et al. 2007, Bursi et al. 2010, Andell et al. 2014), and differences in recognition and management between people with and without COPD (Stefan 2012); this has not been done before in the UK, and no previous studies have attempted to directly investigate the potential contribution of differences in recognition and treatment to differences in outcomes.
3. **Review the evidence for the effect of COPD on differences in presentation, management and outcomes after MI.** This review paper synthesises the literature on differences in presentation, management and outcomes after MI between people with and without COPD. This review extends the discussion on outcomes beyond that of all-cause mortality, and proposes mechanisms by which differences in presentation and management of MI for those with COPD might increase the risk of death following MI.
4 **Investigate the accuracy of prognostic risk scoring after acute coronary syndromes for those with COPD, and the impact of the differences in accuracy between COPD and non-COPD patients in terms of differences in management decisions.** Although others have investigated whether prognostic scores after MI are accurate for other diseases (Eagle et al. 2004), this has not been done for COPD. In addition, no other studies have investigated the impact of different accuracy in terms of whether patients would receive different treatment.
5. **Validate the recording of AECOPD in UK EHR.** There is currently no validated definition of AECOPD in EHR, given the potential for misclassification of AECOPD in EHR, this is an important contribution for the future of COPD research in EHR as well as a necessary step for completion of Objective 7.
6. **Investigate the recording of hospitalisation for AECOPD in UK primary and secondary care EHR.** Again, there is no validated definition of hospitalisation for

AECOPD in EHR. Recent evidence (Crooks et al. 2012, Baker et al. 2015, Millett et al. 2016) has demonstrated that definitions of cause-specific hospitalisation based on primary care data alone may have low validity. Therefore, work is needed to investigate how hospitalisations for AECOPD are recorded in EHR for future COPD research, and for the completion of Objective 7.

7. **Conduct a self-controlled case series to investigate the risk of MI associated with AECOPD.** This study makes use of the validated definitions of AECOPD in EHR developed by the studies reported in Chapters 5 and 6. Using these definitions means that compared to previous studies into the association between AECOPD and MI, many more AECOPD can be identified and included, with greater confidence in the validity of the AECOPD definition. This increased number of AECOPD means that the current study has higher power. As a result, both the magnitude, and the duration of the association between AECOPD and MI can be better quantified. In addition, increased power means that this study extends previous findings by using stratified analysis to investigate whether the risk of MI associated with AECOPD is modified by patient characteristics, such as exacerbator phenotype, and cardiovascular medicines. This information will be important, both for informing future studies into the pathophysiology behind the association, and in the move towards potential interventions to mitigate the increased risk of MI associated with AECOPD.

1.7 Description of thesis

The following chapter is a description of the data sources used, the remaining parts of this thesis are presented as series of research papers before a final overall discussion. The copyright for these articles has been retained by the author and they are all licensed under CC BY 4.0 (proof of retention of copyright is presented in Appendix G). These are presented as pre-print versions for ease of reading. For clarity for the reader of the thesis, all references in research papers are numbered and are listed at the end of the research paper. References in the introduction, description of data sources, preamble and summary of research papers, and the overall conclusion use the name date style and are listed at the end of the thesis.

The research papers presented here are the work of the author of this thesis. The author of this thesis designed each of the research studies, developed the protocols, obtained necessary approvals, obtained the data, managed the data, analysed the data, interpreted the data, wrote the first draft of the papers, and wrote the final draft of the papers after comments from the co-authors. For the systematic review presented in Chapter 3, abstract and full-text screening, and risk of bias assessment was carried out both by the primary author and a medical student acting as a second reviewer under the supervision of the primary author. For the research paper presented in Chapter 7, review of patient material relating to potential AECOPD was carried

out by two respiratory physicians (Dr Jennifer Quint and Dr John Hurst). All codelists used in this thesis were developed by the author in collaboration with others in the electronic healthcare records group at LSHTM.

Five of the papers have already been published in peer-reviewed journals, the references for these are given in the pre-amble for each research paper. One of the papers is currently under review. Finally, the last chapter has been prepared for publication, but has not yet been submitted.

The relationship of different aspects of the thesis are shown in Figure 4.

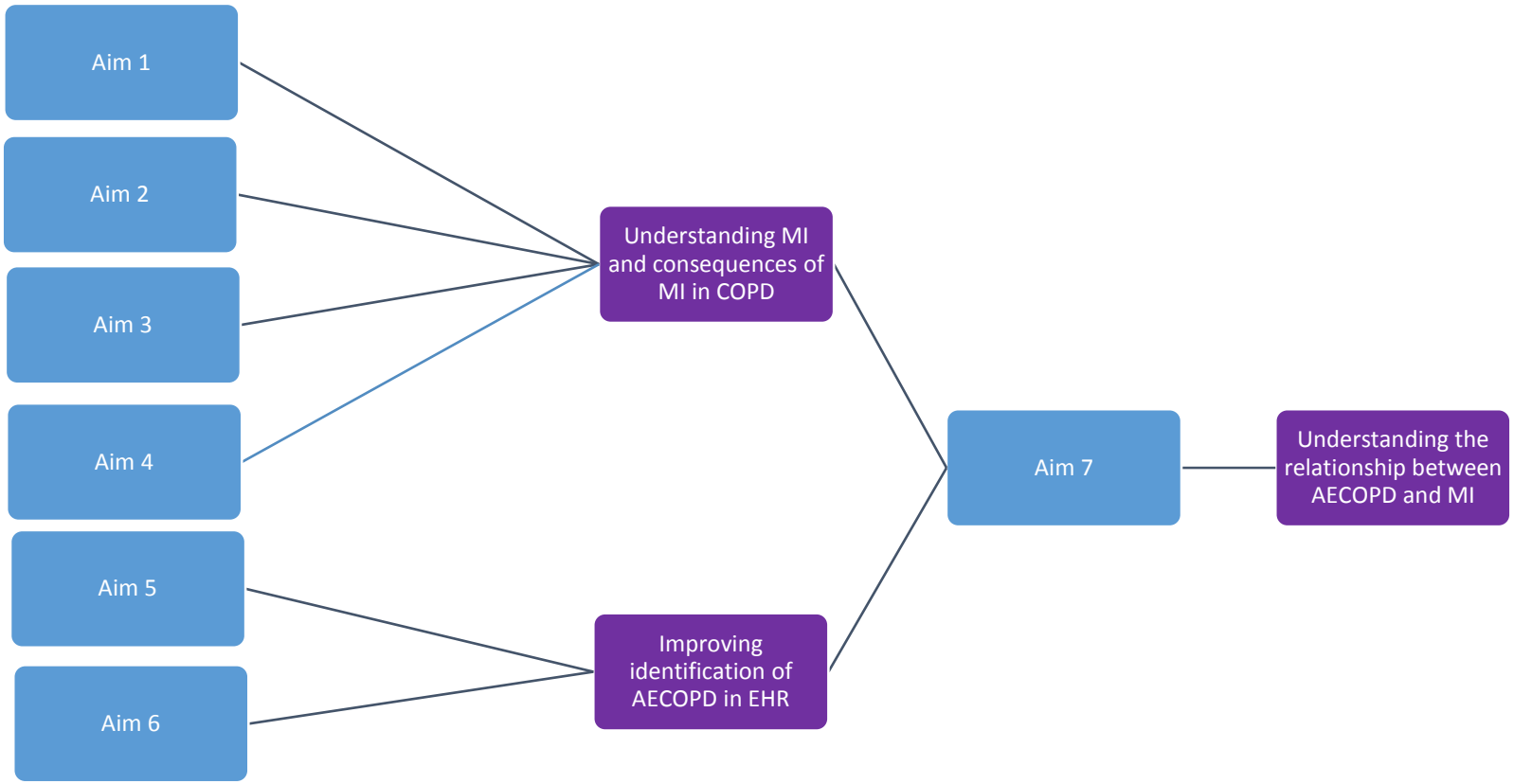

Figure 4. Diagram representing organisation of this thesis.

Chapter 2 Description of data sources

This chapter introduces and describes the data sources used in this thesis, along with their strengths and weaknesses and gives examples for how disease definitions can be constructed using the data they hold.

2.1 The Clinical Practice Research Datalink (CPRD)

The Clinical Practice Research Datalink (CPRD), previously known as VAMP and then GPRD, is a large UK database of primary care data which has been used extensively for research. CPRD contains data on around 11 million people (5.9 million of these are active patients, which is about 6.9% of the population) (Herrett et al. 2015). CPRD contains details of patient diagnoses, signs, symptoms, prescriptions, referrals, immunisations and test results. At present, CPRD collects data from GP practices throughout the UK which use the Vision system (provided by INPS), which has a market share of around 20% of UK GPs. However, efforts are ongoing to integrate data from the GPs practices which use the EMIS system into CPRD. This section first describes how the Vision system is used in clinical practice, before describing how CPRD data it can be used for research.

2.1.1 The Vision system

During a general practice consultation, in Vision, once a patient's personal EHR is selected, clinical details are entered as consultations. "Consultations" do not necessarily imply direct patient contact, and as well as attendances at the practice and telephone calls, they may also refer to, for example: administration tasks (such as change of personal details, or transfer out of the practice), issue of a repeat prescription, details from a recent discharge from hospital, or attendance at an A&E department.

With the exception of immunisation and therapies, clinical details for consultations are mainly entered using a structured clinical vocabulary known as "Read terms". Read terms refer to a wide variety of specific clinical concepts, such as diagnoses, signs, and symptoms, as well as life events and administrative codes. Read terms are each associated with a Read code. Read codes are a hierarchical system of classification and are arranged into several chapters. Chapters 0-9 relate to concepts such as signs, symptoms, investigations, procedures, and patient occupations. Chapters A-Z relate to diagnoses, and are broadly similar to ICD chapters. Within each chapter, codes are arranged in a hierarchy, and become more specific further down the hierarchy. For example:

H…..	Respiratory symptom diseases
H3…	Obstructive airway diseases
H33..	Asthma
H330.11	Allergic asthma

Even further down the hierarchy, however, Read codes may be quite specific, for example, "T531000 Accid alighting aircraft – occupant of spacecraft injured", or vague, for example, "R2yz.11 [D]God only knows"

As the Read term dictionary contains many synonyms, clinicians generally have a wide choice of Read terms to use. For example, "G30..00 Acute myocardial infarction", "G30..15 MI – acute myocardial infarction", "G30..14 Heart attack", and "G30.11 Attack - heart" all refer to the same clinical concept.

Read terms can both be entered directly into the patient's medical history, or into a structured data area, for example, when entering results, such as blood pressure. When Read terms are entered, the Vision system associates these to the corresponding Read code. The Vision system, to an extent, can be customised. One example of this is that Read terms may "auto-populate" with preferred terms, for example if a GP types "MI" in the Read term box, Vision may auto-populate this with the Read term "MI – acute myocardial infarction".

Once a Read code is entered for a consultation, the GP has the opportunity to enter "comments" for each Read code. These are free-text information which may be used to add more details. For example, the free-text associated with the Read term "H06z011 Chest infection" may be: "productive cough 5/7, green sputum, sob, feels unwell, chest quiet lower R zone, for amox and r/v".

Dates are associated with each Read code. Firstly, the system date is the date of the consultation. Secondly, the event date is auto-populated as the system date, but may be changed by the clinician to record historical events, such as an admission to hospital a few weeks previously.

In the Vision system terminology "Therapy" relates to prescriptions. The system uses the Gemscript dictionary, with Gemscript codes as unique identifiers. These dictionaries may be modified to include a "Practice formulary" depending on local prescribing practices. Each Gemscript item will have a product name, and may also additionally have a drug substance

name, route of administration, strength, formulation, and BNF code. The Therapy module within Vision may be modified to auto-populate the dose, duration, and patient advice for certain items, but these may be changed by the clinician. Prescriptions can be printed directly from the Therapy module once these details are entered. For the purposes of the Vision system, immunisation records are separate from other therapies, but as these records are not used in this thesis, they are not described further.

Referrals to secondary care are also generated in Vision and are associated with a Read code. Referrals may be specified further in structured data areas by speciality, urgency and as inpatient or outpatient referrals, but this information is not necessarily always recorded.

Test results are associated with a Read code, and may be automatically uploaded from pathology departments. Alternatively, these may also be entered directly by primary care clinicians. Other measurements and lifestyle factors (such as blood pressure or smoking status) are also associated with a Read code and entered directly by primary care clinicians. These might be triggered automatically, for example, if the Read term "O/E – blood pressure reading" is entered, this opens a structured data area to enter the details.

2.1.2 Using CPRD for research

Data from practices which have consented to take part in CPRD are regularly uploaded to the CPRD servers. Data are then processed and go through quality checks before being pseudonomised and made available for research.

There are two quality assurance processes that CPRD carry out before data are released to researchers. Firstly, individual patients are deemed to be "acceptable" for research if their data passes quality standards. Reasons for being deemed "unacceptable" include, for example, not having a registration date, not having a date of birth, or having a transfer out date before the current registration date. Patients who are unacceptable are not recommended to be used for research. Secondly, CPRD also generate an "up-to-standard" (UTS) date for each included practice. Practices are deemed to be UTS if they have no meaningful gaps in data recording and if their rate of deaths is close to the expected level. Data from each practice can be used for research after the UTS date.

After the necessary study approvals have been obtained, data can be downloaded from the CPRD system. This is done in two stages. In the first stage, the population is defined. This can be done on the basis of patient records containing certain Read codes or product codes. At this stage patients can also be excluded on the basis of Read codes or product codes, or on the basis

of age or sex. The define stage results in a list of unique patient identifiers (patids) who meet the initially entered inclusion criteria. The second stage involves extracting all of the records for the list of patients created in the first stage. The rationale for obtaining all the of the available EHR data for each patient, not just that during the study period is that this data may be required to create co-variates, for example, history of MI prior to the study period, or for inclusion and exclusion criteria.

In CPRD, data are organised into several different types of file. These are: patient, practice, consultation, clinical, test, additional, therapy, staff, and immunisation. Information from staff and immunisation files are not used in this thesis. The relationship between the types of files used in this thesis is displayed in Figure 5.

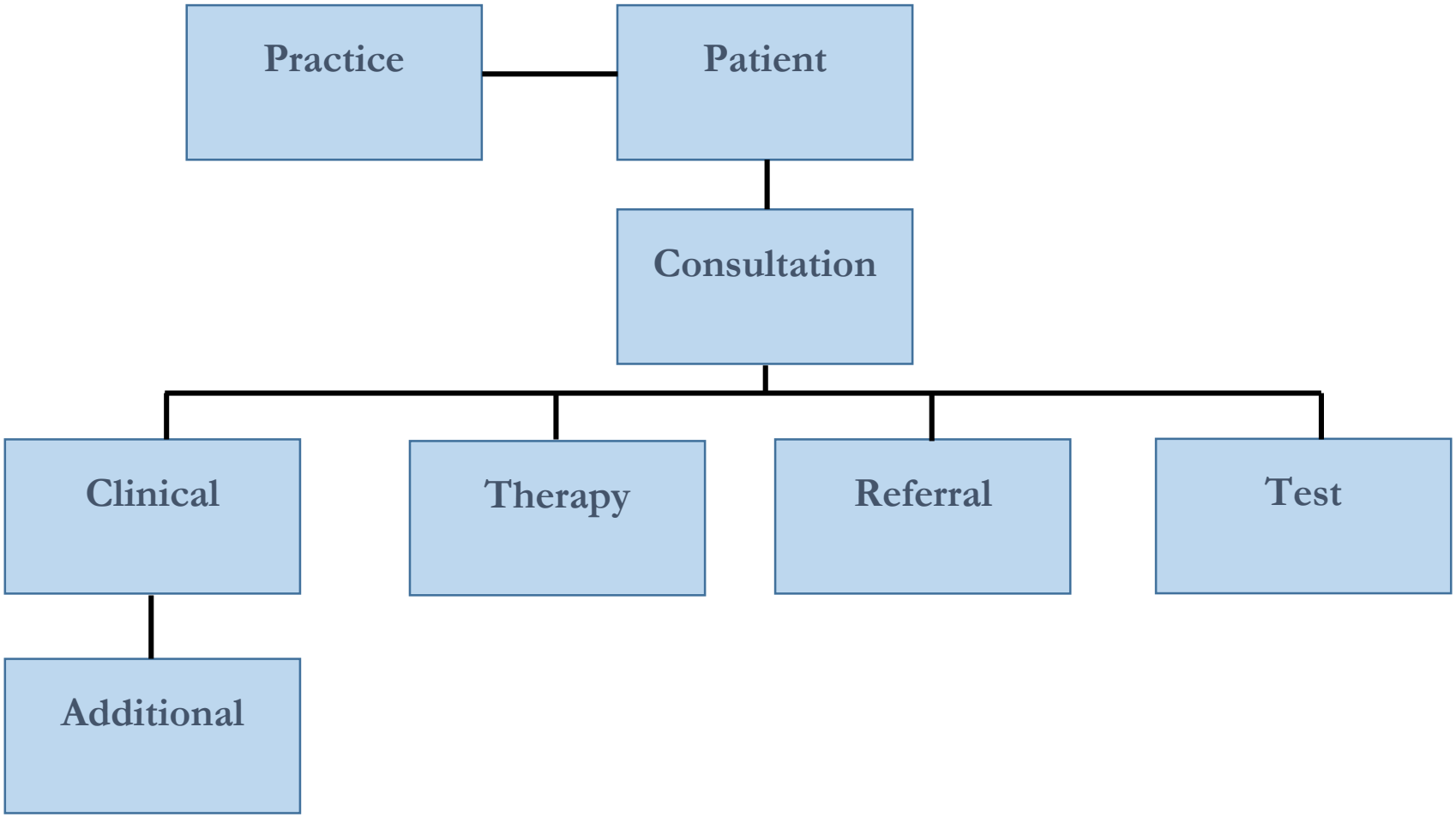

Figure 5. Data structure in CPRD. Adapted from Herrett et al. 2015 (Herrett et al. 2015).

To identify clinical events which are to be used as exposure, outcome or co-variate definitions, codelists of Read codes which might identify the clinical concept in question must be created. These can then be used to search patient's entire EHR to identify these events. If the codelist or strategy has not been validated however, this does require some judgment as to the possible meaning of the codes. For this thesis Read codes were developed by searching the dictionary for possible synonyms of the target concept. In addition, as Read codes are hierarchical, all codes in the "level" above that in question were screened. After this process was conducted, codes were checked against any similar ones available from colleagues or published online. An example of this process is shown in Figure 6. All codelists used in this thesis have been reproduced in the relevant appendix.

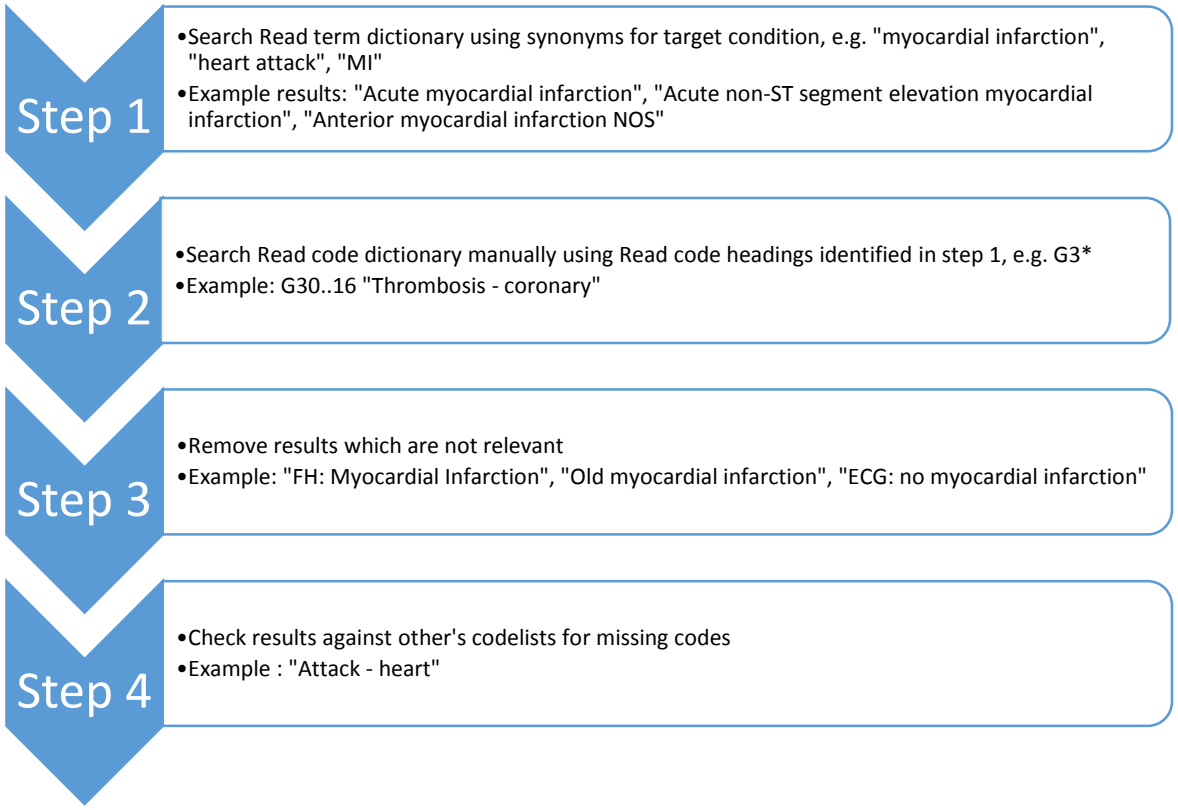

Figure 6. Example strategy for identifying possible acute MI in CPRD.

Information on prescriptions issued to patients are also automatically entered into the patient's EHR as these are generated. Generally, information is also available on daily dose and the quantity prescribed.

Not all data are contained within Read or product codes in CPRD however. Information from numerical test results, for example, are stored directly in the "Test File". An example of an algorithm to identify spirometry results is shown in Figure 7. One added complication is that, for some tests, there are likely to be many results over the course of the patient's observation period. Researchers may choose to use test results at or close to a baseline period, or may wish to "time update" these variables. In addition, strategies may have to be developed for dealing with unlikely results (for example FEV_1 of 67L, or height of 5m 8cm), and possibly contradictory results which occur on the same day or in a short space of time (for example, BMI of 21.3 and 31.2 on the same day).

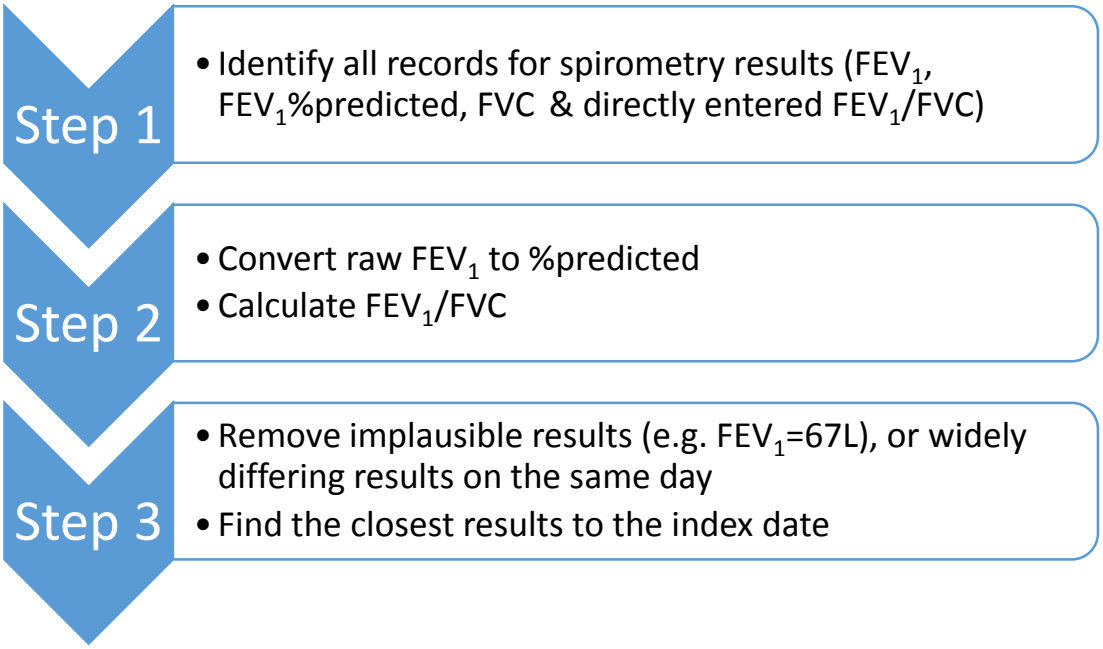

Figure 7. Algorithm for identifying spirometry results (FEV_1/FVC and FEV1%predicted) within EHR.

Completeness of many pieces of lifestyle data was improved following the introduction of the financial incentives as part of the Quality and Outcomes Framework (QOF), which was introduced in 2004. One aspect of QOF incentivises GPs to record key pieces of information, such as smoking status.

There is, therefore, no general way of defining individual concepts in EHR and researchers should consider re-assessing previously used algorithms for each individual study they conduct.

Although information about contact with secondary care which has been sent to the GP should be recorded in the patient's primary care EHR, this is not always complete and may not be recorded in such a way as to be useful for researchers (as free-text, for example). One major advantage of using CPRD data is that it can be linked to other databases which provide this information.

Once exposures, co-variates and outcomes have been identified, individual follow up time for patients can be identified. In CPRD studies, apart from the usual considerations of cohort studies, patients are generally followed up from the date the practice's data became up to standard, and are censored at practice last collection date or patient transfer out of practice. An example of this is shown in Figure 8.

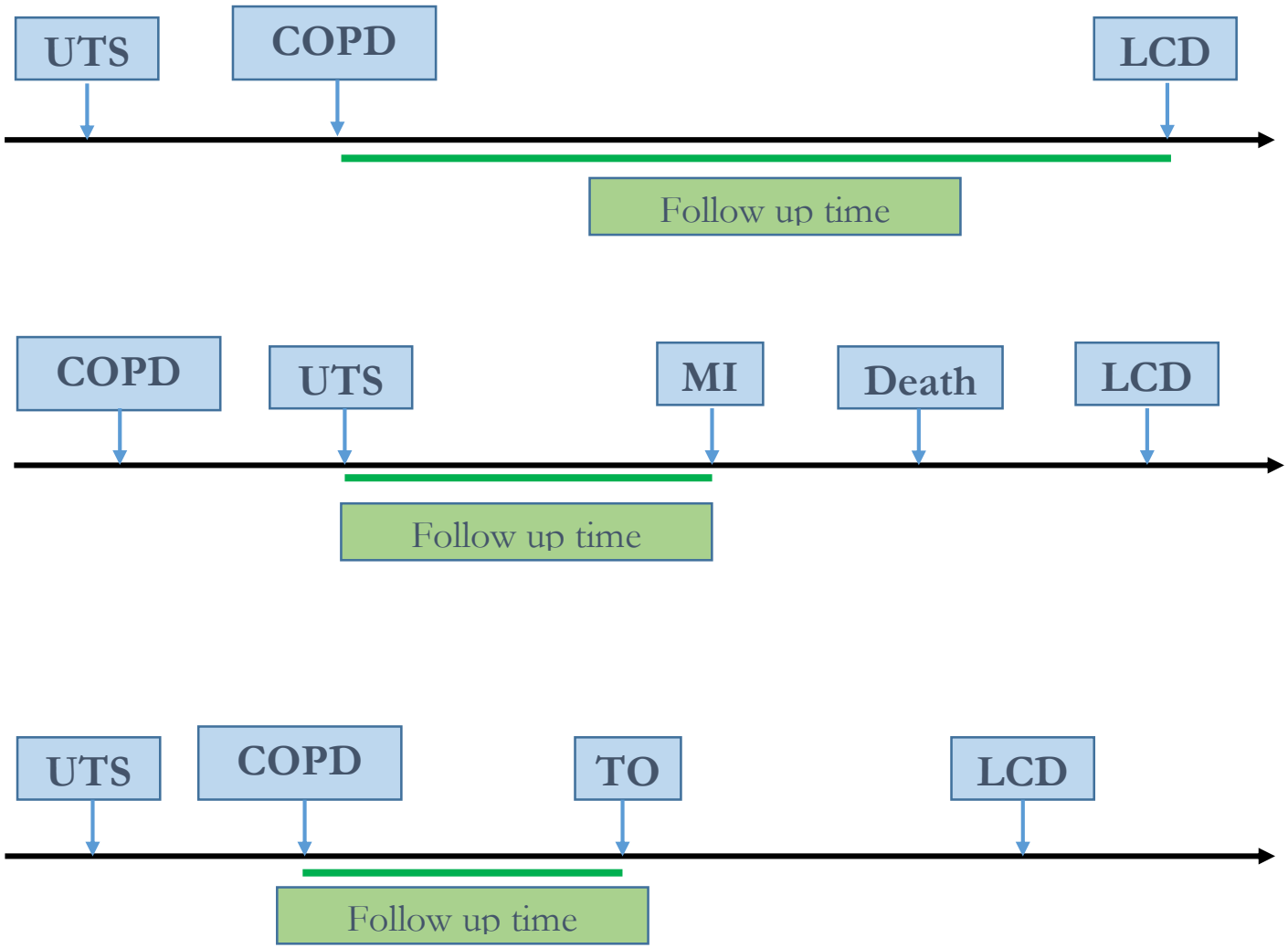

Figure 8. Examples of follow-up time in a hypothetical CPRD study investigating the risk of MI associated with COPD. Patients are followed up from index COPD diagnosis (COPD), or practice up to standard date (UTS) and censored at date of MI (MI), death, transfer out of practice (TO) or practice last collection date (LCD).

2.2 Hospital Episodes Statistics (HES)

Hospital episodes statistics (HES) are administrative data detailing all episodes of admitted patient care (overnight admissions, not including A&E only attendance) in the NHS in England. Details on all episodes of admitted patient care in England have been collected since the 1989/1990 financial year, and are currently collected monthly. HES is an administrative database. The primary purpose of HES data on admitted patient care is to provide information on reason for admission and any co-morbidities, which is used along with age, length of stay, and any procedures carried out to determine hospital remuneration for each episode of care.

Data relating to spells of admitted patient care are organised as "finished consultant episodes" (FCEs). These relate to a period of care under a single consultant. New FCEs in a single hospitalisation often refer to transfer of patients to a different team, for example, from an acute admissions unit to a more specialised ward.

Each FCE is accompanied by up to twenty diagnoses coded using ICD-10, these may relate to either reasons for the current hospitalisation or may be co-morbidities. Like Read codes, ICD-10 codes are also organised as a hierarchy. However, there are fewer synonyms and their use is more strictly controlled in HES.

Certain conditions (such as COPD) are associated with higher remuneration per admitted episode (Department of Health 2012), whether or not the hospitalisation was related to the co-morbidity, and so hospitals have a financial incentive to code several co-morbidites. Diagnoses in each FCE are ordered, and generally the diagnosis in the first position is taken to be the primary diagnosis or reason for admission.

More recent additions to the available HES datasets include A&E and outpatient attendances. Although these add more information in terms of patient contact with secondary care which does not result in hospitalisation, the granularity of the information they contain is much lower than that for episodes of admitted patient care. Data on outpatient attendances only contain information on the speciality of the consultant caring for the patient. HES data on A&E attendance is slightly more detailed, however there are only 56 possible diagnoses. For respiratory problems, these are either classified as "Respiratory conditions - bronchial asthma" or "Respiratory conditions - other non-asthma" (HSCIC 2016).

HES data have been made available for secondary purposes through the Health & Social Care Information Centre (HSCIC). These data are regularly used for service planning and local and national commissioning bodies, as well as for academic and commercial research.

Pseudonomised HES data from 1997 onwards have been linked to a sub-set of CPRD data by HSCIC. Patients registered at CPRD practices in England are eligible to be linked. Currently around 75% of those eligible are registered at practices which have consented to linkage, and this represents almost 60% of those in CPRD (Herrett et al. 2015). Linked HES-CPRD data are generally made available in bi-annual builds, rather than monthly updates. This has implications for study design as study end dates may need to be shortened to make sure all included patients have coverage both in HES and CPRD if linked data are used.

As described in subsequent chapters, for this thesis linked HES-CPRD data are used to identify both AECOPD and MI for COPD patients who are included in CPRD. As a diagnosis of MI would result in admission to hospital, the addition for HES outpatient and A&E data would not be useful. Although COPD patients are likely to attend A&E for treatment of AECOPD, there is not sufficient detail to confidently identify AECOPD. HES outpatient data too, lacks the detail to identify recent AECOPD. Therefore, for this thesis, only HES data on spells of admitted patient care are used.

2.3 Myocardial Ischaemia National Audit Project (MINAP)

The Myocardial Ischaemia National Audit Project (MINAP) is a national clinical audit of care after admission to hospital for acute coronary syndromes (ACS), which includes unstable angina (UA) as well as MI. The purpose of MINAP is to audit the quality of care and outcomes for patients admitted to hospital for ACS, and MINAP aims to collect detailed data from admission to discharge. The primary purpose of MINAP data is to compare the performance of individual hospitals (in terms of process and outcome) against national averages. MINAP started collecting data in 1998.

The exact variables collected by MINAP have changed over time with changing clinical guidelines. Broadly however, data are collected on: date and time of admission, cardiovascular drugs used at admission, final diagnosis, timing and use of reperfusion, drugs used in hospital, use of angiography in hospital, and use of drugs for secondary prevention on discharge. MINAP also has details on important comorbidities, such as heart failure, chronic kidney disease and obstructive airway disease, cardiovascular drugs used at admission, and some other patient characteristics such as age, smoking status, heart rate, systolic blood pressure, and serum creatinine on admission. Data are entered onto a bespoke platform by nurses or clinical coders.

Several variables indicate death in hospital in MINAP and may differ, however reliable data on vital status at 7, 30, and 180 days post-admission are available through linkage to office of national statistics (ONS) mortality data.

MINAP has data available for research from 2003, however the completeness of data for non-STEMIs and UA before 2004 is variable. With over 1,250,000 records, MINAP is the largest database of care and outcomes for people admitted to hospital for ACS in the world.

The strengths of the MINAP database are its size, generalisability to the UK population, and the detailed level of coding of care received while in hospital.

One limitation of MINAP is that patients must be alive when they arrive at hospital before they are entered into the MINAP database. As up to 20% of those who die shortly following their MI die before they reach hospital (Law et al. 2002), this means that many of those with the most severe MIs are likely not to be represented in MINAP.

2.4 Validity of definitions used in this thesis

Validity of measures in epidemiological studies are generally expressed in similar terms to diagnostic accuracy studies. That is in terms of specificity, sensitivity, positive predictive value (PPV), and negative predictive value (NPV).

Specificity relates to the ability of a definition to identify those who do not have a condition, and is the proportion of those who do not have the target condition who are correctly identified as such. Similarly, sensitivity relates to the ability to identify those who do have a condition, and is the proportion of those who have the condition who are correctly identified.

PPV is the proportion of those who are classified as having a condition by a definition who do actually have that condition. NPV is the proportion of those classified as not having a condition who do not indeed have it.

For acute events, such as AECOPD, the most meaningful statistics are PPV, and sensitivity. This is because, generally, for most days of follow up, the vast majority of people will not have the acute condition in question. Under any definition for an acute condition, the NPV and specificity would be very high.

2.4.1 Identification of COPD in EHR

Strategies to identify patients with COPD within CPRD have been previously validated against a reference standard of respiratory physician review of patient notes and questionnaire material (Quint et al. 2014). Using a combination of a specific set of COPD codes, a smoking history,

and in patients aged over 35, COPD can be found with a PPV of 86.5% (95% CI, 77.5–92.3%). Adding use of COPD medicines increases the PPV to 89.4% (95% CI, 80.7–94.5%), but results in a significantly lower number of cases identified. The sensitivity and specificity of these approaches is not clear. In this thesis, both definitions are used. For the two validation studies (Chapters 7 and 8), the definition including COPD medicines is used. To maximise power, the less strict definition was used for the self-controlled case series presented in Chapter 9.

When linked HES data are used in this thesis, COPD is first defined in CPRD, and linked records for these patients are obtained, rather than constructing a definition of COPD in HES.

In MINAP, there is no variable which identifies COPD. Instead, there is a variable for obstructive airway disease, however this may also relate to asthma. In order to identify people with COPD in MINAP, an algorithm was constructed and assessed using a sub-set of the data which was linked to CPRD. This is described in Chapter 4.

2.4.2 Identification of AECOPD in EHR

Due to the numerous ways that GPs may record AECOPD in EHR, the identification of AECOPD is not clear. Previous studies have used combinations of prescriptions of oral corticosteroids and antibiotics in people with COPD to identify AECOPD (Donaldson et al. 2010). The validity of this approach is not clear, and may result in misclassification with other infections. It was therefore decided to validate the recording of AECOPD in EHR. This is the subject of investigation in the research papers presented in Chapters 7 and 8.

2.4.3 Identification of MI in EHR

The recording of MI in EHR has previously been validated in linked CPRD-HES-MINAP data, using MINAP data as a reference standard (Herrett et al. 2013). This study indicated that using either primary care or secondary care data alone underestimated the number of MIs, and that the PPV of both primary care identified (92.2% (95% CI 91.6%-92.8%)) and secondary care identified (91.5% (95% CI, 90.8%-92.1%)) MI was high. For the study presented in Chapter 9, both linked primary care and secondary care data are used to identify MIs.

Chapter 3: Systematic review and meta-analysis of the risk of MI and risk of death after MI for people with COPD (Research Paper I)

3.1 Preamble

This chapter reports a systematic review of evidence for three important areas in the relationship between COPD and MI related to this thesis: 1) the risk of MI associated with COPD; 2) the risk of death following MI in people with and without COPD; and 3) the risk of MI associated with AECOPD. The purpose of this review was to synthesise and appraise the current evidence for these areas so as to inform the rest of the thesis.

Although others have conducted systematic reviews of the association between COPD and MI (Chen et al. 2015, Müllerova et al. 2013), they have not distinguished prevalent MI from incident MI, and therefore did not assess risk. Crucially, neither have others focussed on whether the association is independent from smoking. This is the first systematic review to assess the relationship between AECOPD and MI; and also the first to assess the relationship between COPD and death following acute MI.

This paper was originally published in *BMJ Open*, and is available here:
Rothnie KJ, Yan R, Smeeth L, Quint JK. 'The risk of myocardial infarction (MI) and death following MI in people with chronic obstructive pulmonary disease: A systematic review and meta-analysis'. *BMJ Open.* 2015 **5**(9).

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   1.1. Where was the work published? BMJ Open

   1.2. When was the work published? 11 September 2015

   1.2.1. If the work was published prior to registration for your research degree, give a brief rationale for its inclusion

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   1.3. Was the work subject to academic peer review? Yes

   1.4. Have you retained the copyright for the work? **Yes** ~~No~~
   If yes, please attach evidence of retention.
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   2.2. Please list the paper's authors in the intended authorship order

   .....

   2.3. Stage of publication – Not yet submitted / Submitted / Undergoing revision from peer reviewers' comments / In press

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   Designed study, wrote protocol, conducted literature searches, screend abstracts and full text papers, supervised assistant, analysed data, interpreted data, wrote first draft of paper, wrote final draft of paper after co-author comments.

NAME IN FULL (Block Capitals) KIERAN JOHN ROTHNIE

STUDENT ID NO: 405576

CANDIDATE'S SIGNATURE Kieran Rothnie Date 14/04/16

SUPERVISOR/SENIOR AUTHOR'S SIGNATURE (3 above) .....

3.2 Research paper

The risk of myocardial infarction (MI) and death following MI in people with chronic obstructive pulmonary disease: A systematic review and meta-analysis

Authors Kieran J Rothnie, Ruoling Yan, Liam Smeeth, Jennifer K Quint

Abstract

Objectives Cardiovascular disease is an important co-morbidity in COPD patients. We aimed to systematically review the evidence for: i) risk of MI in people with COPD; ii) risk of MI associated with AECOPD; iii) risk of death after MI in people with COPD.

Design Systematic review and meta-analysis.

Methods MEDLINE, EMBASE and SCI were searched up to January 2015. Two reviewers screened abstracts and full text records, extracted data and assessed studies for risk of bias. We used the generic inverse variance method to pool effect estimates where possible. Evidence was synthesised in a narrative review where meta-analysis was not possible.

Results Searches yielded 8362 records, and 24 observational studies were included. Meta-analysis showed increased risk of MI associated with COPD (HR 1.72, 95% CI 1.22-2.42) for cohort analyses, but not in case-control studies OR 1.18 (0.80-1.76). Both included studies that investigated the risk of MI associated with AECOPD found an increased risk of MI after AECOPD (IRR 2.27, 1.10-4.70, and IRR 13.04, 1.71-99.7). Meta-analysis showed weak evidence for increased risk of death for COPD patients in-hospital after MI (OR 1.13, 0.97-1.31). However meta-analysis showed an increased risk of death after MI for COPD patients during follow-up (HR 1.26, 1.13-1.40).

Conclusions There is good evidence that COPD is associated with increased risk of MI, however it is unclear to what extent this association is due to smoking status. There is some evidence that the risk of MI is higher during AECOPD than stable periods. There is poor evidence that COPD is associated with increased in-hospital mortality after an MI, and good evidence that longer term mortality is higher for COPD patients after an MI.

Strengths and limitations of the study

- This systematic review investigated three important areas relating to the relationship between COPD and cardiovascular disease: 1) the risk of MI associated with COPD; 2) the risk of MI associated with acute exacerbations of COPD; and 3) the risk of death following MI in COPD patients compared to non-COPD patients.

- Strengths of this review were the wide search strategy, broad inclusion criteria, and rigorous risk of bias assessment of included studies.

- We found strong evidence for an increased risk of MI in people with COPD and an increased risk of longer term death after MI for COPD patients, however it is unclear how much of this increased risk may be due to smoking status.

- We found poorer evidence for an increased risk of MI during periods of acute exacerbation of COPD compared to stable periods, and for an increased risk of death in-hospital after MI for COPD patients. We make recommendations on how future studies can improve our understanding of these relationships.

- Due to statistical and clinical heterogeneity, meta-analysis could only be conducted for some of the research questions.

Introduction

Cardiovascular disease is a common co-morbidity and cause of death in people with chronic obstructive pulmonary disease (COPD), with up to one third dying of cardiovascular disease[1]. Reducing the cardiovascular disease in this population is an important strategy for reducing the burden of COPD.

Several studies have shown that people with COPD have a higher risk of myocardial infarction (MI) than people without COPD[2-4]. One of the reasons for the increased risk of MI in patients with COPD is the shared major risk factor of smoking. In addition, several other cardiovascular risk factors including hypertension, diabetes, inactivity, poor diet, and older age are also prevalent in COPD patients[5-7]. In addition, several studies have found an association between reduced FEV_1 and cardiovascular mortality in the general population[8]. However, COPD itself is also thought to be an independent risk factor for MI with increased risk of MI possibly being mediated through increased systemic inflammation, or reduced FEV_1, in people with COPD.

Acute exacerbations of COPD are events in the natural history of COPD which are characterised by an increase in COPD symptoms such as breathlessness, cough, sputum volume, and sputum purulence. It has recently been suggested that acute exacerbations of COPD (AECOPD) represent a period of increased risk of MI for people with COPD[9]. A sub-type of COPD patients appears to have more frequent exacerbations than others. Frequent exacerbators have been defined as individuals who have two or more treated exacerbations per year. Frequent exacerbators may be at higher risk of MI compared to infrequent exacerbators, even during stable periods.

Several investigators have found that patients with COPD have worse mortality in-hospital and following discharge after an MI compared to non-COPD patients[10-12]. However, the finding that COPD patients have greater in-hospital and short term mortality has not been found by all investigators[13-15].

We aimed to systematically review the literature reporting on: i) The risk of MI in people with COPD; ii) The risk of MI associated AECOPD, either during AECOPD or that associated with the frequent exacerbator phenotype; and iii) the risk of death after MI in people with COPD. These questions represent the most salient aspects of current research into the relationship between COPD and cardiovascular disease and no systematic reviews have been published on these topics to date.

Methods

Literature search

MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, EMBASE, BIOSIS & Science Citation Index were searched up to January 2015. A search strategy was devised which would pick up articles relevant to all three research questions. All strategies were based on the MEDLINE search strategy, which is presented in the supplementary material. In brief, the literature was searched for terms which relate to COPD and terms with relate to MI, and these searches were combined using the AND Boolean logic operator. MeSH terms were combined with natural language searching using truncation where appropriate.

Inclusion and exclusion criteria

Inclusion and exclusion criteria were applied for each of the three research questions as follows. Studies were included if they met the population, exposure, comparator and outcome criteria. These are presented below for each research question. Studies were included from database start date and were not restricted by language.

i) Risk of MI in people with COPD

The population of interest was the general population. The exposure of interest was diagnosis of COPD. The un-exposed group were people without a diagnosis of COPD. The outcome of interest was acute MI.

ii) Risk of MI associated with AECOPD

The population of interest was people with a diagnosis of COPD. The exposures of interest were either: 1) discrete episodes of AECOPD or periods within 8 weeks of an AECOPD; or 2) frequent exacerbator phenotype. The comparators of interest were either: 1) periods of stable COPD; or 2) infrequent exacerbator phenotype. Studies were included if they reported a relative risk of MI, or if this could be calculated.

iii) Risk of death after MI in people with COPD

The population of interest was those presenting to a hospital with an MI. Studies were included if they compared those with a diagnosis of COPD to those without a diagnosis of COPD. Outcomes of interest were death in hospital and at any reported time points post-discharge. Studies investigating risk of death for COPD patients after an interventional procedure following an MI (such as percutaneous coronary intervention or coronary artery bypass graft) were specifically excluded under the population criterion.

Selection of included studies

Titles and abstracts, where available, were initially screened for potential inclusion by one reviewer. Full text versions of potentially included studies were then obtained and were screened by two reviewers. Authors were contacted if the information provided in articles was not sufficient to assess whether inclusion criteria were satisfied.

Risk of bias assessment

All included studies, except for those only reported as conference abstracts, were assessed for risk of bias. The risk of bias tool was informed by the Newcastle-Ottawa scale[16], however did not use of a summary score as this is not advisable[17 18]. Risk of bias was assessed across the key domains of: selection of participants, comparability of groups and measurement of outcomes. Several items were included under each domain, and were adapted for different study types. Where reports of studies included more than one analysis (for example, a case control as well as

a cohort analysis) the risk of bias for these analyses were conducted separately. Risk of bias assessment was completed by one reviewer and checked by another.

Evidence synthesis

Characteristics and findings of studies were tabulated and compared. Data on severity of COPD was extracted as GOLD stage or FEV_1 %predicted, where available. Information was also extracted on smoking status and previous cardiovascular disease. Estimates of effect were extracted or calculated and are presented as odds ratios (OR), risk ratios (RR), incidence rate ratios (IRR), or hazard ratios (HR).

Where included studies were reasonably statistically and clinically similar, we pooled results using random effects meta-analysis. We used the generic inverse variance method to pool maximally adjusted effect estimates. Analysis was conducted in Review Manager 5.3. Where studies were too statistically (I^2 over 75%) or clinically heterogeneous, meta-analysis was not conducted, but study summary results were graphed on forest plots without pooling the results. Studies which were not adjusted at all were not included in forest plots. For the question on risk of MI associated with COPD, studies were stratified by adjustment for smoking status (yes or no) and study design (cohort or case-control). For the question on risk of death following MI in COPD compared to non-COPD patients, studies were stratified by outcome time-point (in-hospital mortality or follow-up mortality). For follow-up mortality, studies were further stratified by analysis method (cumulative incidence or time-to-event).

Results

Identified studies

Literature searches yielded 8362 records. After title and abstract screening, 49 records were selected for full text assessment, which resulted in the inclusion of 24 studies. The inclusion and exclusion process is summarised in Figure 1. Of the 24 included studies, 9 investigated the risk of MI in COPD patients compared to non-COPD patients; 2 investigated the risk of MI associated with AECOPD, no studies were found which investigated the risk of MI associated

with the frequent exacerbator phenotype; and 12 investigated outcomes after MI for COPD patients compared to non-COPD patients. Summary characteristics of included studies are presented in Tables 1, 2 and 3.

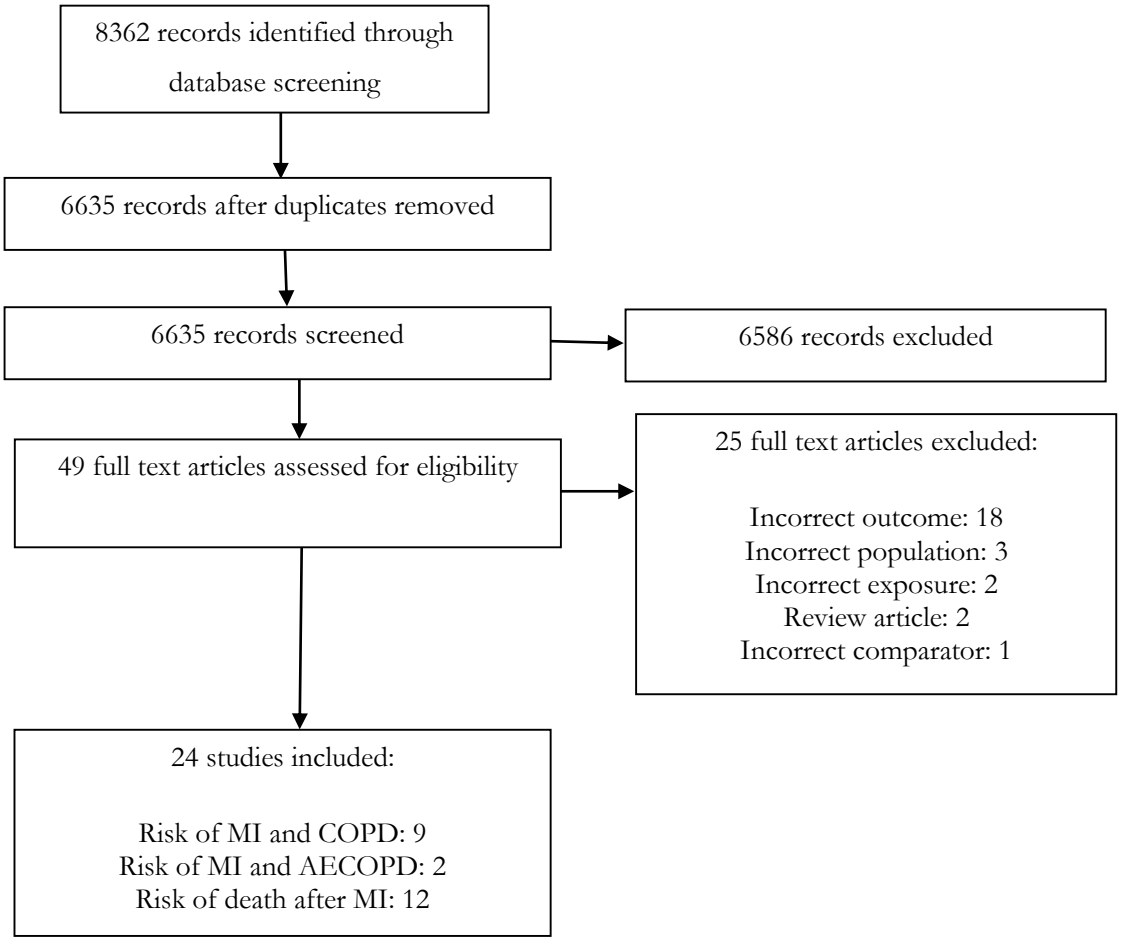

Figure 1. Study selection

Table 1. Detailed Characteristics of included studies – risk of MI associated with COPD

Study	Design and setting	Population	Characteristics of COPD patients	MI definition	Maximally adjusted estimate (95% CI)	Factors adjusted for
Curkendall 2006a and 2006b	Cohort in the Saskatchewan Health databases 1998-2001.	11 493 COPD patients ≥ 40 years, identified by physician claim or hospital discharge COPD code and at least two prescriptions for COPD medicines within 6 months of the index COPD code. 22 986 age and sex matched non-COPD patients	**Age** NR **Sex** NR **COPD severity** NR **Current smokers** 16% **History of CVD** Previous MI - 2.3% Previous angina – 6.6%	**Any MI during follow up:** any inpatient or outpatient diagnosis of MI **Hospitalisation due to MI:** primary hospital discharge diagnosis of MI **Fatal MI:** underlying cause of death which initiated the sequence of events that lead to death recorded as MI	**Any MI during follow up (period prevalence):** OR 1.61 (1.43-1.81) **Hospitalisation due to MI:** IRR 1.49 (0.71-3.13) **Fatal MI:** IRR 1.51 (1.14-2.01)	**Period prevalence of MI:** Age, sex, history of cardiovascular disease, diabetes, hypertension, hypercholesterolaemia **Hospitalisation for MI:** adjusted for history of cardiovascular events, diabetes, hypertension, and hypercholesterolemia using Poisson regression, age and sex by matching. **Fatal MI:** age and sex by matching only.

Feary 2010	Cohort in The Health Improvement Network, 2005-2007	29 870 COPD patients >35 years identified by COPD diagnostic code. 1 174 240 non-COPD patients	**Age** 35-44 – 1.8% 45-54 – 7.0% 55-64 – 20.5% 65-74 – 31.7% ≥75 – 39.0% **Sex** 48.1% male **COPD severity** FEV_1 % predicted 50-80% - 37.5% 30-49% - 19.1% <30% - 5.3% **Current smokers** 65.3% **History of CVD** Prior CVD – 28.0%	Diagnostic code for MI in primary care record	**35-44 years:** HR 10.34 (3.28-32.6) **45-54 years:** HR 1.22 (0.55-2.74) **55-64 years:** HR 1.55 (1.07-2.26) **65-74 years:** HR 1.78 (1.37-2.31) **≥75 years:** 1.34 (1.03-1.73)	Age, sex and smoking status

Huiart 2005	Cohort in the Saskatchewan Health databases 1990-1999	5 648 COPD patients ≥ 50 years, identified by prescription of three or more bronchodilators within the period of one year. Rates of MI compared to those of general Saskatchewan population	**Age** NR **Sex** NR **COPD severity** NR **Current smokers** NR **History of CVD** NR Characteristics were not split by COPD status.	Primary hospital discharge diagnosis of MI	**Standardised IRR:** 1.30 (1.15-1.44)	Age and sex by standardisation
Mapel 2005	Cohort in the Veterans Administration	COPD patients identified by discharge codes (1991-1999) and/or	**Age** Median 60 (IQR, 49-62) **Sex**	Specific ICD-9-CM code for MI during 1999 that was not present in 1998	**COPD patients identified using discharge codes**	Age and sex by matching

	Medical System, 1991-1999	outpatient codes (1997-1999) Age and sex matched controls without COPD	95.7% male **COPD severity** NR **Current smokers** NR **History of CVD** Cardiovascular disease – 71.2%		**IRR:** 1.28 (1.18-1.38) **COPD patients identified using outpatient codes** **IRR:** 5.31 (4.54-6.21)	
Rodriguez 2010	Cohort and case-control study in the General Practice Research Database, 1996-2001	1532 patients with a first COPD diagnosis in 1996, and no history of cardiovascular disease 13 500 age and sex matched non-COPD patients, with no history of cardiovascular disease	**Age** NR **Sex** NR **COPD severity** NR **Current smokers**	Diagnostic code for MI in primary care record	**Cohort analysis:** IRR 1.18 (0.81-1.71) **Case-control analysis:** OR 0.93 (0.62-1.39)	**Cohort analysis:** Age and sex **Case control analysis:** Age, sex, smoking and number of primary care physician visits

			NR **History of CVD** NR			
Schneider 2010	Cohort and nested case-control study in the General Practice Research Database, 1995-2005	35 772 patients with a first COPD diagnosis between 1995-2005 35 772 non-COPD patients matched on age, sex and calendar time and general practice	**Age** 40-49 – 6.8% 50-59 – 19.9% 60-69 – 33.8% >70 – 39.6% **Sex** 51.3% male **COPD severity** NR **Current smokers** 43.3% **History of CVD**	Diagnostic code for MI along with death or hospitalisation within 30 days of the diagnosis; and/or start of new treatment with ACE antagonist, β-blocker, statin, vitamin K antagonist, platelet aggregation inhibitor or aspirin within 90 days of the diagnosis in primary care record	**Cohort analysis:** IRR 1.56 (1.43-1.75) **Case control analysis:** Any COPD : OR 1.40 (1.13-1.73) Mild COPD: OR 1.79 (1.12-2.86) Moderate COPD: OR 1.30 (1.04-1.62) Severe COPD: OR 3.00 (1.53-5.86)	Cohort analysis: matched on age, sex, calendar time and general practice Case-control analysis: Smoking status, BMI, hypertension, hyperlipidaemia, diabetes and NSAID use

			Prior MI/CHD – 18.3% Prior CHF – 8.4%			
Sidney 2005	Cohort in health insurance database. North Carolina, 1996-1999	COPD defined as: hospitalisation or outpatient diagnosis of COPD, two or more prescriptions for COPD medicines, aged over 40 years. Non-COPD patients matched on age, sex and length of care plan membership.	**Age** 40-59 – 35% 60-79 – 55% >80 – 10% **Sex** 55.4% male **COPD severity** NR **Current smokers** NR **History of CVD** Prior MI – 1.8% Prior angina – 1.0% Prior CHF – 7.2%	ICD code for acute MI	Overall: IRR 1.89 (1.71-2.09) Men: IRR 1.77 (1.56-2.01) Women: IRR 2.09 (1.78-2.46) 40-64 years: IRR 2.43 (1.98-2.98) ≥65 years: IRR 1.73 (1.54-1.94)	Age, sex and baseline cardiovascular risk profile.

Sode 2011	Cohort study within the National Danish patient registry, 1980-2006	Entire Danish population. COPD identified through hospital admission codes or COPD as cause of death	**Age** <30 – 7% 30-59 – 54% 60-79 –35 % >80 - 3% **Sex** 55% male **COPD severity** NR **Current smokers** NR **History of CVD** NR	Discharge diagnosis of MI or cause of death from Danish Causes of Death Registry listed as MI	HR 1.26 (1.25-1.27)	Age, sex, Danish ancestry, geographical residency (rurality), and level of education
Yin 2014	Cohort of all residents of Sweden aged over 18, July 2005-December 2008.	51 348 COPD patients identified by diagnostic codes from patient	***Those with no previous MI or stroke*** **Age** Mean 71.1	Diagnostic code for MI, or primary cause of death listed as MI	**No previous MI or stroke:**	Age, sex, socioeconomic status, use of cardiovascular and respiratory medicines.

		records. 6 743 342 non-COPD patients.	**Sex** 44.3% male **COPD severity** NR **Current smokers** NR **History of CVD** No previous MI ***Those with previous MI*** **Age** Mean 69.2 **Sex** 58.4% male **COPD severity**		HR 1.47 (1.41-1.55)* **Previous MI:** HR 1.33 (1.23-1.43)*	

			NR **Current smokers** NR **History of CVD** All had previous MI			

*Data from personal communication (Magnus Back. Email communication. 18/08/2014).

Table 2. Characteristics of included studies – risk of MI associated with AECOPD

Study	**Design and setting**	**Population**	**Characteristics**	**AECOPD definition**	**MI definition**	**Risk periods**	**Risk estimate** (95% CI)
Donaldson 2010	Self controlled case series in The Health Improvement Network, 2003-2005	426 patients with COPD and MI during study period. COPD defined using Quality and Outcomes Framework codes.	**Age** Median 74 years (IQR, 67-80) **Sex** 61% male **Current smokers** NR **COPD severity** Median FEV_1 % predicted: 55.9% (IQR, 43-73) **History of CVD** NR	Three definitions used: 1) Prescription of oral steroids 2) Prescription of pre-specified antibiotic 3) Prescription of pre-specified antibiotic and prescription of oral steroid	Diagnostic code for MI in primary care record	1-5days, 6-10 days, 11-15 days, 16-49 days, and 1-49 days.	**Antibiotics and steroids definition:** 1-5 days: IRR 2.27 (1.10-4.70) 6-10 days: IRR 1.74 (0.80-4.0) 11-15 days: IRR 0.90 (0.30-2.90) 16-49 days: IRR 0.83 (0.50-1.40)

							1-49 days: IRR 1.11(0.70-1.70)
Halpin 2011	Secondary analysis of patients in UPLIFT RCT	3 512 COPD patients who survived at least their first AECOPD. COPD defined as age ≥40 years, smoking history ≥10 pack-years, FEV_1 ≤70% predicted, and FEV_1/FVC≤70%.	**Age** Mean 64 (SD, 8) **Sex** 74% male **COPD severity** GOLD stage II 43% GOLD stage III 46% GOLD stage IV 9% Mean FEV_1 % predicted 38% (SD, 12) **Current smokers** 29% **History of CVD** NR	Increase in or new onset of more than one of: cough, sputum, sputum purulence, wheezing or dyspnoea; lasting 3 or more days and requiring treatment with an antibiotic or oral steroid. Data on timing of AECOPD collected at study visits	MI ascertained during RCT follow-up and recorded as a serious adverse event	30 days after AECOPD, compared to 30 days before AECOPD	IRR 13.04 (1.71-99.7)

Table 3. Characteristics of included studies – risk of death after MI

Study	Design and setting	Population	COPD patient characteristics	Maximally adjusted estimate for mortality (95% CI)	Factors adjusted for
Andell 2014	Cohort study within the Swedish SWEDEHEART registry between 2005-2010.	Consecutive patients admitted to Swedish coronary care units. COPD diagnosis ascertained through linkage to the Swedish National Patient Registry.	**Age** Mean 75 years (SD, 9) **Sex** 54% male **COPD severity** NR **Current smokers** 32.9% **History of CVD** Prior MI 13.7% Prior HF 20.2%	Mortality at one year: HR 1.14 (1.07-1.21)	Age, sex, smoking, comorbidity (previous MI, previous stroke, heart failure, renal failure, hypertension, diabetes, peripheral artery disease, cancer and previous bleeding), in hospital treatment and discharge medications (heparin, fondaparinux, dalteparin, enoxaparin, glycoprotein IIb/IIa inhibitors, angioplasty, coronary stenting, β-blockers, aspirin, clopidogrel, prasugrel, calcium channel blockers, digoxin, diuretics, statins, nitrates and warfarin).

Behar 1992	Cohort study in Israel between 1981-1983	2276 consecutive patients surviving an MI after admission to 13 coronary care units. Patients with a history of chronic bronchitis or chronic airways obstruction and clinical and/or radiographic findings compatible with COPD during hospitalisation for MI were included.	**Age** Mean 66.8 years (SD, 9.7) **Sex** 79.3% male **COPD severity** NR **Current smokers** 43.3% **History of CVD** Prior MI – 28.8% Prior angina – 55.4%	**Unadjusted**:* In –hospital RR 1.39 (1.16-1.67) 1 year RR 1.34 (1.16-1.55) 5 years RR 1.28 (1.18-1.40)	
Bursi 2010	Cohort study of the population in the Rochester Epidemiology project involving residents in Olmsted	Local residents in Olmsted County. MI ascertained from medical records compatible with ICD criteria. Information on COPD was also obtained from ICD codes.	**Age** Mean 73 years (SD, 11) **Sex** 59% male **COPD severity**	HR 1.30 (1.10 to 1.54), mean follow up 4.7 years.	Age, sex, smoking, hypertension, MI type (STEMI/non-STEMI), creatine kinase level, killip class, reperfusion treatment in hospital, use of drugs on discharge (β-blockers, ACEi, diuretics)

	County, Minnesota from 1979 to 2007		NR **Current smokers** 35% **History of CVD** Those with prior CVD excluded		
Dziewierz 2010	Cohort study within Krakow Registry of ACS in February 2005-March 2005 and December 2005-January 2006	1414 patients with MI admitted to hospital in Krakow, Poland. Those with a previous history of COPD and current treatment with a steroid or bronchodilator were classified as COPD patients.	**Age** Mean 71.8 years (SD, 11) **Sex** 62% male **COPD severity** NR **Current smokers** 40.7% **History of CVD** MI 34.6% Angina 80.2% HF 30.9%	HR 2.15 (1.30-3.55)	Age, sex, BMI, diabetes, hypertension, hyperlipidaemia, prior angina, prior MI, prior heart failure, left ventricular ejection fraction, prior PCI, prior CABG, prior stroke or transient ischaemic attack, smoking status, peripheral arterial disease, chronic renal insufficiency, parameters on admission (chest pain, cardiogenic shock, heart rate, systolic blood

					pressure, diastolic blood pressure), time from chest pain onset to admission and type of MI (STEMI or NSTEMI)
Enriquez 2013	Cross sectional study of National Cardiovascular Data Registry in the USA between January 2008 and December 2010	158 890 patients admitted to one of 445 sites with an MI. COPD patients had a history of COPD or were using long term inhaled or oral β-agonists, inhaled anti-inflammatory agents, leukotriene receptor antagonists or inhaled steroids.	**Age** STEMI – median 66 years nSTEMI – median 70 years **Sex** STEMI – 60.4% male nSTEMI – 57.5% male **COPD severity** NR **Current smokers** STEMI – 57.0% nSTEMI – 41.9% **History of CVD** **STEMI**	**In-hospital mortality** STEMI OR 1.05 (0.95-1.17) Non-STEMI OR 1.21 (1.11-1.33)	Age, serum creatinine, systolic blood pressure, troponin elevation, heart failure or cardiogenic shock at presentation, ST-segment changes, heart rate and prior peripheral arterial disease.

			Prior MI – 29.7% Prior CHF – 15.3% **nSTEMI** Prior MI – 39.% Prior CHF – 33.3%		
Hadi 2010	Cross sectional study of patients hospitalised with ACS in May 2006 and January 2007 to June 2007 in six Middle Eastern countries	8169 consecutive patients in the Gulf RACE registry presenting with ACS at 65 centres across six countries. COPD patients were identified from 1) medical records or 2) use of COPD medicines.	**Age** Median 64 (IQR, 56-71) **Sex** NR **COPD severity** NR **Current smokers** 38.7% **History of CVD** Prior MI - 34.8% Prior angina – 54.4%	**In hospital mortality:** OR 0.40 (0.20-1.24)	Age, sex, cardiogenic shock, use of thrombolysis, use of aspirin, use of β-blocker, use of ACEi

Hawkins 2009	Cohort study of patients with acute MI enrolled in VALIANT trial	Patients with MI complicated by LVSD and HF. COPD was identified by a questionnaire completed by trial site investigators.	**Age** Mean 68.1 (SD, 9.9) **Sex** 71.1% male **COPD severity** NR **Current smokers** 42.0% **History of CVD** Prior MI – 39.9% Prior angina – 46.1% Prior HF – 27.3%	HR 1.14 (1.02-1.28)	Age, heart rate, systolic and diastolic blood pressure, weight, baseline creatinine, smoking status, diabetes, dyslipidaemia, hypertension, killip classification, anterior MI, new lower bundle branch block, thrombolytic therapy, primary PCI, coronary artery bypass graft, history of heart failure, atrial fibrillation, previous MI, angina, previous stroke, peripheral arterial disease, renal insufficiency, alcohol abuse, country of enrolment, beta blocker use, randomised treatment
Kjoller 2004	Cohort study of consecutive patients	Danish hospitals between May 1990 and July 1992 as part of TRACE study. COPD was identified using either 1)	**Age** Median 70.5 (5-95 percentiles, 50.7-83.5)	**Cohort entry to 30 days:** HR 0.89 (0.68-1.11)	Age, sex, BMI, hypertension, diabetes, smoking status, previous angina, wall motion index, angina,

	recruited 1-6 days after an MI	medical records or 2) patient report in addition to use of COPD medicines	**Sex** 68.2% men **COPD severity** NR **Current smokers** 60.0% **History of CVD** Previous MI – 25.1% Previous angina – 43.9 Previous CHF – 28.2%	**Cohort entry to 7 years:** HR 1.15 (1.04-1.28)	history of CHF, new CHF, atrial fibrillation, bundle branch block, wall motion index, use of thrombolytic therapy
Quint 2011 (abstract)	Cohort study of patients admitted after a first MI using data from the UK CALIBER database	8 065 patients admitted to UK hospitals with a first MI between Jan 2003-Dec 2008. COPD was identified using primary care records.	**Age** NR **Sex** NR **COPD severity**	**Mortality up to 7 years:** HR 1.37 (1.23-1.52)	Age and sex

			NR **Current smokers** NR **History of CVD** NR		
Raposeiras 2012 (abstract)	Cross sectional and cohort study of patients with ACS	4 497 consecutive patients admitted to Spanish hospitals for ACS. The ascertainment method for COPD was unclear.	**Age** NR **Sex** NR **COPD severity** NR **Current smokers** NR **History of CVD** NR	**In-hospital death** OR 1.04 (1.03-1.04) **Follow up mortality** HR 1.69 (1.41-2.03), median follow up 3.1 years	GRACE score β-blocker therapy

Rha 2009 (abstract)	Case control study in Korea AMI registry from 2005 to 2007	AMI patients in KAMIR	**Age** Mean 71.7 (SD 10.0) **Sex** NR **COPD severity** NR **Current smokers** NR **History of CVD** NR	**Mortality at 8 months** OR 2.69, 95% CI could not be calculated from reported information.	Unadjusted
Salisbury 2007	19 centre prospective study of patients presenting with MI in a cohort study	MI patients in PREMIER study restricted to patients discharged alive after MI. Patients were considered to have COPD if they had a documented history of obstructive pulmonary disease (COPD or asthma) or had	**Age** Mean 64.5 (SD, 12.4) **Sex** 61.8% male **COPD severity**	**Mortality up to 1 year** HR 2.00 (1.44-2.79)	Age, gender, race, avoidance of health care due to cost, smoking, diabetes, hypertension, CHF, ejection fraction, previous CVD, MI diagnosis type, new onset HF after MI, diseased vessels on angiogram, enrolling site,

		therapy specific for obstructive pulmonary disease.	NR **Current smokers** 37.6% **History of CVD** Previous MI – 29.7% Previous HF – 24.3%		percentage of MI quality of care indicators of the centre, treatment type
Stefan 2012	Cross sectional study with follow up of patients hospitalised with AMI at greater Worcester, Massachusetts between 1997-2007	Patients hospitalised with AMI in greater Worcester, Massachusetts medical centres. COPD patients were identified by previous mention of clinical or radiographic evidence for COPD in their medical record.	**Age** Mean 74 years **Sex** 52.4% male **COPD severity** NR **Current smokers** 27.3% **History of CVD**	**In hospital**: OR 1.25 (0.97-1.34) **30 day mortality**: OR 1.31 (1.10-1.58)	Age, sex, year of hospitalisation, history of CVD, history of renal failure, type of MI (STEMI/non-STEMI), length of stay, smoking status used in secondary analysis

			Prior angina – 22.3% Prior HF – 38.6%		

*Calculated from reported data.

All of the included studies which investigated risk of MI in people with COPD used data from either routine clinical or administrative databases. COPD was defined using diagnostic codes, these varied between COPD diagnosis in primary care, outpatient departments, hospital admission or discharge codes and cause of death codes. Three studies also required that COPD patients had been prescribed COPD medicines. One of the studies, Rodriguez 2010[19], included only patients with a recent diagnosis of COPD and followed up for up to 5 years after this to identify MI. Only one study[3] reported a summary of COPD severity, and only two reported prevalence of current smokers. Four studies reported a cohort analysis only. Two studies[4 19] reported a cohort analysis as well as a case control analysis. One study reported the results of a cohort analysis and an analysis of period prevalence. One study[20] compared rates of MI in patients with COPD to standardised populations rates of MI.

Two studies[9 21] were identified which investigated the risk of MI associated with AECOPD. Both studies defined risk periods after the onset of AECOPD and used within person designs to compare the risk to a baseline period.

Nine studies reported mortality for COPD patients after an MI compared to non-COPD patients. Five studies[11 12 14 15 22] reported a comparison of in-hospital mortality after an MI between COPD patients and non-COPD patients. Eight studies[10 12 13 23-27] used a time to event analysis to investigate death after discharge from a hospital admission for MI.

Risk of bias assessment

The proportion of studies (or analyses, where appropriate) which were assessed as either lower, unclear, or higher risk of bias for each of the research questions is presented in Figure 2. Detailed results from the risk of bias assessment for individual studies are presented in the appendix.

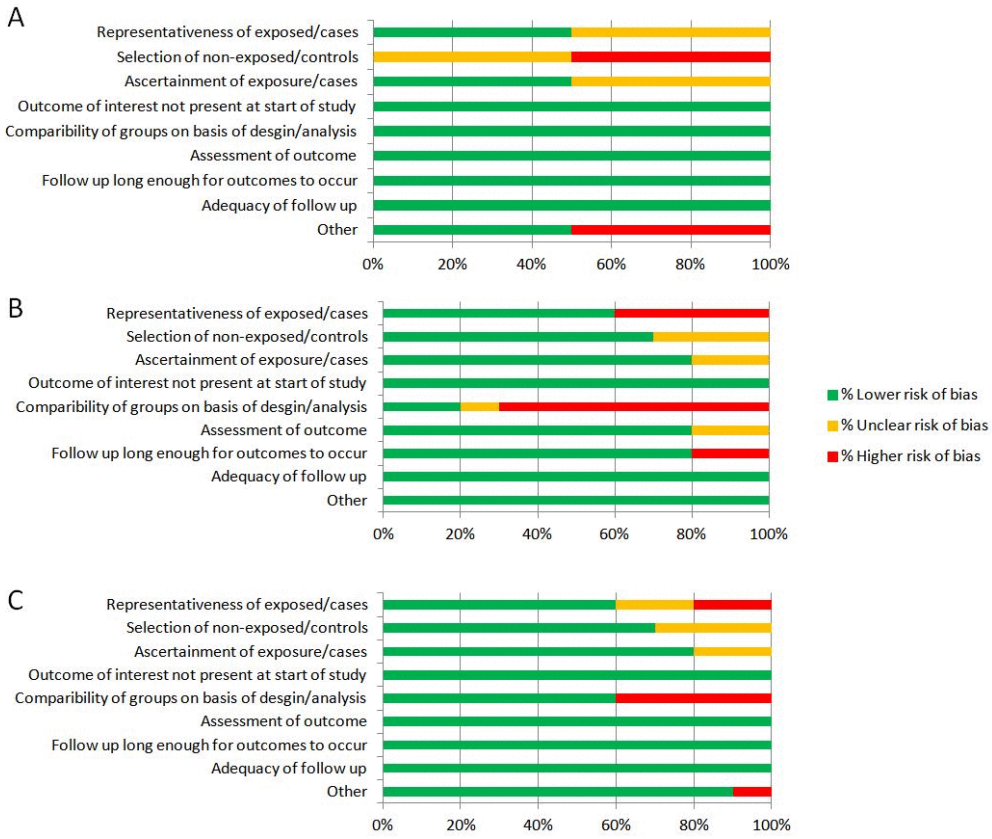

Figure 2. Summary of risk of bias for risk assessments for: A studies investigating risk of MI associated with COPD; B studies investigating risk of MI associated with AECOPD; and C studies investigating risk of death following MI in people with COPD. AECOPD, acute exacerbation of COPD; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction.

Risk of MI in people with COPD

Of 9 included studies, 8 found a higher risk of MI in COPD patients compared to non-COPD patients. Six studies estimated the ratio of incidence rates of MI in COPD patients compared to non-COPD patients. Five studies[4 19 20 28 29] estimated this for all MIs, this ranged from IRR 1.18 (95% CI, 0.81-1.71) to 5.31 (4.54-6.21). One study[2 30] estimated the IRR for hospitalisation due to MI (IRR 1.49, 95% CI 0.71-3.13) and fatal MIs (1.51, 1.14-2.01). Two studies[31 32] estimated the ratio of hazard of MI in COPD patients compared to non-COPD patients one study estimated this to be HR 1.26, 95% CI 1.25-1.27, the other study estimated this to be HR 1.47 (1.41-1.55) for those with no previous MI, and HR 1.33 (1.23-1.43) for those with a previous MI. One study[2 30] estimated the ratio of odds of period prevalence over five years of acute MI in COPD patients compared to non-COPD patients (OR 1.61, 95% CI 1.43-1.81). Only one[3] of the included cohort studies comparing risk of MI in people with COPD and people without COPD adjusted for smoking status. This study reported results stratified by age groups. Meta-analysis of these results showed an increased risk of MI for people with COPD (HR 1.72, 95% CI 1.22-2.42) (Figure 3). Two of the included case-control studies adjusted for smoking status. Meta-analysis of these results did not show an increased risk of MI for people with COPD (OR 1.18, 95% CI 0.80-1.76) (Figure4). Meta-analysis was not conducted for the studies which did not adjust for smoking as heterogeneity was too high (I^2=93%). These results are graphically summarised in Figure 5.

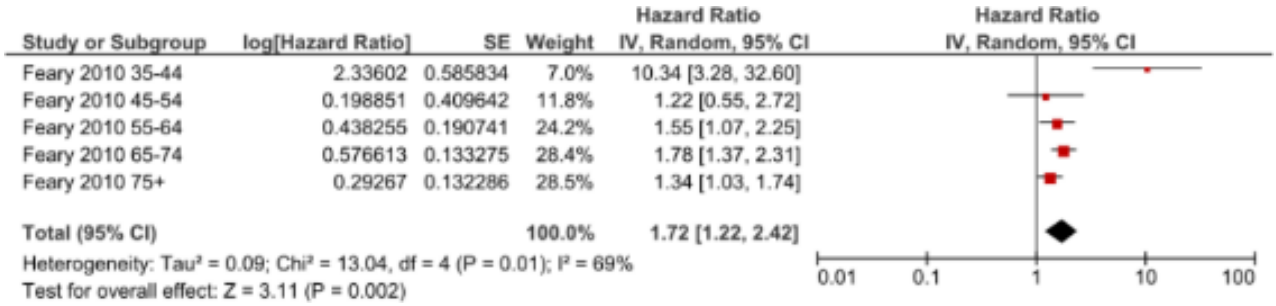

Figure 3. Forest plot showing risk of MI associated with COPD in cohort studies which adjusted for smoking status. CIs may vary slightly from those quoted in tables due to transformation during meta-analysis. COPD, chronic obstructive pulmonary disease; MI, myocardial infarction.

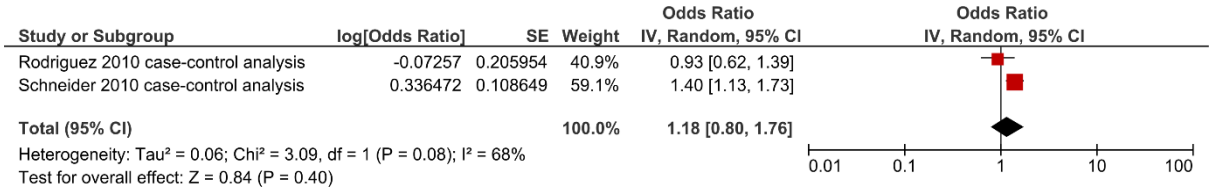

Figure 4. Forest plot showing risk of MI associated with COPD in case-control studies which are adjusted for smoking status. CIs may vary slightly from those quoted in tables due to transformation during meta-analysis. COPD, chronic obstructive pulmonary disease; MI, myocardial infarction.

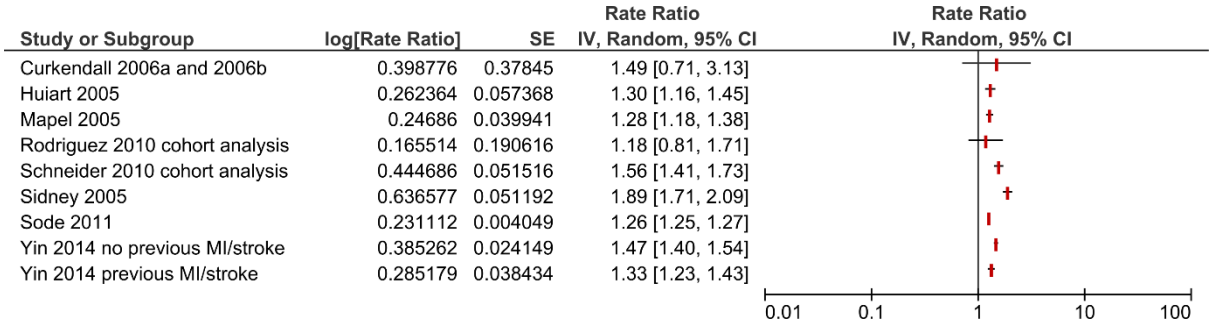

Figure 5. Forest plot showing risk of MI associated with COPD in cohort studies which did not adjust for smoking status. CIs may vary slightly from those quoted in tables due to transformation during meta-analysis. COPD, chronic obstructive pulmonary disease; MI, myocardial infarction.

Some studies investigated whether the effect of COPD on the risk of MI was different in terms of age and severity of airflow obstruction. Feary 2010[3] found that the effect of COPD on risk of MI was higher in the 35-44 year age group (HR 10.34, 95% CI 3.28-32.6) compared to older age groups (45-54 years HR 1.22 (95% CI, 0.55-2.74), 55-64 years HR 1.55 (95% CI, 1.07-2.26), 65-74 years HR 1.78 (95% CI, 1.37-2.31), ≥75 years HR 1.34 (95% CI, 1.03-1.73)). Sidney 2005[29] reported similar findings, the effect of COPD on risk of MI was higher in those who

were aged 40-64 years (HR 2.43, 95% CI 1.98-2.98) compared to those who were aged over 64 years (HR 1.73, 95% CI 1.54-1.94). Schneider 2010[4] investigated the risk of MI by sub-group of COPD severity. They found that the effect of COPD on the risk of MI was greater in those with severe COPD (OR 3.00, 95% CI 1.53-5.86) compared to those with moderate (OR 1.30, 95% CI 1.04-1.62) or mild COPD (OR 1.79, 95% CI 1.12-2.86).

Risk of MI associated with AECOPD

Donaldson 2010[9] conducted a self controlled case series using data from The Health Improvement Network (THIN). They used prescription of antibiotics and steroids in COPD patient to identify AECOPD and report an increased risk of MI in the 1-5 days following the onset of AECOPD (IRR 2.27, 95% CI 1.10-4.70). No difference in the risk of MI was found for the period 6-49 days, or at any time point when the alternative definitions of AECOPD of prescription of steroids alone or antibiotics alone were used. Halpin 2011[21] reported a secondary analysis of the UPLIFT trial, which was an RCT comparing inhaled tiotropium and placebo in COPD patients with a primary outcome of reduction in FEV_1 decline. Time to first AECOPD was a secondary outcome. AECOPD were identified using a symptom based definition and were reported to trial staff at regular study visits. Data on MI were collected as serious adverse events. This study found that compared to the 30 days prior to AECOPD risk of MI in the 30 days following AECOPD was increased (IRR 13.04; 95% CI 1.71-99.7).These results are graphically summarised in Figure 6. Due to different exposure time periods, the results for within person studies investigating the risk of MI associated with AECOPD were not pooled in meta-analysis.

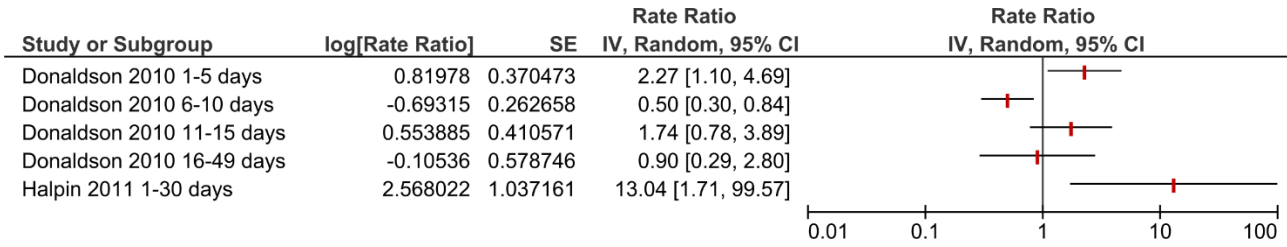

Figure 6. Forest plot showing risk of MI associated with acute exacerbations of COPD. CIs may vary slightly from those quoted in tables due to transformation during meta-analysis. COPD, chronic obstructive pulmonary disease; MI, myocardial infarction.

Risk of death after MI in people with COPD

Of the studies investigating differences in in-hospital mortality after an MI, two[12 22] found an increased risk of mortality for COPD patients (RR 1.39, 95% CI 1.16-1.67 (unadjusted); and OR 1.04, 95% CI 1.03-1.04). Two studies[14 15] did not find evidence for increased in-hospital mortality for COPD patients (OR 0.40, 95% CI 0.20-1.24; OR 1.25, 95% CI 0.97-1.34). One study[11] reported results split by type of MI and did not find an increased in-hospital mortality for COPD patients after a STEMI (OR 1.05, 95% CI 0.95-1.17), but did after a non-STEMI (OR 1.21, 95% CI 1.11-1.33). Meta-analysis of adjusted results showed weak evidence for an increased risk of in-hospital death for COPD patients (OR 1.13, 95% CI 0.97-1.31) (Figure 7).

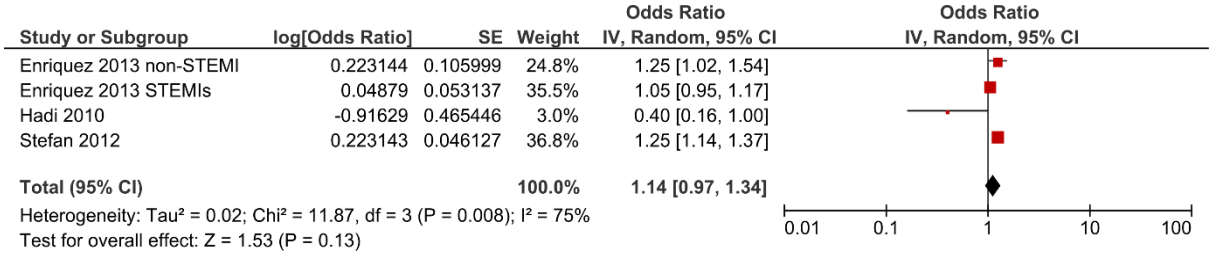

Figure 7. Forest plot showing risk of in-hospital death following MI for patients with COPD compared to patients without COPD. CIs may vary slightly from those quoted in tables due to transformation during meta-analysis. COPD, chronic obstructive pulmonary disease; MI, myocardial infarction.

One study[14] reported mortality at 30-days for COPD patients compared to non-COPD patients. This study found increased mortality for COPD patients (OR 1.31, 1.10-1.58). Another study[33] reported mortality at 8 months, and in an unadjusted analysis, found increased mortality for COPD patients compared to non-COPD patients (OR 2.69, 95% CI was not reported and

could not be calculated). One study[22] also found, on unadjusted analysis, that mortality was greater for COPD patients at 1 (RR 1.34, 95% CI 1.16-1.55) and 5 years (RR 1.28, 95% CI 1.18-1.40) after MI.

Eight studies[10 12 13 23-27] reported results of survival analysis of mortality during follow up after an MI. All of the studies reported higher mortality for COPD patients compared to non-COPD patients during follow up after discharge following an MI. Hazard ratios ranged from 1.15 (95% CI, 1.04-1.28) to 2.15 (95% CI, 1.30-3.55). However, one of these studies[13] found no evidence of a difference in mortality when restricting the time period to the first 30 days following discharge (HR 0.89, 95% CI 0.68-1.11). Meta-analysis of studies which reported adjusted results showed an increased risk of death after discharge following MI for COPD patients compared to non-COPD patients (HR 1.26, 1.13-1.40) (Figure 8). Four of the studies included under this question were excluded from meta-analysis for methodological[12 33] or clinical heterogeneity[25 27].

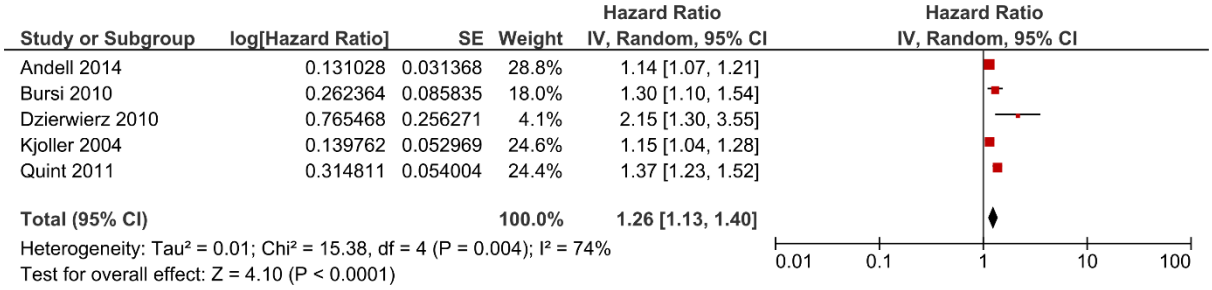

Figure 8. Forest plot showing risk of death after discharge following MI for patients with COPD compared to patients without COPD. CIs may vary slightly from those quoted in tables due to transformation during meta-analysis. COPD, chronic obstructive pulmonary disease; MI, myocardial infarction.

Discussion

Main findings

Most studies which investigated the risk of MI in people with COPD found that those with COPD have higher risk of MI than people who do not have COPD, however it is unclear how much of this increased risk is due to smoking status. The included cohort study which adjusted for smoking status showed an increased risk of MI in people with COPD, but this was not apparent in pooled analysis of the case-control studies which adjusted for smoking status. Both

of the included studies which investigated the risk of MI associated with AECOPD found an increased risk of MI in the weeks following AECOPD. Most studies which investigated mortality after an MI for COPD patients compared to non-COPD patients found that mortality after discharge was greater for those with COPD, and an increased risk of death was found on pooled analysis. However, findings on in-hospital mortality after an MI were mixed, and there was only weak evidence for increased risk of death in-hospital for COPD patients on pooled analysis.

Limitations of included studies and future work

One common limitation among the included studies, particularly those which investigated the risk of MI associated with COPD was missing information on smoking status. As smoking is very strongly associated with both COPD and risk of MI, it is likely to be a major confounder in all studies investigating this association. All of the studies in this review which investigated this association used either clinical or administrative routine data sources. Routine data is a potentially rich source of information on huge numbers of patients. However, data on smoking is not routinely recorded in all administrative databases. Indeed, all of those studies which did not have data for smoking in this question used administrative databases. Future studies on the association between COPD and cardiovascular disease should use data sources which contain reliable information on smoking status.

Further studies should be carried out to confirm findings that AECOPD are periods of increased risk of MI for people with COPD. These studies should ensure they use validated exposure measures and are adequately powered. Possible reasons for an increased risk of MI during AECOPD include both increased inflammation and the potential cardiovascular effects of the drugs used to treat AECOPD. If indeed the finding of increased risk during AECOPD is confirmed, future studies should attempt to disentangle the reasons for increased risk of MI. In addition, studies should investigate factors which might modify this relationship, such as drugs used for treatment of COPD and cardiovascular prevention. Another potential bias in studies

which investigate the relationship between AECOPD and MI which could explain some of the increased risk of MI after AECOPD is differential misclassification of episodes of angina as AECOPD.

No studies were found which investigated the risk of MI associated with the frequent exacerbator phenotype. The frequent exacerbator phenotype may prove to be a useful characteristic for stratifying cardiovascular risk among COPD patients. Future cohort studies of cardiovascular disease in people with COPD should, where possible, phenotype participants and investigate the relationship between exacerbator phenotype and risk of MI. Few included studies assessed the influence of severity of COPD on risk of MI, further research should investigate this relationship as well as the influence of severity of COPD on risk of death following MI.

A further limitation of several of the included studies into death following MI was availability of information on cause of death. Collection of information on cause of death in future studies would allow investigators to draw more confidence conclusions about the reasons for increased risk of death following MI for people with COPD.

Strengths and limitations of this review

This review benefitted from using a comprehensive search strategy which covered several bibliographic databases. As the relationship between AECOPD and MI has not been extensively studied, the inclusion criteria for this research question were kept purposively broad. This allowed all information pertaining to this relationship to be included in the evidence synthesis. One potential limitation of systematic reviews is publication bias. The potential for publication bias was highest for the review of outcomes after MI. In order to reduce the risk of this bias, we only included studies which specifically investigated the risk of COPD on MI rather than several different potential prognostic factors, as studies which investigated several factors which did not find an association between COPD and MI may not have reported this in

the abstract, or even in the text. Due to clinical and statistical heterogeneity, meta-analysis could only be conducted for some of the research questions. Where meta-analysis was conducted, statistical heterogeneity was in general high, and this may limit the generalisability of pooled estimates.

Conclusions

There is good evidence of an increased risk of MI in people with COPD, however it is unclear to what extent this association is due to smoking status.

There is some evidence that among people with COPD, AECOPD represent periods of increased risk of MI. However, further larger studies using validated exposure methods are needed to support this finding.

There is weak evidence that in-hospital mortality is higher for people with COPD after an MI. There is good evidence that post-discharge mortality after an MI is higher for people with COPD.

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3.3 Summary

- People with COPD are at higher risk of MI than those who do not have COPD
- This increased risk of MI cannot be completely explained by smoking or other confounders
- There is some suggestion that AECOPD represent periods of increased risk of MI for those with COPD, however studies have been limited by lack of validated AECOPD definitions and low power
- There is weak evidence that COPD patients have higher in-hospital mortality after MI compared to those who do not have COPD
- There is good evidence that COPD patients have higher risk of death following discharge from hospital after MI compare to those who do not have COPD

Chapter 4: Closing the mortality gap after a myocardial infarction in people with and without Chronic Obstructive Pulmonary Disease (Research paper II)

4.1 Preamble

Following the systematic review (Research Paper I), it was clear that there was evidence for an increased risk of death following MI for those with COPD. Previous work has also suggested that COPD patients receive different treatment compared to people without COPD (Stefan et al. 2012), and that COPD patients would benefit from increased prescription of β-blockers following MI (Quint et al. 2013).

As previously mentioned, 50% of the decrease in mortality due to MI has been attributed to improved care after acute MI (Smolina et al. 2012). This study therefore aimed to investigate the risk of death following MI in those with COPD compared to those without COPD, and to investigate whether any differences in mortality could be explained by differences in recognition and management between people with and without COPD.

This paper was published in *Heart*, and is available here:

Rothnie KJ, Smeeth L, Herrett E, Pearce N, Hemingway H, Wedzicha J, Timmis A, Quint JK. 'Closing the mortality gap after a myocardial infarction in people with and without Chronic Obstructive Pulmonary Disease'. *Heart.* 2015 **101**:1103-1110.

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CANDIDATE'S SIGNATURE Kieran Rothnie Date 14/04/16

SUPERVISOR/SENIOR AUTHOR'S SIGNATURE (3 above) .....

4.2 Research paper

Closing the mortality gap after a myocardial infarction in people with and without COPD

Authors Kieran J Rothnie[1], Liam Smeeth[1,5], Emily Herrett[1], Neil Pearce[1], Harry Hemingway[2,5], Jadwiga Wedzicha[3], Adam Timmis[4,5], Jennifer K Quint[1]

Abstract

Objective Patients with chronic obstructive pulmonary disease (COPD) have increased mortality following myocardial infarction (MI) compared with patients without COPD. We investigated the extent to which differences in recognition and management after MI could explain the mortality difference.

Methods 300 161 patients with a first MI between 2003 and 2013 were identified in the UK Myocardial Ischaemia National Audit Project database. Logistic regression was used to compare mortality in hospital and at 180 days postdischarge between patients with and without COPD. Variables relating to inhospital factors (delay in diagnosis, use of reperfusion and time to reperfusion/use of angiography) and use of secondary prevention were sequentially added to models.

Results Mortality was higher for patients with COPD both inhospital (4.6% vs 3.2%) and at 180 days (12.8% vs 7.7%). After adjusting for inhospital factors, the effect of COPD on inhospital mortality after MI was reduced for both ST-elevation myocardial infarctions (STEMIs) and non-STEMIs (STEMIs OR 1.24 (95% CI 1.10 to 1.41) to 1.13 (95% CI 0.99 to 1.29); non-STEMIs OR 1.34 (95% CI 1.24 to 1.45) to 1.16 (95% CI 1.07 to 1.26)). Adjusting for inhospital factors reduced the effect of COPD on mortality after non-STEMI at 180 days (OR 1.56 (95% CI 1.47 to 1.65) to 1.37 (95% CI 1.31 to 1.44)). Adjusting for use of secondary prevention also reduced the effect of COPD on mortality at 180 days for STEMIs and non-STEMIs (STEMIs OR 1.45 (95% CI 1.31 to 1.61) to 1.25 (95% CI 1.11 to 1.41); non-STEMIs OR 1.37 (95% CI 1.31 to 1.44) to 1.26 (95% CI 1.17 to 1.35).

Conclusions Delayed diagnosis, timing and use of reperfusion of a STEMI, use of angiography after a non-STEMI and use of secondary prevention medicines are all potential explanations for the mortality gap after MI in people with COPD.

Key Messages

What is already known about the subject?

People with chronic obstructive pulmonary disease (COPD) have both a higher risk for myocardial infarction (MI) and poorer long-term outcomes following MI. Previous studies have also shown that patients with COPD are less likely to receive β blockers on discharge after an MI and are less likely to receive PCI after an ST-elevation myocardial infarction (STEMI). Findings for differences in inhospital mortality have been mixed, with some studies finding higher mortality for patients with COPD and some studies finding no difference. The heterogeneity in findings may be due to differences in treatment practices. The extent to which differences in treatment can explain differences in mortality at the population level, the 'mortality gap', is unclear.

What does this study add?

This study aimed to determine whether differences in inhospital treatment and discharge between patients with and without COPD could explain all or some of the difference in mortality for both inhospital and at 180 days postdischarge at the population level. We found that delayed diagnosis of MI, decreased use of reperfusion and increased time to reperfusion after a STEMI, decreased use of angiography after a non-STEMI and decreased use of secondary prevention medicines might all explain some of the mortality gap for people with COPD after an MI.

How might this impact on clinical practice?

We have found that differences in potentially modifiable inhospital processes may explain some of the mortality gap between patients with and without COPD after an MI. Clinicians need to be aware that it may be easier to miss MIs in people with COPD and may need to be aware of more unusual presentations of MI in people with COPD. In addition, our results suggest that patients with COPD may benefit from more aggressive treatment after an MI.

Introduction

People with chronic obstructive pulmonary disease (COPD) are at higher risk of cardiovascular disease,[1, 2], and are known to have poorer medium and longer term outcomes after myocardial infarction (MI) compared to people without COPD, however findings for in-hospital mortality have been mixed,[3, 4, 5, 6]. The heterogeneity in findings on in-hospital mortality may be due to differences in treatment practices. COPD is currently the third leading cause of death worldwide,[7]. As up to a third of deaths in people with COPD are due to cardiovascular disease,[8], reducing deaths after MI in this population is important. In addition, there is a lack of evidence for the effectiveness of treatments in those with co-morbidities.

Recent years have seen improvements in outcomes for patients after MI,[9]. However, several recent studies have continued to report poorer mortality for COPD patients after an MI. Although the reasons for increased mortality after MI in patients with COPD are likely to include biological factors related to COPD, differences in recognition and management between patients with and without COPD may play a role. Recent work has demonstrated that patients with COPD are less likely to receive reperfusion treatment or β-blockers after an MI,[10], and that not prescribing β-blockers to patients with COPD impacts on mortality,[11].

Little is known about potential differences in prescribing of other secondary prevention medicines, inhospital treatment, or on the effects that any differences in these potentially modifiable factors may have on mortality.

We used Myocardial Ischaemia National Audit Project (MINAP), a national register of hospital care for acute coronary syndromes (ACS), to investigate the extent to which differences in recognition and management of an MI might account for the mortality gap in patients with COPD at the population level.

Methods

Data source

The MINAP database is a registry of all admissions for MI and other ACS to hospitals in the UK. The dataset includes information on patient demographics, comorbidities, drugs on admission, initial diagnosis, final diagnosis, inhospital drug treatment, timing of reperfusion therapies, inhospital outcome and drugs given on discharge.,[12].

We included all patients with a first diagnosis of ST-elevation myocardial infarction (STEMI) from January 2003 to June 2013 or non-ST-elevation myocardial infarction (non-STEMI) from January 2004 to December 2012. Records were excluded if they did not have a patient unique identifier, if patients had missing values for presence of obstructive airway disease or smoking history or if Office of National Statistics (ONS) mortality data were missing.

Exposure identification

The obstructive airway disease variable in MINAP does not differentiate between COPD and asthma. In order to identify patients with COPD for this analysis, a strategy was developed and tested in a subset of the data linked with data from the Clinical Practice Research Datalink (CPRD). CPRD is a large UK clinical database of primary care medical records which includes over 5.5 million active patients (8% of the population). [13]. Around half of the CPRD records have been linked to the MINAP database through the CALIBER linkage scheme. [14] Patients with COPD can be identified in CPRD through the use of validated diagnostic codes. Using this subset of linked data, we developed strategy for identifying COPD patients in MINAP using CPRD-identified COPD as a reference standard. In this subset of data, patients with COPD were identified using a combination of MINAP-recorded obstructive airway disease and a smoking history (ex or current smoker). This strategy resulted in adequate identification of patients with COPD in MINAP, with agreement of 90.9%.

Outcome definitions

Recognition and management

Delay in diagnosis of MI, reperfusion after a STEMI, use of angiography in hospital after a non-STEMI and discharge on secondary prevention drugs were investigated. Two definitions of delay in diagnosis were investigated for patients with a final diagnosis of STEMI: (1) delay in diagnosis of definite STEMI (defined as those who did not have an initial diagnosis of definite STEMI) and (2) delay in diagnosis of ACS (defined as those whose initial diagnosis was not STEMI, probable MI or ACS). For those patients with a final diagnosis of non-STEMI, one definition for delay in diagnosis was investigated: delay in diagnosis of ACS (defined as those whose initial diagnosis was not STEMI, probable MI or ACS).

Mortality outcomes

The UK ONS collects data on all recorded deaths in England and Wales. MINAP is linked with ONS mortality data, which provides data on vital status at 180 days postdischarge. Mortality at 180 days postdischarge was assessed for those who survived until discharge.

Statistical analysis

Demographic and clinical characteristics were tabulated for patients with COPD and non-COPD patients. All analyses were stratified by type of MI (STEMI or non-STEMI). The models were adjusted for smoking status, age, sex and calendar year, comorbidities including prior angina, cerebrovascular disease, chronic kidney failure, diabetes, congestive heart failure, hypertension, hyperlipidaemia, peripheral vascular disease, previous percutaneous coronary intervention (PCI) and previous coronary artery bypass graft and cardiovascular drugs (ACE inhibitor or angiotensin receptor blocker, β blocker, statin and thienopyridine) use on admission. Following the suggested practice for missing data in MINAP,[15] missing values for comorbidities and drugs on admission were recoded to 'no'. Other variables were not recoded and analyses were conducted on the basis of complete case analysis. Data were analysed using Stata V.13.0.

Analysis was conducted in three parts:

i) Describing the problem: differences in mortality after MI between patients with COPD and non-COPD patients

We compared crude proportions of patients with COPD dying inhospital and at 180 days postdischarge to patients without COPD. We then used logistic regression to adjust the comparisons of mortality for possible confounders for age, sex, smoking status, calendar year, comorbidities and drugs used on arrival.

ii) Possible inhospital explanations: differences in recognition and management after an MI between patients with COPD and non-COPD patients

For STEMIs, we investigated differences in delay in STEMI diagnosis, use of primary PCI (pPCI), use of thrombolysis, time to reperfusion from hospital admission and use of secondary prevention drugs on discharge. We investigated the impact of delay in diagnosis on time to reperfusion, and we assessed whether COPD modified this relationship. For non-STEMIs, we investigated delay in diagnosis of MI, use of angiography in hospital and use of secondary prevention drugs on discharge.

iii) Accounting for differences in mortality after MI between patients with COPD and non-COPD patients in terms of hospital processes

In order to investigate to what extent differences in diagnosis and treatment of patients with COPD after an MI might account for differences in mortality, variables relating to inhospital processes investigated in (2) were sequentially added to mortality models created in (1) with reference to a directed acyclic graph (See supplementary material). Attributable risk of death due to COPD following MI was calculated before and after adjustment for inhospital processes using the formula (OR-1)/OR×100.

We conducted sensitivity analyses to investigate the potential impact of misclassification of asthma with COPD, and to investigate the impact of suboptimal management on risk of death among people with COPD (supplementary material).

Results

Characteristics of participants

Of the 300 146 patients with first MI identified over the period, 34 027 (11.3%) had COPD. The inclusion and exclusion of records in the MINAP database are detailed in Figure 1. The characteristics of the patients included in the study are detailed in Table 1. Mortality was higher for COPD patients both in-hospital (4.6% vs 3.2%) and at 180 days (12.8% vs 7.7%).

Table 1. Characteristics of patients in the study.

Characteristic	COPD n (%)	Non-COPD n (%)
Sex		
Male	21 053 (61.9)	178 611 (67.1)
Female	12 908 (37.9)	86 504 (32.5)
Missing	80 (0.2)	956 (0.36)
Age		
<60	7627 (22.6)	90 557 (34.1)
60-70	8830 (26.0)	62 947 (23.7)
71-80	10 622 (31.3)	61549 (23.2)
>80	6786 (20.0)	50 126 (18.9)
Missing	0	0
Smoking status		
Current	14 666 (43.2)	90 026 (34.0)
Ex	19 244 (56.8)	87 612 (33.0)
Never	0	87 541 (33.0)
Missing	0	0
Previous Angina		
Yes	7 426 (21.8)	41 417 (15.6)
No	25 936 (76.2)	223 089 (83.9)
Missing	679 (2.0)	1 565 (0.6)
Previous PCI		
Yes	908 (2.7)	6 622 (2.5)
No	32 082 (94.3)	255 449 (96.0)
Missing	1 051 (3.1)	3 916 (1.5)
Previous CABG		
Yes	786 (2.3)	5 704 (2.1)
No	32 227 (94.7)	256 574 (96.4)
Missing	1 028 (3.0)	3 793 (1.4)
Diabetes		
Yes – diet controlled	1 193 (3.5)	8 322 (3.1)
Yes – oral	2 902 (8.5)	21 418 (8.1)
Yes – insulin	1 241 (3.7)	8 986 (3.4)
Yes – insulin and oral	176 (0.5)	1 178 (0.4)
No	28 030 (82.3)	223 040 (83.8)
Missing	499 (1.5)	3 127 (1.2)
Treated for hypertension		
Yes	15 304 (45.0)	117 886 (44.3)
No	18 151 (53.3)	146 459 (55.1)
Missing	586 (1.7)	1 726 (0.7)
Treated for hyperlipidaemia		
Yes	9 091 (26.7)	73 641 (27.7)
No	23 399 (68.7)	185 043 (69.6)
Missing	1 551 (4.6)	7 387 (2.8)
Peripheral vascular disease		
Yes	1 962 (5.8)	9 061 (3.4)

No	30 872 (90.7)	253 720 (95.4)
Missing	1 207 (3.6)	3 290 (1.2)
Previous cerebrovascular disease		
Yes	2 823 (8.3)	16 829 (6.3)
No	30 354 (89.2)	247 418 (93.0)
Missing	864 (2.5)	1 824 (0.7)
Heart failure		
Yes	2 037 (6.0)	7 426 (2.8)
No	31 080 (91.3)	256 677 (96.5)
Missing	924 (2.71)	1 968 (0.7)
Renal failure		
Yes	1 681 (4.9)	8 428 (3.2)
No	31 452 (92.4)	255 732 (96.1)
Missing	908 (2.7)	1 911 (0.7)
Beta blocker on arrival		
Yes	3 016 (8.9)	44 585 (16.8)
No	23 544 (69.1)	162 876 (61.2)
Missing	7 481 (22.0)	58 610 (22.0)
ACEi/ARB on arrival		
Yes	8 228 (24.2)	57 288 (21.53)
No	18 331 (53.9)	150 036 (56.4)
Missing	7 482 (22.0)	58 747 (22.1)
Statin on arrival		
Yes	9 446 (27.8)	65 062 (24.5)
No	17 409 (51.1)	144 498 (54.3)
Missing	7 186 (21.1)	56 511 (21.2)
Thienopyridine on arrival	2 948 (8.7)	23 240 (8.7)
Yes	22 729 (66.8)	176 548 (66.4)
No	8 364 (24.6)	66 283 (24.9)
Missing		
Death in hospital	1 561 (4.6)	8 574 (3.2)
Death at 180 days (survivors to discharge)	4 166 (12.8)	19 693 (7.7)

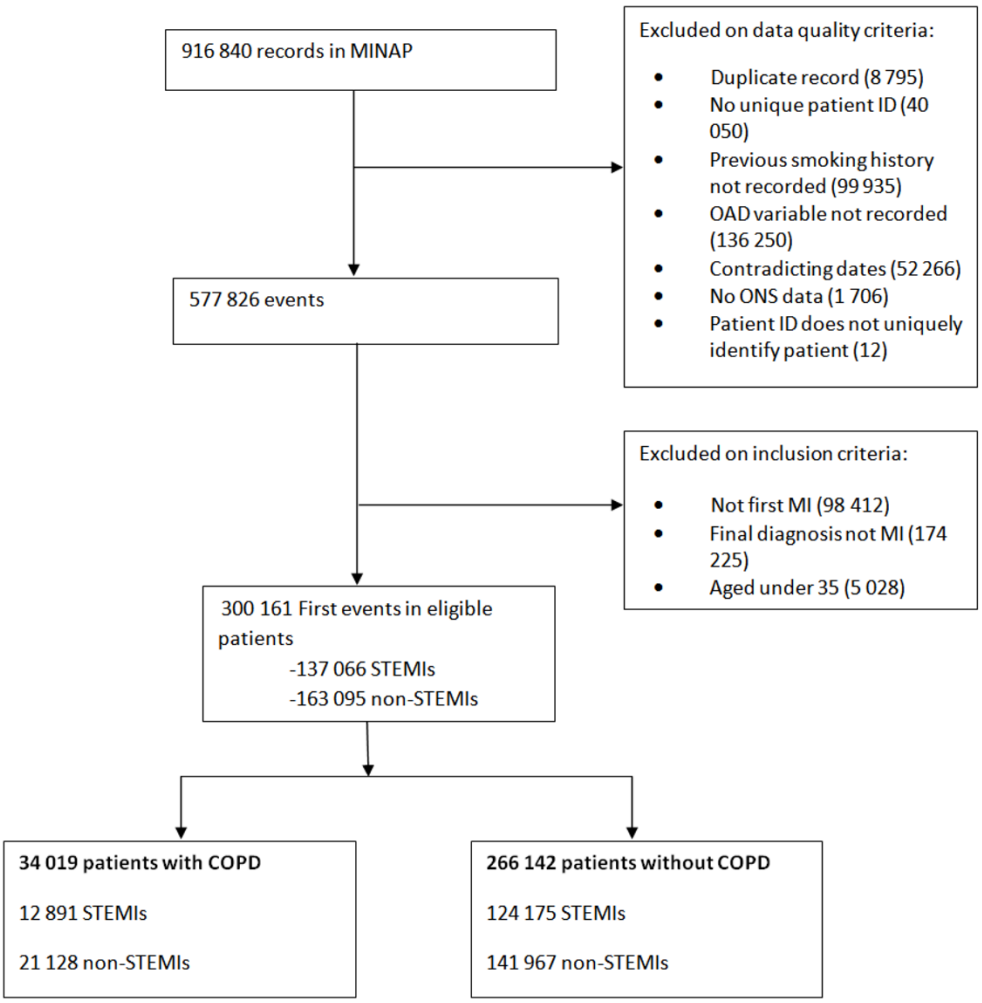

Figure 1. Study selection.

ST-elevation myocardial infarctions

i) Describing the problem: differences in mortality after MI between patients with COPD and non-COPD patients

After adjusting for age, sex, smoking status, calendar year, comorbidities and drugs on arrival, mortality in patients with COPD was higher than non-COPD patients in hospital (OR 1.24, 95% CI 1.10 to 1.41), and 180 days after discharge (OR 1.45, 95% CI 1.33 to 1.59).

ii) Possible inhospital explanations: differences in recognition and management after an MI between patients with COPD and non-COPD patients

Differences in diagnosis and inhospital recognition management are presented in Table 2. Patients with COPD who had a STEMI were more likely to have an initial diagnosis other than definite STEMI (OR 1.24, 95% CI 1.19 to 1.30) or ACS (OR 1.52, 95% CI 1.42 to 1.62). After a STEMI, patients with COPD were less likely to have pPCI (OR 0.87, 95% CI 0.83 to 0.92). There was no evidence that patients with COPD were less likely to receive thrombolysis (OR 0.96, 95% CI 0.91 to 1.10).

Table 2. Differences in recognition and treatment of STEMIs between patients with COPD and non-COPD patients

In-hospital treatment and diagnosis	**COPD N (%)**	**Non-COPD N (%)**	**Unadjusted OR (95% CI)**	**Minimally adjusted OR (95% CI)***	**Adjusted OR (95% CI)****
Initial diagnosis other than definite STEMI (for final diagnosis is STEMI)	3 080 (23.9)	24 752 (19.9)	1.26 (1.21-1.32)	1.28 (1.23-1.34)	1.24 (1.19-1.30)
Initial diagnosis other than ACS	1 186 (9.2)	7 398 (6.0)	1.59 (1.50-1.71)	1.68 (1.64-1.73)	1.52 (1.42-1.62)
Primary PCI	4108 (31.8)	44177 (35.6)	0.84 (0.81-1.87)	0.69 (0.67-0.71)	0.87 (0.83-0.92)
Thrombolysis	5449 (42.6)	52414 (42.7)	0.99 (0.96-1.03)	1.00 (0.96-1.03)	0.96 (0.91-1.10)
Time to reperfusion	**COPD Minutes (median IQR)**	**Non-COPD Minutes(median IQR)**	**Unadjusted exponentiated regression coefficient (95% CI)**	**Minimally adjusted exponentiated regression coefficient (95% CI)***	**Adjusted exponentiated regression coefficient (95% CI)****
Time to reperfusion from admission (overall)	37.1 (21.8-67.7)	35.0 (21.8-63.4)	1.07 (1.04-1.09)	1.05 (1.03-1.07)	1.04 (1.02-1.07)
Time to reperfusion from admission (initial diagnosis other than STEMI)	152.9 (74.3-705.6)	109.2 (50.2-260.0)	1.44 (1.24-1.67)	1.35 (1.16-1.58)	1.47 (1.15-1.88)
Time to reperfusion from admission (initial diagnosis STEMI)	35.0 (21.8-63.4)	35.0 (21.8-61.2)	1.04 (95% CI, 1.01-1.06)	1.03 (1.01-1.05)	1.03 (1.00-1.05)
Discharge treatment	**COPD n (%)**	**Non-COPD n (%)**	**Unadjusted OR (95% CI)**	**Minimally adjusted OR* (95% CI)**	**Adjusted OR (95% CI)****
Discharge on β-blockers	5776 (44.7)	94784 (76.4)	0.25 (0.24-0.26)	0.25 (0.24-0.26)	0.26 (0.25-0.27)

Discharge on ACE inhibitor or angiotensin receptor blocker	9579 (74.2)	96508 (77.8)	0.83 (0.79-0.86)	0.87 (0.83-0.91)	0.89 (0.85-0.93)
Discharge on aspirin	10344 (80.1)	102925 (82.9)	0.83 (0.79-0.87)	0.87 (0.83-0.92)	0.90 (0.85-0.94)
Discharge on statin	10373 (80.4)	102785 (82.8)	0.85 (0.81-0.89)	0.88 (0.84-0.93)	0.91 (0.86-0.95)
Discharge on thienopyridine	7799 (60.4)	77543 (62.5)	0.91 (0.88-0.95)	0.96 (0.92-1.01)	0.98 (0.94-1.03)

*Adjusted for age, sex smoking status and calendar year

**Adjusted for age, sex, smoking status, calendar year, drugs on admission and co-morbidities

In adjusted results, differences in time to reperfusion have been expressed in terms of exponentiated linear regression coefficients which, in this case, represent ratios of geometric means. The relationship between COPD and time to reperfusion was found to be different depending on whether diagnosis of MI was delayed (p value for interaction <0.001). The median time to reperfusion was 43.7 min longer for patients with COPD compared with non-COPD patients among those who had a delay in diagnosis (median time to reperfusion 152.9 min (IQR, 74.3–705.6 min) for patients with COPD, and 109.2 min (IQR, 50.2–260.0 min) for non-COPD patients). This difference remained on adjusted analysis and corresponded to 47% (95% CI 15% to 88%) longer time to reperfusion for patients with COPD with delayed diagnosis of MI, compared with non-COPD patients with delayed diagnosis of MI. There was no difference in time to reperfusion between patients with COPD and non-COPD patients among those without a delay in diagnosis (see details in online supplementary appendix). Patients with COPD were less likely to receive any of the secondary prevention drugs, apart from thienopyridines, on discharge compared with non-COPD patients, β blockers significantly more so than other drugs (OR 0.26 (95% CI 0.25 to 0.27)).

iii) Accounting for differences in mortality after MI between patients with COPD and non-COPD patients in terms of hospital processes

When compared with the result found in i), inhospital mortality was reduced after adjusting separately for both diagnostic delay (OR 1.20 (95% CI 1.06 to 1.36)) and time to reperfusion and use of pPCI (OR 1.11 (95% CI 0.94 to 1.311; Table 3). After adjusting for all inhospital factors, the OR for mortality was 1.13 (95% CI 0.99 to 1.29). For mortality at 180 days, the OR was 1.45 (95% CI 1.33 to 1.59) after adjusting for age, sex, smoking, calendar year, drugs used on admission and comorbidities, and was 1.45 (95% CI 1.31 to 1.61) after additionally adjusting for diagnostic delay, use of pPCI and time to reperfusion. Adjusting for use of secondary prevention drugs on discharge substantially reduced ORs for 180 day mortality compared with models only adjusting for inhospital factors (OR 1.25 (95% CI 1.11 to 1.41)).

Table 3. Mortality after STEMI

	Adjusted for age, sex, smoking status and year	Adjusted for model 1 variables and co-morbidities and drugs on arrival	Adjusted for model 1 and 2 variables and diagnostic delay	Adjusted for model 1 and 2 variables and use of reperfusion and time to reperfusion	Adjusted for model 1, 2, 3 and 4	Adjusted for model 1, 2, 3 and 4 variables and secondary prevention	
	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6	
	OR (95% CI)						
In- hospital mortality	1.27 (1.16-1.39)	1.24 (1.10-1.41)	1.20 (1.06-1.36)	1.11 (0.94-1.31)	1.13 (0.99-1.29)	-	All ORs
180 day mortality	1.43 (1.29-1.58)	1.45 (1.33-1.59)	1.43 (1.32-1.54)	1.46 (1.32-1.62)	1.45 (1.31-1.61)	1.25 (1.11-1.41)	

compare patients with COPD with non-COPD patients

After adjusting for inhospital processes, the estimated attributable risk of inhospital death following a STEMI due to COPD in patients with COPD decreased from 19.4% (95% CI 9.1% to 29.1%) to 11.5% (95% CI −1.0% to 22.4%). After adjusting for inhospital processes, the estimated attributable risk for death at 180 days due to COPD in patients with COPD following a STEMI decreased from 31.0% (95% CI 24.8% to 37.1%) to 20.0% (95% CI 9.9% to 29.1%).

Non-ST-elevation myocardial infarctions

i) Describing the problem: differences in mortality after MI between patients with COPD and non-COPD patients

After adjusting for age, sex, smoking status, calendar year, comorbidities and drugs on arrival, mortality in patients with COPD was higher than non-COPD patients in hospital (OR 1.34 (95% CI 1.24 to 1.45)) and 180 days after discharge (OR 1.56 (95% CI 1.47 to 1.65)).

ii) Possible inhospital mechanisms: differences in diagnosis and management after an MI between patients with COPD and non-COPD patients

Results from the comparison of treatment and diagnosis after a non-STEMI are presented in Table 4. Patients with COPD were more likely to have an initial diagnosis other than ACS after a non-STEMI (OR 1.46 (95% CI 1.41 to 1.50)). After a non-STEMI, patients with COPD were less likely to receive angiography in hospital (OR 0.69 (95% CI 0.66 to 0.71)). Patients with COPD were less likely to receive any of the secondary prevention drugs on discharge, apart from thienopyridines, compared with non-COPD patients, β blockers significantly more so than other secondary prevention drugs (OR 0.25 (95% CI 0.24 to 0.25)).

Table 4. Differences in recognition and inhospital treatment of non-STEMIs between patients with COPD and non-COPD patients

In-hospital treatment and diagnosis	**COPD N (%)**	**Non-COPD N (%)**	**Unadjusted OR (95% CI)**	**Minimally adjusted OR* (95% CI)**	**Adjusted OR (95% CI)****
Initial diagnosis other than MI	9 551 (45.2)	50 365 (35.5)	1.50 (1.46-1.54)	1.68 (1.64-1.73)	1.46 (1.41-1.50)
Angiography in hospital	8 629 (40.9)	74 304 (52.2)	0.77 (0.76-0.79)	0.63 (0.61-0.65)	0.69 (0.66-0.71)
Discharge treatment	**COPD n (%)**	**Non-COPD n (%)**	**Unadjusted OR (95% CI)**	**Minimally adjusted OR* (95% CI)**	**Adjusted OR (95% CI)****
Discharge on beta blockers	6 632 (31.4)	925059 (64.9)	0.25 (0.24-0.26)	0.24 (0.23-0.25)	0.25 (0.24-0.25)
Discharge on ACE inhibitor or angiotensin receptor blocker	12 762 (60.4)	89368 (63.0)	0.90 (0.87-0.92)	0.91 (0.88-0.94)	0.94 (0.91-0.97)
Discharge on aspirin	15 234 (72.1)	106 652 (75.1)	0.86 (0.83-0.88)	0.88 (0.85-0.91)	0.91(0.88-0.94)
Discharge on statin	15 141 (71.7)	104 804 (73.8)	0.90 (0.87-0.93)	0.90 (0.87-0.93)	0.93 (0.90-0.96)
Discharge on thienopyridine	11 277 (53.4)	78 233 (55.1)	0.93 (0.90-0.96)	0.95 (0.91-0.98)	0.97 (0.94-1.01)

*Adjusted for age, sex smoking status and calendar year

**Adjusted for age, sex, smoking status, calendar year, drugs on admission and co-morbidities.

iii) Accounting for differences in mortality after MI between patients with COPD and non-COPD patients in terms of hospital processes

When compared with results found in (1), inhospital mortality was reduced after adjusting separately for both delay in diagnosis (OR 1.29 (95% CI 1.19 to 1.39)) and use of angiography (OR 1.18 (95% CI 1.09 to 1.29); Table 5). After adjusting for both delay in diagnosis and use of angiography the OR for inhospital mortality was 1.16 (95% CI 1.07 to 1.26). Inhospital factors also appeared to explain some of the mortality difference after a non-STEMI at 180 days. For mortality at 180 days, the OR was reduced from 1.56 (95% CI 1.47 to 1.65) to 1.37 (95% CI 1.31 to 1.44). Use of secondary prevention also seemed to explain some of the gap in mortality at 180 days. Compared with the model which only adjusted for inhospital processes, the OR for mortality at 180 days was reduced from 1.37 (95% CI 1.31 to 1.44) to 1.26 (95% CI 1.17 to 1.35).

Table 5. Mortality after non-STEMI.

	Adjusted for age, sex, smoking status and year	Adjusted for model 1 variables and co-morbidities and drugs on arrival	Adjusted for model 1 and 2 variables and diagnostic delay	Adjusted for model 1 and 2 variables and use of angiography in hospital	Adjusted for model 1, 2, 3 and 4 variables	Adjusted for model 1, 2, 3 and 4 variables and secondary prevention
	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6
	OR (95% CI)					
In-hospital mortality	1.40 (1.30-1.52)	1.34 (1.24-1.45)	1.29 (1.19-1.39)	1.18 (1.09-1.29)	1.16 (1.07-1.26)	-
180 day mortality	1.63 (1.56-1.70)	1.56 (1.47-1.65)	1.45 (1.38-1.52)	1.43 (1.34-1.50)	1.37 (1.31-1.44)	1.26 (1.17-1.35)

All ORs compare patients with COPD with non-COPD patients

After adjusting for inhospital processes, the estimated attributable risk for inhospital death following a non-STEMI due to COPD in patients with COPD decreased from 25.4% (95% CI 19.4% to 31.0%) to 13.8% (95% CI 6.5% to 21.6%). After adjusting for inhospital processes, the estimated attributable risk for death at 180-days due to COPD in patients with COPD following a non-STEMI decreased from 35.9% (95% CI 32.0% to 39.4%) to 20.6% (95% CI 14.5% to 25.9%).

Discussion

Summary of main findings

For STEMIs, some of the in inhospital mortality difference between patients with COPD and non-COPD patients may be attributable to delays in diagnosis and use of and increased time to reperfusion. Some of the increased mortality for STEMIs at longer time periods up to 6 months may be attributable to decreased use of secondary prevention medicines, especially β blockers, but not inhospital processes. For non-STEMIs, some of the difference in inhospital mortality may be attributable to delays in diagnosis and decreased use of angiography shortly after MI. Some of the increased mortality for non-STEMIs at longer time periods up to 6 months may be attributable to decreased use of secondary prevention medicines, and to inhospital delays in diagnosis and decreased use of angiography in hospital.

Interpretation and comparison with other studies

Several studies have shown both the increased risk for death following MI for people with COPD and differences in management. These studies specifically showed reduced use of secondary prevention and pPCI after a STEMI in patients with COPD,[5, 10, 16, 17, 18], these findings have been replicated here. This study has also shown that these differences in treatment are possible explanations for some of the mortality gap at the population level for both STEMIs and non-STEMIs. In particular, we were able to make use of the detailed timing variables available in MINAP to investigate differences in time to reperfusion after a STEMI.

F or STEMIs, we found that diagnosis of MI is more likely to be delayed for patients with COPD compared with non-COPD patients, and that time to reperfusion is longer after a STEMI. We also showed that the effect of delay in diagnosis of MI on the time to reperfusion was greater in patients with COPD compared with non-COPD patients. Patients with COPD were more likely to have a delay in diagnosis and the effect of this delay in diagnosis in time to reperfusion was more severe for them than non-COPD patients. The reason for the delay in diagnosis of MI in patients with COPD may be because symptoms of MI in patients with COPD may be incorrectly attributed to their COPD rather than an MI.

We found that after a non-STEMI, patients with COPD were less likely to receive angiography in hospital than non-COPD patients, and this explained some of the excess inhospital and 180-day mortality. Use of angiography is driven by risk scoring, and patients at moderate and higher risk of death within 6 months should be offered angiography within 96 h of admission to hospital after a non-STEMI. [19]. It is unclear why, as a population, that although patients with COPD are at a higher risk of mortality they are less likely to receive angiography in hospital.

After both STEMIs and non-STEMIs, patients with COPD were less likely to be prescribed secondary prevention medicines than non-COPD patients. This may only have been to a clinically relevant degree for β blockers. It is known that patients with COPD are less likely to be prescribed β blockers after an MI, and that prescribing them improves survival. [11] This study has demonstrated that the increased mortality associated with not prescribing secondary prevention medicines could explain some of the mortality gap up to 6 months at the population level.

We found that recognition of MI in patients with COPD was impaired compared with non-COPD patients. However, all patients included in this analysis were eventually diagnosed with MI. This suggests that patients with COPD may be at higher risk of having a completely missed MI. Indeed, recent work has suggested that as many as 1 in 12 patients admitted to hospital with

an exacerbation of COPD meet the criteria for MI, and that this represents underdiagnosis of MI in patients with COPD. [20] However, as troponin may also be increased during stable periods of COPD,[21] there is also a potential for overdiagnosis of MI in people with COPD. Any future intervention which aims to increase recognition of MI in people with COPD should also investigate the potential effects of overdiagnosis.

Strengths and limitations

The major strengths of this study were its size, representativeness and level of detail on in-hospital management and outcomes. The study included over 300,000 people and used data collected from all hospitals in the UK which admit patients for ACS. As secondary prevention treatment is known to be different for COPD patients compared to non-COPD patients, only using first MIs allowed us to assess the effect of COPD on mortality after an MI without bias due to differences in previous treatment. Another strength of this study was our ability to separate factors which could explain increased in-hospital mortality from increased mortality following discharge. If COPD patients were more likely to die in-hospital, as we found, the reasons that they did not receive certain treatments may have been because they were more likely to die before they received these treatments compared to non-COPD patients. In order to avoid this bias, for mortality at 180 days, we only analysed data for those who had survived until at least discharge. This also allowed the potential contribution of secondary prevention to the mortality gap to be investigated.

One of the limitations of this study is potential misclassification of COPD status. The strategy used to identify may have misclassified asthmatic smokers as COPD patients, and may have misclassified COPD patients as non-COPD patients. However, the prevalence of COPD in our study is similar to that of previous work in similar settings,[5, 10, 16, 22]. The presence of asthmatics in our COPD group and COPD patients in the non-COPD group is likely to have biased our findings towards the null. However, this would not change our findings. In addition, the sensitivity analysis which compared mortality for asthmatic patients compared to non-

asthmatic patients found that mortality was not increased in the asthmatic group (supplementary material). One of the limitations of using an audit database such as MINAP is the lack of available data which would not have been collected at hospital admission. Ideally, information on COPD severity and cause of death would have been collected. In addition, ideally information on socioeconomic status would have been available as this is a potential confounder for the relationship between COPD and mortality after MI. Future studies should investigate the relationship between COPD severity and explanations for the mortality gap in COPD patients after MI and cause of death in COPD patients following MI.

Conclusions

Patients with COPD appear to receive poorer treatment after an MI compared with non-COPD patients. These differences in recognition and treatment of MI seem to explain some of the mortality gap between patients with COPD and non-COPD patients both inhospital and at 6 months postdischarge. Delayed diagnosis, timing and use of reperfusion of a STEMI, use of angiography after a non-STEMI and use of secondary prevention medicines are all potential explanations for the mortality gap after MI in people with COPD.

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4.3 Summary

- People with COPD are more likely to experience a delay in diagnosis of MI than those who do not have COPD, less likely to have reperfusion after a STEMI or angiography in hospital after a non-STEMI, and are less likely to be discharged on secondary prevention medicines, notably β-blockers
- COPD patients are more likely than those without COPD to die in hospital and at 180 days following MI
- The effect of COPD on risk of death following MI is higher for non-STEMIs than it is for STEMIs
- Some of the increased risk of death following MI for those with COPD can be explained by the differences in recognition and management of MI, highlighting the importance of cardiovascular medicine and other therapies in reducing cardiovascular risk for those with COPD

Chapter 5 Chronic obstructive pulmonary disease and acute myocardial infarction: effects on presentation, management, and outcomes (Research paper III)

5.1 Preamble

The research paper presented in this chapter is a review article which I was commissioned to write following the publication of research papers I and II. The aim of this article was to outline the current evidence for differences in presentation, management, and outcomes following MI between people with and without COPD. Although there is some repetition of earlier findings on mortality, this article extends the discussion on outcomes to include other outcomes such as stroke, re-current MI, and the development of heart failure. The paper concludes with a conceptual model combining the findings on differences in presentation, management and outcomes after MI for those with COPD, and how these might relate to each other.

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SUPERVISOR/SENIOR AUTHOR'S SIGNATURE (3 above) .....

5.2 Research paper

COPD and myocardial infarction: effects on presentation, management and outcomes

Authors: Kieran J Rothnie & Jennifer K Quint

Abstract

Cardiovascular disease is a common cause of death in patients with chronic obstructive pulmonary disease (COPD) and is a key target for improving outcomes. However, there are concerns that patients with COPD may not have enjoyed the same mortality reductions from acute myocardial infarction (AMI) in recent decades as the general population. This has raised questions about differences in presentation, management and outcomes in COPD patients compared to non-COPD patients. The evidence points to an increased risk of death after AMI in patients with COPD, but it is unclear to what extent this is attributable to COPD itself or to modifiable factors including under-treatment with guideline-recommended interventions and drugs. We review the evidence for differences between COPD and non-COPD patients in terms of the presentation of AMI, its treatment, and outcomes both in hospital and in the longer term.

Background

Myocardial infarction (MI) is a very common reason for admission to hospital and is associated with substantial morbidity and mortality. Recent decades have seen a large decrease in the incidence of and mortality from acute MI[1]. Much of the decrease in the incidence of MI has been attributable to a decrease in ST-elevation MI (STEMI). Rates of non-ST-elevation MI (non-STEMI) may not have decreased and may well be increasing[2]. People who have a non-STEMI rather than STEMI tend to be older and are more likely to have co-morbidities. The reasons for the increasing prevalence of non-STEMI may include increased prevalence of risk factors, or better clinical awareness. It has been recognised that comorbidity is a major risk factor for death following an MI, and that multimorbidity due to population ageing has created a more complex population of those with acute MI[3]. As well as prevention of MI, much of the decrease in MI mortality has been attributed to improved care after MI[4]. Although drives to improve acute care and secondary prevention of MI have drastically decreased mortality after MI, it is not clear if this has been optimised for all patient groups. Some groups have received a lot of attention, for example, in people with diabetes, thresholds are lower for treating risk factors for MI (for example, blood pressure) and it is recognised that presentation may be different, for example, without chest pain. One common co-morbid condition which has previously been understudied, but is now coming under increasing attention is chronic obstructive pulmonary disease (COPD).

Chronic obstructive pulmonary disease (COPD) is a common and progressive lung disease characterised by airflow limitation which is not fully reversible. The prevalence of diagnosed COPD varies between countries. In Europe the average prevalence of diagnosed COPD is around 1.5% of the adult population, however the true prevalence may be as high as 10% as many remain undiagnosed[5]. In the developed world, the biggest risk factor for COPD is tobacco smoking [6]. COPD is also associated with increasing age, indoor and outdoor pollution, poor nutrition and low socioeconomic status[6].

COPD is associated with an increased risk of many other diseases, which are thought to be due, in part, to "spill over" of inflammation in the lung to the systemic circulation[7] (Figure 1). Cardiovascular disease is perhaps the most common and important co-morbidity in those with COPD. People with COPD are at higher risk of MI than those who do not have COPD, independent of smoking status[8, 9]. As well as increased inflammation, it is thought that this increased risk may be due to increased endothelial dysfunction and increased arterial stiffness in those with COPD[10]. This increased burden of MI attributable to COPD seems to be borne by younger COPD patients[9]. Most people with COPD do not die from respiratory diseases[11], and one of the most common reasons for death in those with COPD is cardiovascular disease, with up to 30% of people with COPD dying from cardiovascular disease[12]. Due to both shared risk factors and the increased risk of MI for those with COPD, COPD is very common in those with acute MI. The prevalence of COPD in those with acute MI varies between countries, and has been estimated to be 10-17%[13-16].

This article aims to review the literature on the effect of COPD on presentation, management and outcomes after acute MI and how these may be interrelated.

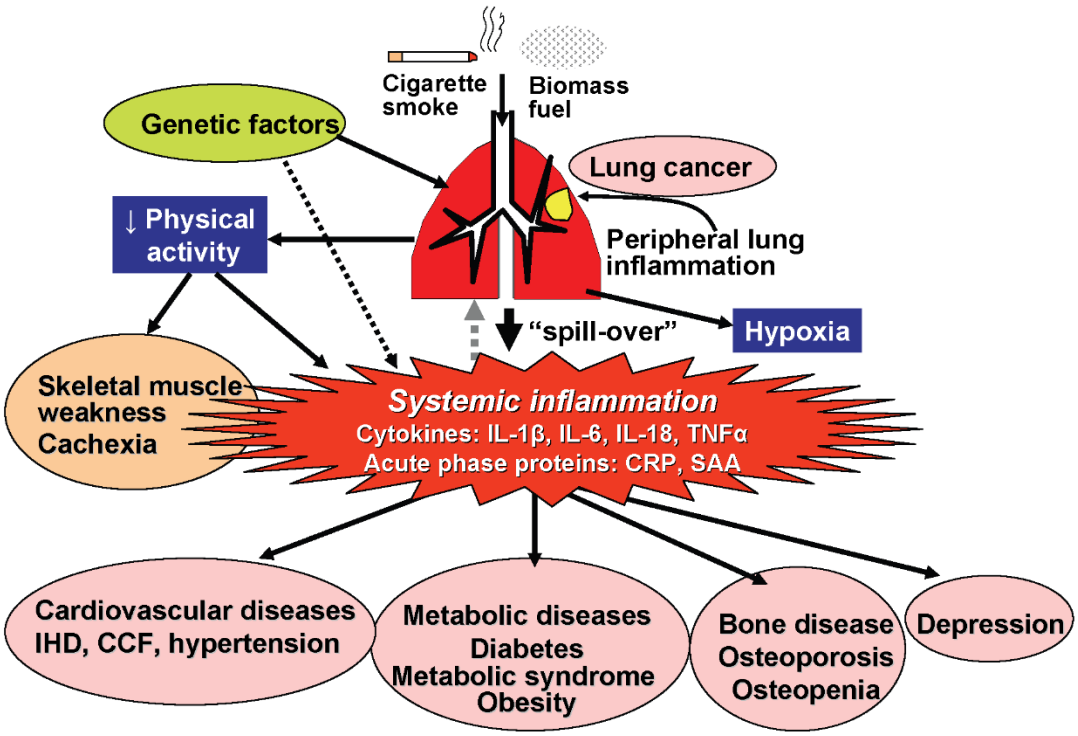

Figure 1. Diagram representing how inflammation in chronic obstructive pulmonary disease may 'spill over' into the systemic circulation and increase the risk of several diseases including cardiovascular disease. Original image from Barnes.[7]

Presentation of acute myocardial infarction

Several studies have investigated differences in presentation between those with COPD and those without COPD. The prevalence of previously diagnosed COPD among all people presenting to hospital with an MI has been estimated to be between 10-17%[13-16]. Particularly, as COPD is a risk factor for MI, however, the true prevalence including those with undiagnosed COPD may be significantly higher. In terms of presenting symptoms, several studies have reported that COPD patients with MI are less likely to present with typical chest pain, and are more likely than non-COPD patients to present with breathlessness[13-15], atypical chest pain[13], and palpitations[13]. In terms of type of MI, two studies have found that COPD patients are more likely to present with a non-STEMI than a STEMI compared to non-COPD patients[16, 17]. Intriguingly, several studies have found that COPD patients had lower levels of peak cardiac enzymes after an MI and this was true for both troponin[18] and creatine kinase[19]. In addition, Bursi et al[19] found that COPD patients had a higher average heart rate than non-COPD patients and were more likely to have a delay (>12 hours) in presentation to hospital after MI.

Differences in recognition and management of MI between COPD and non-COPD patients

One possible consequence of differences in presentation after an MI between COPD and non-COPD patients is delay in recognition of MI. For people with COPD, even with presentation of typical MI symptoms, these symptoms may be erroneously attributed to their COPD. This is of particular importance for those with STEMI, as early identification of MI should reduce time to reperfusion and therefore would be expected to improve outcomes. In an analysis of over 300,000 first MIs in the UK Rothnie et al.[16] found that after a STEMI, COPD patients were more likely to have an initial incorrect diagnosis (i.e. not MI) and had a longer median time to reperfusion. This was 153 min (IQR, 74-706 min) for those with COPD and 109 min (IQR, 50-260 min) for those without COPD, and was only apparent in COPD patients with a delay in diagnosis of MI compared to non-COPD patients with a delay in diagnosis of MI. This difference also remained on analysis adjusted for age, sex and comorbidities.

Recent studies conducted in Sweden and the UK have shown that COPD patients are less likely to receive primary percutaneous intervention or other reperfusion strategies after a STEMI[14, 16]. Older studies in the USA also showed that those with COPD were less likely to receive primary percutaneous coronary intervention (pPCI) after a STEMI [15, 19], however a more recent study has found no difference in the proportion of COPD and non-COPD patients receiving pPCI after STEMI in the USA, suggesting they have started to recognise previous discrepancies in recognition and management and are changing clinical practice[18].

After a non-STEMI, current guidelines[20, 21] suggest that patients who are at moderate (3%) or higher predicted risk of death within 6 months receive angiography in-hospital within 72 hours of the event. Angiography, and then subsequent PCI if indicated improves outcomes after non-STEMI and it is known that those who are at higher risk have more to gain from this intervention[22, 23]. Several studies[14-16, 18, 19] have shown that those with COPD are less likely to receive angiography in hospital after a non-STEMI compared to non-COPD patients, despite being at higher risk of death. One explanation for this difference could be that COPD patients are older and more likely to be deemed sicker or frailer than non-COPD patients, and as a result are not thought to be appropriate for more aggressive intervention. However, one study[16] conducted a sensitivity analysis excluding those who were deemed inappropriate for angiography for example, due to advanced cancer or dementia, and this did not change the findings that those with COPD appear to be under treated compared to non-COPD patients with similar patient characteristics.

After a MI, current guidelines[20, 21] suggest that unless these are contraindicated, patients should be prescribed a β-blocker, an ACE inhibitor or angiotensin receptor blocker, a statin, and dual antiplatelet therapy (aspirin indefinitely and $P2Y_{12}$ receptor antagonist for one year following the event). For some time it was thought that β-blockers were contraindicated in those with COPD as it was thought that they might cause bronchospasm. However, many studies have since

demonstrated that cardioselective β-blockers are not associated with either change in FEV_1 or an increase in exacerbations of COPD [24]. Despite this, β-blockers continue to be underused in those with COPD with several studies demonstrating they are much less likely to be prescribed following MI than in non-COPD patients[14-16, 19]. Smaller differences are apparent for other secondary prevention medicines although discrepancies do exist. Some studies have reported that COPD patients are slightly less likely to receive aspirin, statins and ACE inhibitors/angiotensin receptor blockers[14-19], however no studies reported significant differences in the prescription of $P2Y_{12}$ receptor antagonist. Findings from studies which have investigated differences in treatment between COPD and non-COPD patients after an MI are summarised in Table 1. An interesting observation is that differences in management between COPD and non-COPD patients are not apparent in all settings and appear to have changed over time. As previously mentioned, differences between rates of pPCI after a STEMI between COPD and non-COPD patients appears to have narrowed over time in the USA[18]. There is also evidence that prescription of β-blockers to those with COPD after MI by physicians in the USA has also improved markedly over time[15], however it is not apparent that this increase has also occurred in European countries [14, 16]. These differences between countries suggest two things: that differences in treatment between COPD and non-COPD patients do represent undertreatment, and that change is possible.

Table 1. Summary of studies which investigated differences in treatment after MI between COPD and non-COPD patients

Study	Design and setting	Population	Differences in management
Andell 2014[14]	Cohort study within the Swedish SWEDEHEART registry between 2005-2010.	Consecutive patients admitted to Swedish coronary care units. COPD diagnosis ascertained through linkage to the Swedish National Patient Registry.	**In-hospital management:** Percutaneous coronary intervention COPD: 37.7 % Non-COPD: 55.7% p<0.001 Coronary angiography: COPD: 72.5% Non-COPD: 55.4% P<0.001 **Discharge medicines:** ACE inhibitors COPD: 50.6% Non-COPD: 55.5% p<0.001 Angiotensin receptor blockers COPD: 12.6% Non-COPD: 11.1% p=0.001 Aspirin COPD: 85.5% Non-COPD: 90.1% p<0.001 β-blockers COPD: 77.7%

			Non-COPD: 86.1% p<0.001 Statin COPD: 68.4% Non-COPD: 79.2% p<0.001 P2Y12 inhibitor COPD: 62.5% Non-COPD: 72.2% P<0.001
Bursi 2010	Cohort study in Olmsted County, Minnesota from 1979-2007	3438 local residents in Olmsted County. ICD-10 codes used to ascertain COPD.	**In-hospital management:** Reperfusion COPD: 41% Non-COPD: 52% p<0.01 Angiography-in hospital COPD: 51% Non-COPD: 59% p<0.01 **Discharge medicines:** ACE inhibitor COPD: 37% Non-COPD: 29% p<0.01 β-blocker

			COPD: 47% Non-COPD: 61% p<0.01 Diuretic COPD: 34% Non-COPD: 23% p<0.01 Statin COPD: 29% Non-COPD: 30% P=0.61
Enriquez 2013	Cross sectional study of National Cardiovascular Data Registry in the USA between January 2008-December 2010	158,890 patients with an acute MI. COPD was ascertained from history of COPD or were using long term inhaled or oral β-agonists, inhaled anti-inflammatory agents, leukotriene receptor antagonists or inhaled steroids.	**STEMIs** **In-hospital management** Primary percutaneous coronary intervention COPD: 83.1% Non-COPD: 85.4% p<0.001 Overall reperfusion COPD:92.8% Non-COPD: 94.3% p<0.001 **Discharge medicines:** Aspirin COPD: 97.8% Non-COPD: 98.7% P<0.001

			β-blocker COPD: 89.4% Non-COPD: 93.1% P<0.001 ACE inhibitor or angiotensin receptor blocker COPD: 78.0% Non-COPD: 78.4% p= "not statistically significant" Statin COPD: 92.9% Non-COPD: 94.7% p<0.001 P2Y12 inhibitor COPD: 79.6% Non-COPD: 86.6% P<0.001 **nSTEMIs** **In-hospital management** Cardiac catheterisation COPD: 69.9% Non-COPD:81.2% p<0.001 Percutaneous coronary intervention within 48 hours COPD: 37.2% Non-COPD 48.9%

			p<0.001 **Discharge medicines:** Aspirin COPD: 95.9% Non-COPD: 97.3 p<0.001 β-blocker COPD: 85.5% Non-COPD: 90.5% p<0.001 ACE inhibitor or angiotensin receptor blocker COPD: 69.6% Non-COPD: 69.6% p= "not statistically significant" Statin COPD: 85.9% Non-COPD: 89.5% p<0.001 P2Y12 inhibitor COPD: 65.5% Non-COPD: 71.6% p<0.001
Rothnie 2015	All UK patients admitted to hospital in the MINAP registry between 2003-2013	300161 patients with a first MI	**STEMI** **In-hospital management**

			Primary PCI OR 0.87 (95% CI, 0.83-0.92)* **Discharge medicines** Aspirin OR 0.90 (95% CI, 0.85-0.94)* β-blocker OR 0.26 (95% CI, 0.25-0.27)* ACE inhibitor or angiotensin receptor blocker OR 0.89 (95% CI, 0.85-0.93)* Statin OR 0.91 (95% CI, 0.86-0.95)* P2Y12 inhibitor OR 0.98 (95% CI, 0.94-1.03)* **Non-STEMI** **In-hospital management** Angiography in-hospital OR 0.69 (95% CI,0.66-0.71)* **Discharge medicines** Aspirin OR 0.91 (95% CI, 0.88-0.94)* β-blocker

			OR 0.25 (95% CI, 0.24-0.25)* ACE inhibitor or angiotensin receptor blocker OR 0.94 (95% CI, 0.91-0.97)* Statin OR 0.93 (95% CI, 0.90-0.96)* P2Y12 inhibitor OR 0.97 (95% CI, 0.94-1.01)* * All ORs compared COPD to non-COPD patients and are adjusted for age, sex, smoking status and co-morbidities
Salisbury 2007	Cohort study in 19 centres in the USA between 2003-2004	2481 MI patients in PREMIER study restricted to patients discharged alive after MI	**In-hospital management** Cardiac catheterisation COPD: 45.7% Non-COPD: 41.2% p=0.094 Percutaneous coronary intervention COPD: 50.9% Non-COPD: 62.9% p<0.001 **Discharge medicines** Aspirin COPD: 87.8% Non-COPD: 94.5% p<0.001

			β-blocker COPD: 86.2% Non-COPD: 92.6% p<0.001
Stefan 2012	Cohort study up of patients hospitalised with acute MI at greater Worcester, Massachusetts between 1997-2007	6,290 Patients hospitalised with acute MI in greater Worcester, Massachusetts medical centres	**In-hospital management** Cardiac catheterisation OR 0.56 (95% CI, 0.48-0.65)** Percutaneous coronary intervention OR 0.64 (95% CI, 0.54-0.77)** **Discharge medicines** β-blocker OR 0.44 (95% CI, 0.35-0.50)** Anticoagulant OR 0.81 (95% CI, 0.69-0.95)** Statin OR 0.70 (95% CI,0.60-0.82)** Calcium channel blocker OR 1.31 (95% CI, 1.13-1.52)** ** ORs compare COPD to non-COPD patients and are adjusted for age, sex, year, cardiovascular disease history, renal failure, length of stay and type of MI (STEMI or non-STEMI)

Outcomes after MI in people with COPD

All-cause mortality

Several studies in different settings have demonstrated an increased risk of death after MI for those with COPD compared to non-COPD patients. However, there have been mixed findings concerning an increased risk of in-hospital death for those with COPD, with some finding an increased risk[14, 15, 18, 19, 25-28], and others finding no difference[13, 29]. A recently conducted systematic review and meta-analysis[8] which appraised this evidence concluded that after pooling maximally adjusted estimates from several studies, there is weak evidence for a difference in in-hospital mortality for those with COPD (OR 1.13, 95% CI 0.97-1.31) and strong evidence for an increased risk of death during follow-up (HR 1.26, 1.13-1.40, Figure 2). However, heterogeneity of effects for these meta-analyses was moderately high. It is known that differences in treatment for MI between COPD and non-COPD patients varies between countries. If some of the increased risk of death associated with COPD is due to this difference in treatment, this may explain some of the heterogeneity in findings.

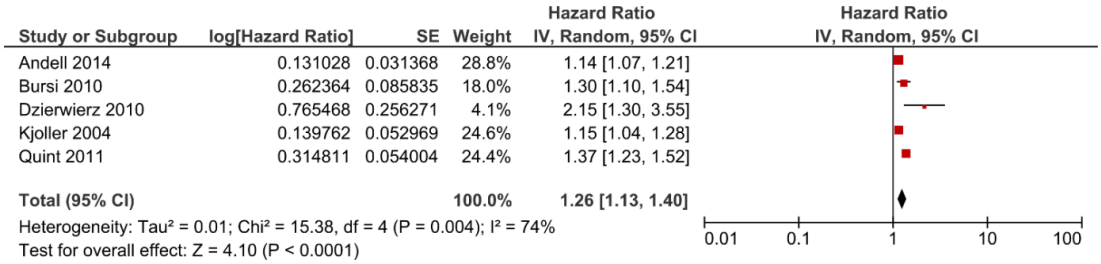

Figure 2. Long term risk of death following MI comparing COPD to non-COPD patients. Original image from Rothnie et al. 2015[8].

Interestingly, the effect of COPD on risk of death following MI is modified by some patient characteristics. A recent study in the UK demonstrated that after adjusting for potential confounders the effect of COPD on the risk of death after MI was higher after a non-STEMI than a STEMI for both in-hospital (OR 1.40 (95% CI, 1.30-1.52) compared to OR 1.27 (95% CI, 1.16-1.39)) and 6-month mortality (OR 1.63 (95% CI, 1.56-1.70) compared to OR 1.43 (95% CI, 1.29-1.58)). A study in the USA also demonstrated an increased effect of COPD on

risk of death after a non-STEMI (OR 1.21, 95% CI 1.11-1.33) compared to that for STEMIs (OR 1.05, 95% CI 0.95-1.17)[18]. In addition, it appears that the effect of COPD on risk of MI is greater for younger compared to older patients (Figure 3). This suggests that the "excess" risk of death, and therefore potentially avoidable deaths, for COPD patients attributable to COPD are clustered in younger patients. This effect was also demonstrated in a study by Dziewierz et al[27] who only found an increase in the risk of death in those under the age of 75 after MI for those with COPD compared to non-COPD patients.

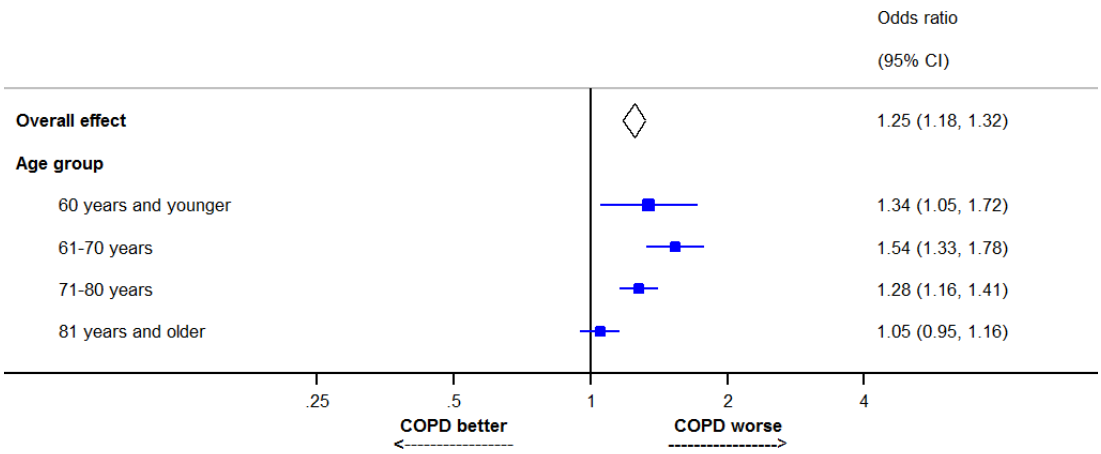

Figure 3. Effect of COPD on risk of death 6 months after MI split by age group. Adapted from data presented in Rothnie et al. 2015[16].

As previous studies have demonstrated that there may be a significant degree of delay in diagnosis of MI for those with COPD. It would seem likely that there are a proportion of COPD patients who have an MI and this is missed entirely. The prevalence and impact of this potential problem is currently unclear. In addition, all of the studies which have investigated the risk of death for COPD patients compared to non-COPD patients after MI have done so in patients admitted to hospital. As many of those who have an MI do not survive until admission to hospital, the impact of COPD on risk of death after MI may be underestimated.

Other outcomes

As well as death following MI, other outcomes are important and have been investigated in those with COPD.

In terms of in hospital adverse events, Stefan et al[15] found that after adjusting for possible confounders, people with COPD were more likely to experience acute heart failure (OR 1.59, 95% CI 1.37-1.83), but not atrial fibrillation, cardiogenic shock or stroke. In unadjusted analysis, Hadi et al[13] also found an increased risk of acute heart failure in people with COPD, but not cardiogenic shock, re-infarction or stroke in hospital. In another unadjusted analysis, Enriquez et al[18] found an increased risk of acute heart failure, cardiogenic shock, re-infarction, stroke and major bleeding for in hospital COPD patients following an MI.

In terms of adverse events following discharge from hospital, two studies have investigated the risk of heart failure for COPD patients after MI. Andell 2014 et al[14] found that COPD patients were at higher risk of new-onset heart failure during the year following MI (HR 1.35, 95% CI 1.24-1.47). In a study including those with both MI and heart failure or left ventricular systolic dysfunction, COPD patients were more likely to have a hospitalisation for heart failure in the three years following MI (HR 1.19, 95% CI 1.05-1.34)[30]. Hawkins 2009 also found that COPD patients had a higher risk of sudden death compared to non-COPD patients (HR 1.26, 95% CI 1.03-1.53). However, this study was conducted in a population who all had heart failure or left ventricular systolic dysfunction and had been selected for a randomised controlled trial of treatment for heart failure and therefore may not be representative of the general population.

After a MI, COPD patients do not appear to be at higher risk of re-current MI[14, 30], stroke[30], angina[17], or major bleeds[14] compared to non-COPD patients.

Are differences in recognition and management related to differences in outcomes?

As it is known that people with COPD have poorer outcomes compared to people without COPD, that they are less likely to have their MI recognised, and that they are less likely to receive guideline recommended treatment and investigation, one important question is whether these differences in management explain some of the differences in outcomes.

It is known that people with atypical presentations of MI have poorer outcomes compared to individuals with typical presentations, and that this might be related to differences in treatment[31, 32]. People who present atypically are less likely to receive any reperfusion therapy after a STEMI, or angiography and percutaneous coronary intervention after a non-STEMI, and are less likely to receive β-blockers, statins or antiplatelet therapy on discharge from hospital[32]. It has been known for some time that older individuals, women, and people with diabetes or heart failure are more likely to have atypical presentations of MI. However, it has not been widely recognised that those with COPD may present with atypical symptoms of MI.

A recent study[16] aimed to investigate whether differences in recognition and management of MI could explain some of the difference in mortality after MI for those with COPD. The findings showed that both recognition and management explained some of the difference in mortality after MI between COPD and non-COPD patients. Particularly, delay in diagnosis, timing and use of reperfusion after a STEMI, use of angiography after a non-STEMI and use of secondary prevention medicines were all potential explanations for the difference in mortality between COPD and non-COPD patients after an MI. Similarly, Andell et al[14] found that adjusting for differences in in-hospital and discharge treatment reduced the HR comparing mortality in COPD patients to non-COPD patients from an HR of 1.32 (95% CI, 1.24-1.40) to an HR of 1.14 (95% CI, 1.07-1.21). However, adding treatment into the regression models in a study by Salisbury et al[17] made no difference to the effect of COPD on mortality. These findings suggest that much of the difference in mortality between COPD and non-COPD patients after MI may be mediated by differences in recognition and treatment of MI rather than differences in treatment confounding the effect of COPD on risk of death. Differences in treatment between countries may be a possible reason for heterogeneity in effects of COPD on risk of death after MI. This is an important finding as, although some of the increased risk of death is likely to be due to COPD itself, if a proportion is due to differences in treatment, then this could potentially be modified.

One of the largest differences in management after MI between COPD and non-COPD patients in prescription of β-blockers as secondary prevention. As well as being safe for COPD patients recent work has demonstrated their effectiveness for secondary prevention after MI. Quint et al[33] conduced a propensity score matched cohort study among those with COPD after MI comparing those prescribed β-blockers and those not prescribed β-blockers after MI. Those started on a β-blocker during hospital admission for MI had significantly better survival than those not prescribed β-blockers (HR 0.50, 95% CI 0.36-0.69). Similarly, in a population of people with heart failure, Hawkins et al 2009[30] found that COPD patients prescribed a β-blocker following an MI had better survival than those not prescribed a β-blocker (HR 0.74, 95% CI 0.68-0.80). COPD did not appear to modify the effect of β-blockers on mortality. The reluctance to prescribe β-blockers to COPD patients may drive much of the increased risk of heart failure and death in the months and years following an MI in those with COPD.

A schematic diagram of the possible mechanisms underlying the relationship between COPD and risk of death after MI is presented in Figure 4.

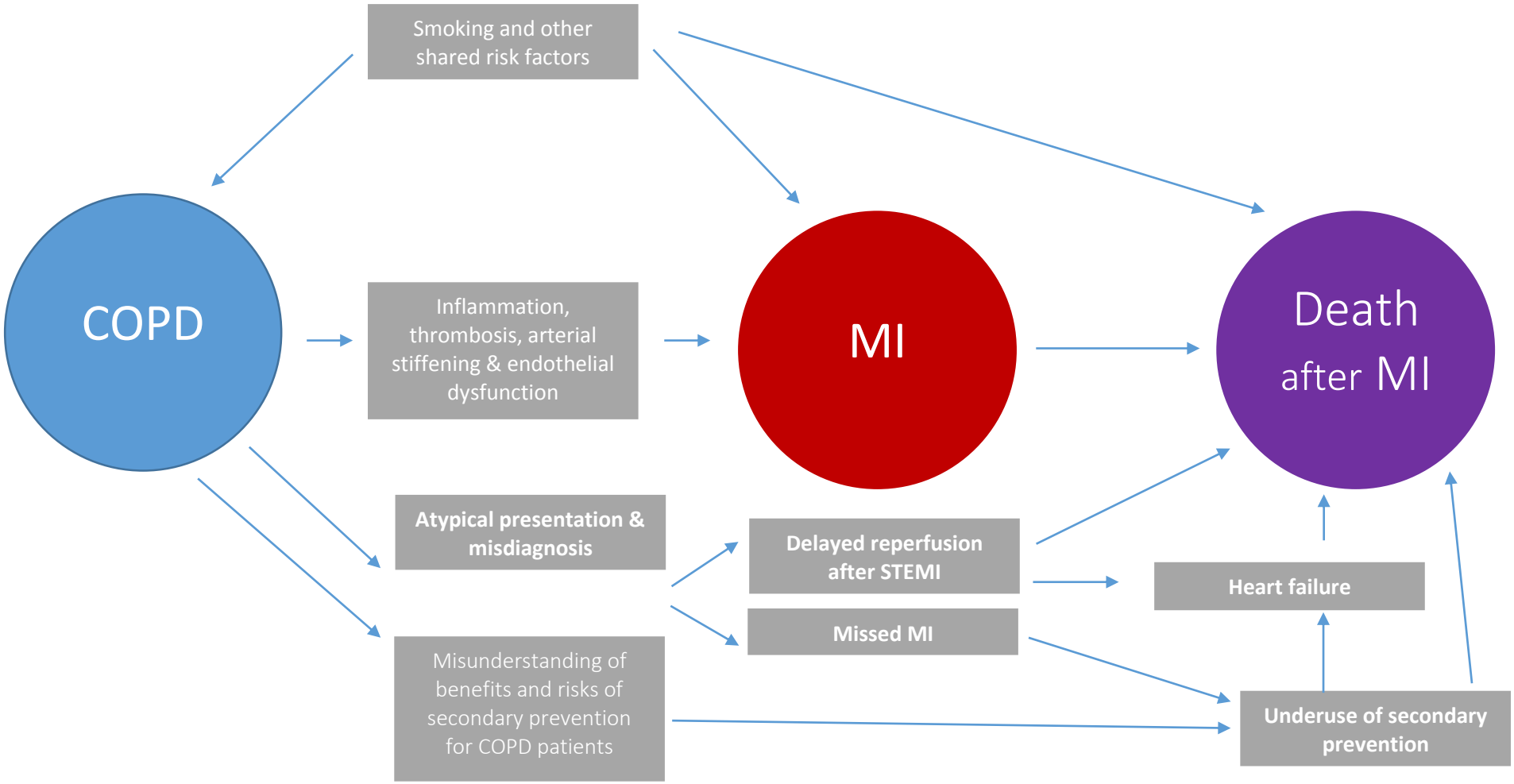

Figure 4. Schematic diagram of the possible mechanisms underlying the relationship between COPD and risk of death after MI

Areas for future research

Are MIs completely missed with those with COPD?

Evidence has shown that there is sometimes delayed recognition of acute MI in people with COPD. One likely explanation for this is that the symptoms of their MI, such as breathlessness, may be misattributed to their COPD. In addition, atypical presentation may also contribute to the delay in diagnosis. It is therefore possible that the diagnosis of many MIs in those with COPD are not only delayed, but may also be missed completely. Indeed, it is known that around 8% of patients admitted to hospital with an acute exacerbation of COPD meet the Universal Definition for Myocardial Infarction (raised troponin with ECG changes and/or chest pain)[34]. As it is known that exacerbations of COPD are a period of higher risk of MI for COPD patients, it is unclear how many of these are MIs triggered by an exacerbation and how many are MIs initially misdiagnosed as exacerbations. In another study, among those hospitalised for an acute exacerbation of COPD, it was found that around 2/3 of all COPD patients with evidence of a previous MI as assessed by the cardiac infarction injury score had a recorded diagnosis of MI, and that this was even higher among women with COPD[35]. Missed diagnosis of MI has been a long established finding in those with diabetes, and is associated with increased mortality in this group[31]. Further research should investigate the prevalence of missed diagnosis of MI and the impact of this potential problem.

What other aspects of COPD are related to mortality after MI?

Although several studies have investigated mortality after MI for those with COPD, none have investigated which aspects of COPD itself may modify this relationship.

COPD severity defined by degree of airflow obstruction appears to be a risk factor for MI[36]. It is unclear however, if degree of airflow obstruction is also a risk factor for death after MI in those with COPD. Much of the research on risk of death after MI in those with COPD has been conducted using national MI registries, and as such do not have data on lung function.

After an MI, one of the most effective things a current smoker can do to reduce their risk of death and further MI is to quit smoking[37]. As many COPD patients are current smokers and can be very heavily dependent on nicotine, quit rates may be lower in those with COPD and recidivism may be higher in those COPD patients who do quit. Recent work has suggested that smokers are not frequently prescribed recommended smoking cessation pharmacotherapy[38] and that in contrast to those with stable coronary artery disease, pharmacotherapy may not be effective for smoking cessation after acute MI[39]. However, COPD patients may well represent a group in whom this therapy could be targeted towards.

COPD exacerbations are an acute worsening of symptoms of cough, breathlessness and sputum volume and/or purulence beyond normal day-to-day variation and which may require a change in treatment. Acute exacerbations of COPD are associated with increased systematic inflammation and are important drivers of morbidity and mortality in those with COPD[40]. Some COPD patients appear to be particularly susceptible to exacerbations, and these patients have been termed frequent exacerbators. Periods of exacerbation have been found to be associated with increased risk of MI for those with COPD[8, 41, 42]. Further research is needed to investigate what effect, if any, the frequent exacerbator phenotype has on outcomes after MI.

Predicting risk of death after MI in people with COPD and differences in treatment

The risk management paradox refers to the observation that although those who are at highest predicted risk of death after MI are most likely to benefit from early aggressive intervention, especially after a non-STEMI, they are the least likely to receive it[43]. As those with COPD certainly seem to be at higher risk of death after MI, and less likely to receive early aggressive intervention, such as cardiac catheterisation within 72 hours after a non-STEMI, this may apply to those with COPD. There may be several reasons for this paradox in those with COPD. The first is that current systems which score patients based on risk of death after MI do not perform well in those with COPD compared to non-COPD patients. Early findings from a study of the performance of the GRACE score in those with COPD compared to those who do not have

COPD suggests that it does not perform as well at predicting risk of death after acute coronary syndromes in COPD patients[44]. However, evidence also suggests that even when COPD patients have the same GRACE score predicted risk of death as non-COPD patients, they are less likely to receive guidelines recommended investigation and treatment, suggesting there may be other forces at play[44]. The second is perhaps therapeutic nihilism towards treating comorbidities in those with COPD. It may be that COPD patients are seen as older, frailer patients in whom secondary prevention is not worthwhile. However, as previously discussed, many COPD patients do in fact die from cardiovascular disease. In addition, much of the excess deaths after MI in those with COPD are among younger patients and even in studies which adjusted for age and comorbidities, differences in treatment did seem to be associated with poorer mortality for those with COPD. Both performance of risk scores after MI and clinical decision making around the selection of patients for invasive treatment and secondary prevention drugs is needed.

Conclusions

It is clear that COPD patients have poorer long term mortality after MI compared to non-COPD patients. The effect of COPD on risk of death after MI is higher for younger people and for those with a non-STEMI. They do not appear to be at higher risk of recurrent MI, however they do seem more likely than non-COPD patients to develop heart failure. COPD patients also seem to be at higher risk of in-hospital death after MI in some settings, however this may depend on quality of care for COPD patients after MI. Some of the difference in in-hospital and longer term mortality appears to be due to differences in recognition and management of MI in those with COPD.

Those with COPD present differently after acute MI than non-COPD patients. They are more likely to present with breathlessness and atypical chest pain. This may contribute to a delay in recognition of MI in those with COPD, and may also mean that many MIs in those with COPD are missed entirely.

In terms of in-hospital care, COPD patients are less likely to receive reperfusion after a STEMI, and prompt angiography after a non-STEMI. COPD patients are also less likely to receive secondary prevention drugs after an MI, in particular β-blockers. β-blockers are safe and effective for secondary prevention after MI in those with COPD and should not be withheld from this group.

Further research is needed to investigate the extent and impact of missed diagnosis of MI in those with COPD. In addition, identifying those with undiagnosed COPD after an MI is vital for reducing mortality in this group. Researchers should also focus on investigating how risk scores function in those with COPD and how they are used to guide treatment in this group.

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5.3 Summary

- People with COPD are more likely to present atypically following MI than those who do not have COPD
- Several studies indicate that age is an important effect modifier for the effect of COPD on risk of death following MI
- Differences in recognition and management of MI have been found in a range of settings, as well as the UK
- COPD patients are at higher risk of death and development of heart failure following MI, but do not appear to be at higher risk of other vascular outcomes, compared to those who do not have COPD

Chapter 6 Predicting mortality after acute coronary syndromes in people with chronic obstructive pulmonary disease (Research paper IV)

6.1 Preamble

Findings from the previous chapters have indicated that COPD patients have higher mortality following MI than those who do not have COPD, and that this may be explained, in part, by differences in treatment.

This research paper uses data from the MINAP dataset. In addition to data from MI, data from admissions for unstable angina are also included. Unstable angina is a less severe form of acute coronary syndrome (ACS). Unstable angina is similar to non-STEMI, however relates to partial or transient occlusion of a coronary artery which is not severe enough to cause necrosis (or at least not severe enough such that any increase in serum troponin is detectable). Unstable angina episodes are included here as they are necessary to fit the GRACE score prognostic models.

In the UK, NICE recommend the use of the GRACE score to guide treatment following non-STEMI and unstable angina (NICE 2010). Those with a predicted risk of death at 6 months of over 3% should be considered for angiography in hospital, and subsequent treatment if necessary. The findings from Chapter 3 indicated that although they are at higher risk of death, those with COPD are less likely to have angiography in hospital, even after adjustment for age, sex, smoking status and co-morbidites. This finding could be explained if the GRACE score does not provide as accurate risk stratification in COPD patients as it does in those who do not have COPD. Although the accuracy of the GRACE score has been investigated in other diseases, this has not been done in COPD (Eagle et al. 2004).

In presenting the results of this analysis, I felt it was important to represent differences in potential models in a clinically meaningful way. Therefore, as well as expressing results in terms of statistical concepts of calibration (Hosmer-Lemeshow statistic) and discrimination (C-statistic), more clinically meaningful measures, such as the relative risk of death for COPD patients compared to those without COPD with the same predicted risk of death. Also, the percentage of COPD patients who could be considered for different treatment under a more accurate scoring system are presented. Calibration refers to the ability of a model to accurately predict the probability of an event, higher p-values for the Hosmer-Lemeshow static indicate better calibration. Discrimination refers to whether patients who do have an event have higher

predicted probabilities, higher C-statistics indicate better discrimination. A recent addition to diagnostic statistics for prognostic models is the net-reclassification index (NRI) (Kerr et al. 2014), and this relates to the ability of a new addition to a prognostic model to classify those with the event upwards (that is increase their predicted probability of the event), while classifying those who do not have the event downwards (that is decrease their predicted probability of the event). A positive NRI indicates better classification.

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6.2 Research paper

Predicting mortality after acute coronary syndromes in people with chronic obstructive pulmonary disease

Authors Kieran J Rothnie, Liam Smeeth, Neil Pearce, Emily Herrett, Adam Timmis, Harry Hemingway, Jadwiga Wedzicha, Jennifer K Quint

Abstract

Objective

To assess the accuracy of Global Registry of Acute Coronary Events (GRACE) scores in predicting mortality at 6 months for people with COPD and to investigate how it might be improved.

Methods

Data were obtained on 481,849 patients with acute coronary syndrome (ACS) admitted to UK hospitals between January 2003-June 2013 from the myocardial ischaemia national audit project (MINAP) database. We compared risk of death between chronic obstructive pulmonary disease (COPD) and non-COPD patients at 6 months, adjusting for predicted risk of death. We then assessed whether several modifications improved the accuracy of the GRACE score for people with COPD.

Results

The risk of death after adjusting for GRACE score predicted risk of death was higher for COPD patients than for other patients (RR 1.29, 95% CI 1.28-1.33). Adding smoking into the GRACE score model did not improve accuracy for COPD patients. Either adding COPD into the model (RR 1.00, 0.94-1.02) or multiplying the GRACE score by 1.3 resulted in better performance (RR 0.99, 0.96-1.01).

Conclusion

GRACE scores underestimate risk of death for people with COPD. A more accurate prediction of risk of death can be obtained by adding COPD into the GRACE score equation, or by multiplying the GRACE score predicted risk of death by 1.3 for people with COPD. This means that one third of COPD patients currently classified as low risk should be classified as moderate risk, and could be considered for more aggressive early treatment after non-ST-elevation myocardial infarction or unstable angina.

What is already known about this subject?

Despite being at higher risk of death following admission for acute coronary syndromes, those with chronic obstructive pulmonary disease (COPD) are less likely to receive investigation and treatment than non-COPD patients and this difference may explain some of the difference in mortality. It is recommended that those at moderate (3-6%) or high (>6%) Global Registry of Acute Coronary Events (GRACE) score predicted risk of death at 6 months after admission to hospital for non-ST-segment elevation myocardial infarction or unstable angina receive earlier aggressive investigation and treatment.

What does this study add?

This nationwide multicentre study involving 481,849 hospital admissions demonstrates that GRACE scores underestimate risk of death after acute coronary syndromes for those with COPD. This study also found that multiplying the predicted risk of death for those with COPD by 1.3 provides a better approximation for their risk of death.

How might this impact on clinical practice?

Using a more accurate estimate of risk of death for those with COPD after admission for acute coronary syndromes one third of COPD patients previously categorised as low risk would be reclassified as moderate risk, and therefore would be eligible for earlier, more aggressive investigation and treatment.

Introduction

Accurate prediction of risk of death after acute coronary syndromes (ACS) is important not only for prognostication, but also for decision making about treatment, as individuals at higher risk of death after ACS benefit most from early aggressive treatment[1, 2]. Early and accurate assessment of future risk allows clinicians to identify patients who might benefit most from therapies and to avoid unnecessary treatment for those who are less likely to benefit.

GRACE (Global Registry of Acute Coronary Events) scores are used internationally to predict the probability of death at six-months after admission to hospital for ACS. They have been developed and validated in several different settings[3, 4, 5, 6, 7]. The predicted risk of death can be used to stratify patients into low (<3%), moderate (3-6%) and high (>6%) risk of death at 6 months post-ACS. Current guidelines recommend that those classified as moderate-high risk of death using the GRACE score should receive more aggressive early therapy after non-ST elevation myocardial infarction (non-STEMI) or unstable angina[8, 9].

People with chronic obstructive pulmonary disease (COPD) have a higher risk of MI than people without COPD, and cardiovascular disease is an important cause of death in people with COPD. In addition, COPD is very common in people with MI, with prevalences ranging from 10-17%[10, 11]. Several studies have also found an increased risk of death after MI in people with COPD compared to people without COPD[10, 12, 13]. Previous work [14] has shown that, after adjusting for confounders, even though people with COPD have a higher mortality at 6-months post discharge than non-COPD patients, they are less likely to receive angiography in-hospital after a non-STEMI, or to receive secondary prevention drugs after any MI. One of the reasons for this may be that GRACE scores may not predict risk of death in COPD patients as well as they do in non-COPD patients.

Using data from the UK Myocardial Ischaemia National Audit Project (MINAP) registry, we investigated whether GRACE scores performed as well in people with COPD as they do in people without COPD, and how they might be improved for people with COPD.

Methods

Data source

MINAP is a UK registry of all admissions for ACS to hospitals in England and Wales. The following variables were collected which are needed for the equation for 6-month mortality (post-admission): age, heart rate, systolic blood pressure, creatinine, heart failure, cardiac arrest at admission, ST-segment deviation and elevated cardiac enzymes[15]. Vital status is available through linkage with the Office of National Statistics (ONS) mortality data.

We included all patients with a diagnosis of ST-elevation myocardial infarction (STEMI) from January 2003 to June 2013, or non-STEMI or unstable angina from January 2004 to December 2012. Diagnosis of STEMI, non-STEMI and unstable angina were based on physician diagnosis and records of electrocardiogram and cardiac biomarker findings. Records were excluded if they did not have a patient unique identifier; if patients had missing values for presence of obstructive airway disease or smoking history; or if ONS mortality data were missing.

We identified COPD in MINAP using a strategy previously validated in MINAP data linked with primary care[14]. Briefly, we used the obstructive airway disease indicator and a smoking history (ex or current smoker) to identify COPD, and this identified COPD with a misclassification rate of less than 10%.

Statistical methods

GRACE scores

GRACE scores and predicted risks of death at 6 months were constructed using published nomograms for the Fox model[16]. Values available from nomograms were used to construct

algorithms to score patients and to convert these to predicted risk death. As Killip class is not recorded in MINAP, we used a previously validated[17] method to score patients based on Killip class of heart failure by using in-hospital prescription of diuretics as a proxy.

We estimated the observed and GRACE score predicted risks of death at six months and compared these between people with and without COPD. We estimated the Mantel-Haenszel risk ratio averaged over the GRACE score deciles to estimate the average relative risk for death at six months post-admission for COPD patients with the same GRACE score as non-COPD patients. If GRACE scores work equally well in COPD patients and non-COPD patients, then the risk ratio would be 1. A risk ratio of less than 1 would suggest that GRACE scores overestimate the risks of death in COPD patients after admission; a risk ratio of more than 1 would suggest that GRACE scores underestimate the risks of death in COPD patients. We also compared the risk of death for people with diabetes to people who do not have diabetes, adjusted for GRACE score predicted risk of death.

We then investigated the observed risk of death between COPD and non-COPD patients within GRACE score predicted levels of risk (0-3% low, 3-6% moderate, and >6% high).

We explored the extent of and possible reasons for missingness of GRACE score variables and performed a multiple imputation analysis (details in supplementary material).

Model modifications

We investigated several strategies for improving GRACE scores for people with COPD. We prespecified three potential modifications to the GRACE models which might improve their accuracy for COPD patients: 1) Adding COPD into the models as a risk factor; 2) Adding smoking history into the models as a risk factor; and 3) multiplying the predicted risk of death for COPD patients by the RR for risk of death for COPD patients compared to non-COPD patients after adjusting for GRACE score predicted risk of death.

For the approaches which involved adding new variables to the models (smoking and COPD), we had to re-specify the GRACE models. We did this by building logistic regression models which included all of the GRACE variables (with or without smoking or COPD) with death at 6 months as the outcome and used these to predict risk of death. As an internal validation procedure, we also bootstrapped the logistic regression models with 100 reps each, and compared the parameter estimates with those from the main analysis.

In order to assess which models performed best, we calculated the Mantel-Haenszel risk ratios to compare the risk of death at 6 months between COPD and non-COPD patients adjusting for predicted risk of death for the model in question. We also calculated C-statistics and Hosmer-Lemeshow goodness of fit tests. Strategies involving multiplication of risk for COPD patients using the existing GRACE model were compared to the existing GRACE model. In order to make a fair comparison, models which involved adding other variables (smoking or COPD) were compared to our models which included all of the GRACE variables. In order to assess how well each model stratified risk, we also plotted the proportion of all deaths by deciles of predicted risk of death at 6 months for the normal GRACE model and for modifications. We calculated how many people would be re-classified in terms of risk level (low, moderate or high) for each modification, we also performed this analysis stratified by type of ACS. Finally, we also calculated the continuous net reclassification improvement (NRI) statistic[18] for adding COPD to the GRACE score model.

Ethics

This study was approved by LSHTM Observational Ethics Committee (6468) and the MINAP academic group (13-MNP-07).

Results

Patient characteristics

In total, 481,489 patients with ACS were included, of whom 58,739 (12.2%) had COPD (Figure 1). Patient characteristics of COPD and non-COPD patients are shown in Table 1. In terms of mortality, COPD patients were more likely to have died by 6 months post-admission compared to non-COPD patients (17.7% compared to 11.6%). COPD patients, on average also had higher GRACE score predicted risk of death than non-COPD patients (14.0% (SD, 12.7) compared to 11.7% (SD, 12.3)).

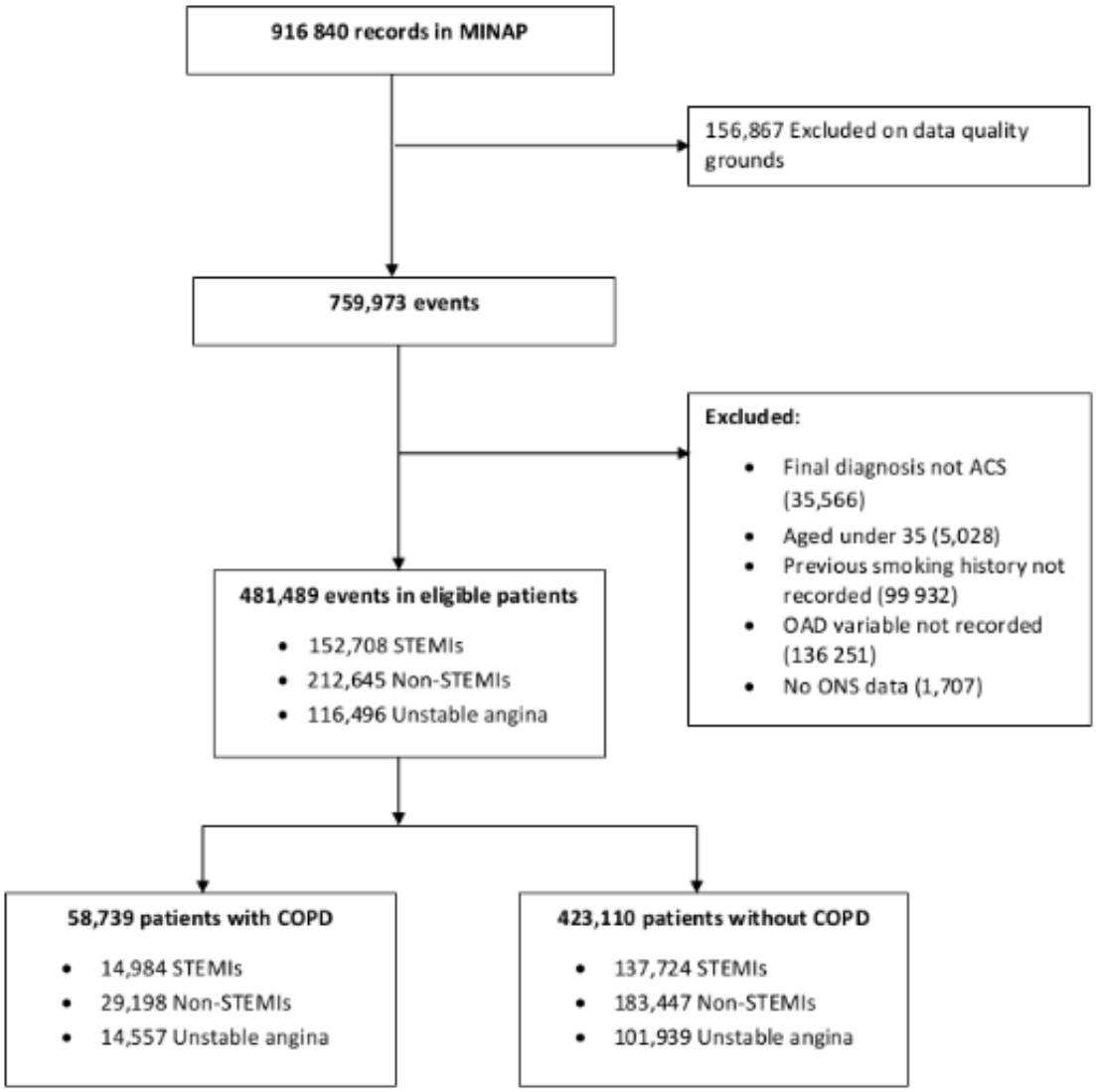

Figure 1. Flow of participants through the study. ACS, acute coronary syndromes; COPD, chronic obstructive pulmonary disease; MINAP, Myocardial Ischaemia National Audit Project; non-STEMI, non-ST-elevation myocardial infarction; OAD, obstructive airway disease; ONS, Office of National Statistics.

Table 1 Characteristics of patients included in the analysis

Characteristic	Non-COPD	COPD
Age group (n=481,489)		
<55	79,603 (18.8%)	6,575 (11.2%)
55-64	92,446 (21.8%)	10,858 (18.5%)
65-74	101,654 (24.0%)	17,402 (29.6%)
75-84	100,660 (23.8%)	18,011 (30.7%)
≥85	48,747 (11.5%)	5,893 (10.0%)
Sex (n=481,489)		
Male	285,502 (67.5%)	37,135 (63.2%)
Female	137,608 (32.5%)	21,604 (36.8%)
Diagnosis (n=481,489)		
STEMI	137,724 (32.6%)	14,984 (25.5%)
Non-STEMI	183,447 (43.4%)	29,198 (49.7%)
Unstable angina	101,393 (24.1%)	3,136 (24.8%)
Previous MI (n=478,530)	79,733 (18.9%)	14,485 (25.1%)
Previous angina (n=477,494)	107,991 (25.7%)	19,962 (34.7%)
Previously treated hyperlipidemia (n=467,096)	135,236 (32.9%)	18,573 (33.2%)
Previously treated hypertension (n=477,515)	201,174 (47.9%)	28,256 (49.0%)
Peripheral vascular disease (n=473,652)	17,216 (4.1%)	4,182 (7.4%)
Cerebrovascular disease (n=476,863)	31,563 (7.5%)	5,858 (10.3%)
Chronic renal failure (n=476,351)	17,368 (4.1%)	3,697 (6.5%)
Chronic heart failure (n=476,324)	18,216 (4.3%)	4,955 (8.7%)
Previous percutaneous coronary intervention (n=472,614)	29077 (7.0%)	4,256 (7.5%)
Previous coronary artery bypass graft (n=473,891)	22,567 (5.4%)	3,320 (5.8%)
Smoking history (n=481,849)		
Never smoker	142,254 (33.6%)	0 (0%)
Ex-smoker	151,560 (35.8%)	35,103 (59.8%)
Current smoker	129,296 (30.6%)	23,636 (40.2%)
Raised cardiac markers* (n=481,849)	365,730 (91.8%)	51,206 (92.2%)
ST segment deviation* (n=413,253)	221,205 (60.7%)	27,165 (55.3%)
Use of diuretic in hospital* (n=481,849)	93,116 (22.0%)	19,069 (32.5%)
Mean heart rate* (n=433,721)	80.2 ±21.9	87.2 ±23.7
Mean systolic blood pressure* (n=432,854)	139.9 ±28.6	138.2 ±29
Mean serum creatinine* (n=287,893)	101 ±56.6	103.4 ±58.3

* Mean ±SD

COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; STEMI, ST-segment elevation myocardial infarction; non-STEMI, non-ST-segment elevation myocardial infarction.

GRACE score performance

The Mantel-Haenszel pooled risk ratio comparing risks of death for COPD patients to non-COPD patients after adjusting for GRACE score predicted risk of death was 1.30 (95% CI, 1.27-1.33). Observed and predicted mortality for COPD and non-COPD patients, split by deciles of GRACE score predicted risk of death, is presented in Table 2. These results stratified by year of admission are presented in the supplementary material (Table S1). People with diabetes also had a higher risk of death than those without diabetes with the same GRACE score predicted risk of death; however, this was lower than for people with COPD (RR 1.14, 95% CI, 1.12-1.16).

Table 2 Predicted and observed mortality using normal GRACE model

GRACE predicted risk decile	Average predicted mortality (%)	Observed mortality - non-COPD (%)	Observed mortality – COPD (%)
1	1.3	0.6	0.8
2	2.5	1.3	2.4
3	4.0	2.4	4.6
4	5.0	3.2	6.4
5	6.5	4.5	7.4
6	8.9	7.1	12.2
7	12.4	10.7	17.1
8	17.2	16.7	21.9
9	26.6	27.2	32.1
10	48.4	44.0	47.9

Model modifications

Findings from model modifications are displayed in Table 3. Compared to the MINAP derived GRACE score model using the original variables, the model including COPD as a risk factor resulted in better predictions for COPD patients. Including smoking history as a risk factor in the model did not result in better predictions for COPD patients. Bootstrapped results did not differ from the main analysis. Multiplying the GRACE score predicted risk of death by the RR for risk of death for COPD patients adjusted for GRACE score predicted risk of death (1.3) resulted in a very close approximation to adding COPD into the model as a risk factor. C-statistics were improved for the model which multiplied the risk of death for COPD patients by

1.3 and the model which included COPD as a risk factor. Adding smoking to the GRACE score model did not significantly change the C-statistic. Hosmer-Lemeshow statistics showed that all models tested had adequate calibration.

Table 3 – Predictive ability of modifications to the GRACE score in COPD patients

Method for obtaining predicted risk of death	**M-H pooled RR (95% CI) for death at 6 months adjusted for predicted risk of death**	**C-statistic**	**Hosmer-Lemshow p-value**
Normal GRACE score (comparator for 1)	**1.29 (1.28-1.33)**	**0.8166**	**>0.999**
1. Normal GRACE score – multiply risk of death by 1.3 for COPD patients	0.99 (0.96-1.01)	0.8181 (p<0.001)*	**>0.999**
MINAP derived GRACE score (comparator for 2-3)	**1.23 (1.20-1.26)**	**0.8322**	**>0.999**
2. MINAP derived GRACE score + smoking	1.20 (1.17-1.23)	0.8323 (p=0.274)*	**>0.999**
3. MINAP derived GRACE score + COPD	1.00 (0.94-1.02)	0.8333 (p<0.001)*	**>0.999**

***p-values compare the C-statistics for the modified models compared to either the normal GRACE score or the MINAP derived GRACE score.**

The proportions of all deaths in COPD patients in deciles of predicted risk for the normal GRACE model, the GRACE model multiplied by 1.3, and the MINAP derived model including COPD are displayed in Figure 2. The plot shows a steeper increase in the proportion of deaths in each decile for the GRACE model multiplied by 1.3, and the MINAP derived model including COPD compared to the normal GRACE model, indicating better stratification for these two modifications. Observed mortality within GRACE score predicted risk groups for the normal GRACE model and for the modifications for COPD and non-COPD patients in presented in Table 4.

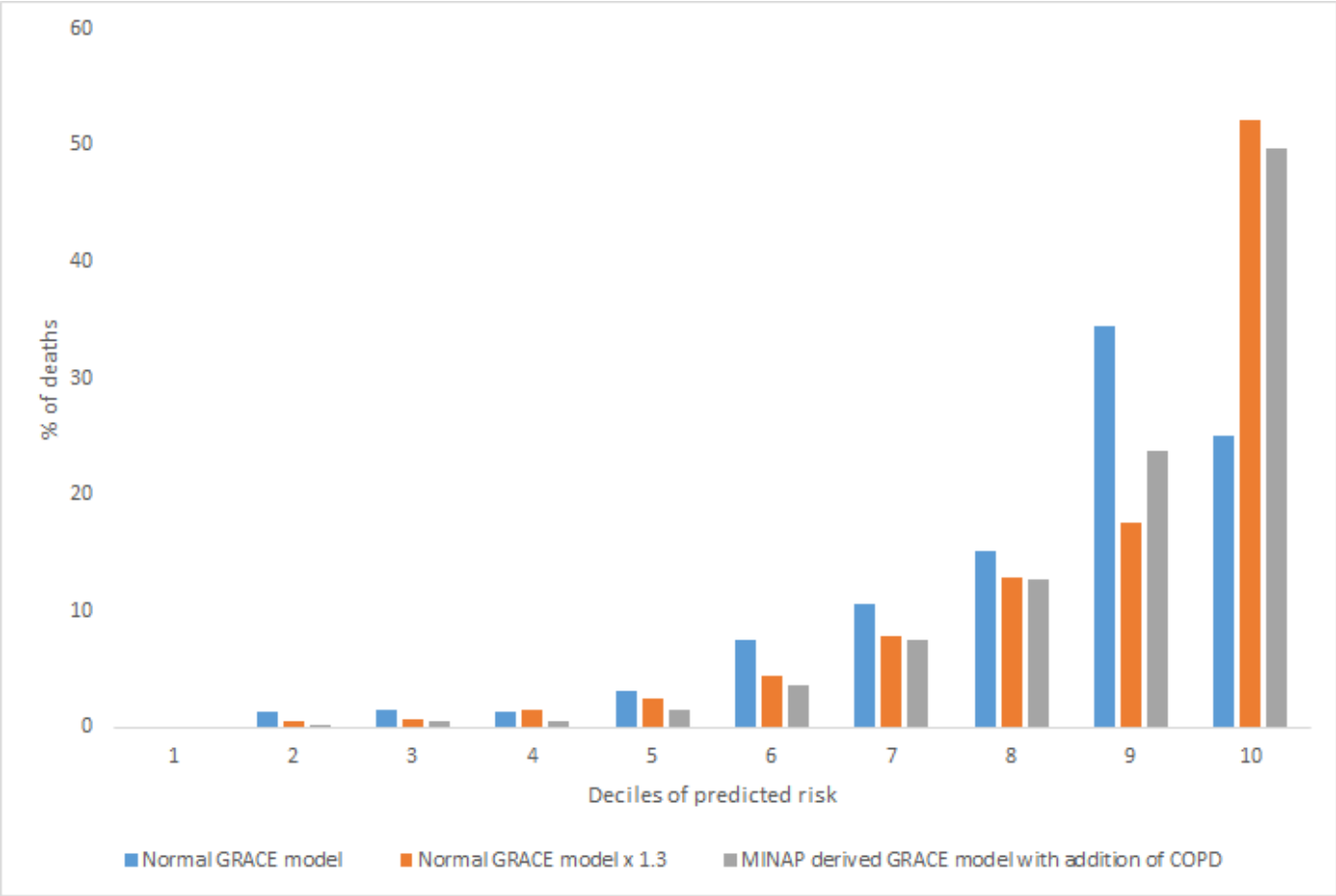

Figure 2. Proportion of deaths occurring in COPD patients in each decile of predicted risk for the Normal GRACE model, the GRACE model multiplied by 1.3 for COPD patients, and the MINAP derived model including COPD. GRACE=Global Registry of Acute Coronary Events; COPD= chronic obstructive pulmonary disease.

Table 4 – Observed mortality at 6 months for COPD and non-COPD patients stratified by different versions of the GRACE score predicted risk of death

Normal GRACE score		
GRACE score predicted risk level	**Observed mortality - non-COPD (%)**	**Observed mortality – COPD (%)**
Low (<3%)	1.0	1.9
Med (3-6%)	3.1	5.8
High (>6%)	18.4	23.3
Normal GRACE score x 1.3 for COPD patients		
GRACE score predicted risk level	**Observed mortality - non-COPD (%)**	**Observed mortality – COPD (%)**
Low (<3%)	1.0	1.3
Med (3-6%)	3.1	3.8
High (>6%)	18.4	21.4
MINAP derived GRACE score		
GRACE score predicted risk level	**Non Observed mortality - non-COPD (%)**	**Observed mortality – COPD (%)**
Low (<3%)	1.1	1.1
Med (3-6%)	3.4	6.0
High (>6%)	20.6	25.2
MINAP derived GRACE score & COPD		
GRACE score predicted risk level	**Observed mortality - non-COPD (%)**	**Observed mortality – COPD (%)**
Low (<3%)	1.1	1.4
Med (3-6%)	3.7	4
High (>6%)	21.0	23.3

The findings for re-classification of risk levels after different model modifications are displayed in Table 5. Compared to the normal GRACE score model, when patients with COPD were stratified into risk groups based on the multiplying the GRACE score predicted risk of death by 1.3, 33.9% of those classified as low risk (<3%) were reclassified as moderate risk (3-6%), and 64.3% of those who were classified as moderate risk were reclassified as high risk (>6%). When stratified by type of ACS, the results were similar to the main analysis, with the exception of change in risk group after a STEMI in the MINAP derived model including COPD (Supplementary material, Tables S2-S4). The NRI for adding COPD to the GRACE score model was 0.133 ($p<0.001$) indicating an improvement in classification of subjects when COPD is added to the model.

The findings from the multiple imputation analysis were similar to those form the main analysis, and are presented in the supplementary material (Table S5).

Table 5 Changes in level of risk for COPD patients after modifications

	Multiplying risk by 1.3		
GRACE score predicted risk of death	**Low risk (<3%)**	**Moderate risk (3-6%)**	**High risk (≥6%)**
Low risk (<3%)	4,107 (66.1%)	2,108 (33.9%)	0
Moderate risk (3-6%)	0	2,000 (35.7%)	3,609 (64.3%)
High risk (>6%)	0	0	20,799 (100.0%)
	Adding COPD into MINAP derived GRACE model		
GRACE score predicted risk of death	**Low risk (<3%)**	**Moderate risk (3-6%)**	**High risk (≥6%)**
Low risk (<3%)	4,635 (71.5%)	1,582 (25.5%)	184 (3.0%)
Moderate risk (3-6%)	681 (12.2%)	2,792 (50.0%)	2,117 (37.9%)
High risk (>6%)	15 (0.1%)	994 (4.8%)	19,527 (95.1%)

Discussion

We found that GRACE scores for predicting risk of death at 6 months after ACS do not perform as well for people with COPD compared to those who do not have COPD. On average, COPD patients had a 30% higher risk of death than non-COPD patients with the same GRACE score. In order to improve GRACE scores for COPD patients, one option would be to re-specify the GRACE model including COPD as a risk factor. Alternatively, multiplying GRACE score predicted risk of death by 1.3 for COPD patients provides a very close approximation.

We found that, conditional on GRACE score predicted risk of death, COPD patients had a higher risk of death than non-COPD patients, indicating that these scores underestimate the risks of death in those with COPD. One might argue that this might be true for any co-morbidity; however, when we also estimated the relative risk of death comparing those with diabetes to those without diabetes adjusted for GRACE score predicted risk of death, although

we found an increased risk, this was much lower than for COPD. Although the relative risk of death for COPD might seem modest, this may have a large impact on patient treatment. Indeed, our results suggest that a large portion of COPD patients would have been reclassified upwards in terms of level of risk if either of our suggested modifications (multiplying the risk for COPD patients by 1.3 and adding COPD to the model) to the GRACE score had been used. Although we found that GRACE score predicted risk was closer to observed risk in those with COPD, the explanation for this is likely to be that for patients with the same predicted risk of death, COPD patients have always been at higher risk and observed mortality for all patients has fallen since GRACE scores were created such that they now by chance align well for those with COPD. This is consistent with our findings when we tabulated predicted and observed risk stratified by admission year. Although the GRACE score is the most accurate and widely used score for predicting risk of death after admission for ACS, others are in use. Clinicians should be aware that scores which use similar parameters are likely to underestimate risk of death for COPD patients to a similar degree.

Our findings are an important contribution to discussion around the risk-treatment paradox. The paradox is that although those who are at highest risk of death after ACS are most likely to benefit from early aggressive therapy, they are the least likely to receive it[19]. This may go some way in explaining why COPD patients receive less in-hospital treatment after MI, such as in-hospital angiography after non-STEMI. Using risk scores and recommendations based on these to guide treatment decisions is one way to resolve this paradox. However, these risk scores must be able to predict risk of death well, they must be able to do this around levels of risk important for decision making, and they must do this for those at high risk of death.

A strength of our study is that it is large and representative of the national population, including all hospital admissions for ACS in England and Wales. A well as our complete case analysis, we also explored reasons for missing data and conducted a multiple imputation analysis. This further analysis did not change our conclusions. We calculated the proportion of COPD

patients who would have changed risk category as a result of the increase in predicted risk of death. This allowed us to demonstrate that although the relative risk of death adjusting for GRACE score predicted risk of death may seem modest, at the critical region of 0-6% predicted risk of death, this could have resulted in a change in management for a substantial proportion of COPD patients. One limitation of our study was that we used the NICE amended mini-GRACE score[17] rather than the model including Killip class. We used prescription of diuretics in hospital as a surrogate for acute heart failure. However, it is highly unlikely that the differences between COPD and non-COPD patients could be explained by this. In addition, recent work[17] has shown that this GRACE score is a very good approximation to the full GRACE score, and the amended mini-GRACE score is being used in practice as it is now available on the GRACE 2.0 calculator[20].

There are several possible reasons why GRACE score predicted risk of death is not as accurate for COPD patients. Our previous work showed that the relative risk of death after MI for COPD patients is greater after non-STEMIs than STEMIs[14], and non-STEMIs will be scored lower than STEMIs, all other things being equal. In addition, the effect of COPD on risk of death after MI was greater for younger COPD patients, and younger people will be scored lower on average. In the development of the GRACE score, although several clinical characteristics, including diabetes, hypertension and hyperlipidemia were tested for inclusion as risk factors, COPD was not[21]. Although some of the increased risk of death may be due to differences in treatment, others have concluded that the GRACE score maintains its predictive ability even in groups with different treatment[22]. In addition, among a wide range of in-hospital treatments tested, none entered the GRACE score model as predictors of death[21]. Previous work has investigated the performance of the GRACE score in other high risk groups such as people with diabetes and people with chronic renal failure[23]. However, this work only assessed the C-statistic in these groups, and did not involve assessing the GRACE score in those with COPD. Our findings have important clinical implications for the care of COPD patients after admission to hospital for ACS. Multiplying the GRACE score predicted risk of

death by 1.3 for COPD patients would mean that 34% of people with COPD would move from being classified as low risk to moderate risk (<3% to 3-6%). These changes have important implications as recommendations for treatment after non-STEMI and unstable angina are based on classification as moderate or high predicted risk of death. This is particularly relevant as it is known that COPD patients are more likely to present with a non-STEMI than non-COPD patients and that the effect of COPD on risk of death after MI is highest in non-STEMIs, and after adjusting for patient characteristics, they are less likely to receive early invasive treatment after a non-STEMI compared to non-COPD patients[14, 24].

Conclusions

GRACE score predicted risk of death after ACS does not predict risk of death for people with COPD as well as they do for those who do not have COPD, and underestimates risk of death for this group. When future versions of the GRACE score model are created, those developing the scores may want to include COPD as a risk factor for death. Clinicians should multiply GRACE score predicted risk of death by 1.3 to obtain a more accurate prediction. Using this rule would mean that one third of COPD patients previously considered to be low risk, should be considered moderate risk and would be considered for more aggressive early treatment under current guidelines for non-STEMI and unstable angina.

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6.3 Summary

- The GRACE score does not perform as well in COPD patients as it does in those who do not have COPD, and underestimates risk of death at 6 months following MI for those with COPD. This may be because age is an effect modifier for the risk of death following MI for people with COPD
- Prediction of risk of death can be made more accurate for people with COPD by multiplying the predicted risk of death by 1.3, and this may result in a change in management for a significant proportion of COPD patients

Chapter 7: Validation of the recording of acute exacerbations of COPD in UK primary care electronic healthcare records (Research paper V)

7.1 Preamble

Currently, there is no validated definition of AECOPD in UK EHR. There are many ways in which a GP might code a diagnosis of AECOPD, for example, this may be done using a code for AECOPD, a code for LRTI, a code for a symptom of AECOPD (such as cough) or may simply just be recorded as a prescription for an antibiotic.

The research paper presented in this chapter aims to validate the recording for AECOPD in UK primary care EHR, and uses data from the CPRD as well as information from questionnaires which were sent to GPs. The validity of 15 pre-specified algorithms is assessed against a reference standard of respiratory physician review of questionnaire material.

In terms of this thesis, the primary motivation for validating the recording of AECOPD is to provide a definition of AECOPD to be used in the investigation of the relationship between AECOPD and MI. The previous study (Donaldson et al. 2010) of the relationship between AECOPD and MI using UK EHR data used three definitions of AECOPD: 1) prescription of oral corticosteroids, 2) prescription of antibiotics, and 3) prescription of oral corticosteroids and antibiotics on the same day. A major concern with using prescription of antibiotics as a definition of AECOPD as the exposure in the later study relating this to MI is misclassification of other infections with AECOPD. This is important as other infections, for example urinary tract infections, are known to be associated with risk of MI (Smeeth et al. 2004). These definitions, as well as others are assessed here.

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   Designed study, wrote protocol, obtained approvals, obtained data, designed questionnaire, managed data, analysed data, interpreted data, wrote 1st draft of paper, wrote final draft of paper after co-author comments.

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7.2 Research paper

Validation of the recording of acute exacerbations of COPD in UK primary care electronic healthcare records

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Abstract

Background

Acute Exacerbations of COPD (AECOPD) identified from electronic healthcare records (EHR) are important for research, public health and to inform healthcare utilisation and service provision. However, there is no standardised method of identifying AECOPD in UK EHR. We aimed to validate the recording of AECOPD in UK EHR.

Methods

We randomly selected 1385 patients with COPD from the Clinical Practice Research Datalink. We selected dates of possible AECOPD based on 15 different algorithms between January 2004 and August 2013. Questionnaires were sent to GPs asking for confirmation of their patients' AECOPD on the dates identified and for any additional relevant information. Responses were reviewed independently by two respiratory physicians. Positive predictive value (PPV) and sensitivity were calculated.

Results

The response rate was 71.3%. AECOPD diagnostic codes, lower respiratory tract infection (LRTI) codes, and prescriptions of antibiotics and oral corticosteroids (OCS) together for 5-14 days had a high PPV (>75%) for identifying AECOPD. Symptom-based algorithms and prescription of antibiotics or OCS alone had lower PPVs (60-75%). A combined strategy of antibiotic and OCS prescriptions for 5-14 days, or LRTI or AECOPD code resulted in a PPV of 85.5% (95% CI, 82.7-88.3%) and a sensitivity of 62.9% (55.4-70.4%).

Conclusion

Using a combination of diagnostic and therapy codes, the validity of AECOPD identified from EHR can be high. These strategies are useful for understanding health-care utilisation for AECOPD, informing service provision and for researchers. These results highlight the need for common coding strategies to be adopted in primary care to allow easy and accurate identification of events.

Introduction

Chronic obstructive pulmonary disease (COPD) is a common, progressive disease characterised by airflow obstruction which is not fully reversible. As the third leading cause of death worldwide[1], COPD represents a substantial public health problem. Acute exacerbations of COPD (AECOPD) are important drivers of mortality[2, 3] and reduced quality of life[4] in COPD patients and as the second most common reason for emergency hospital admission[5], they are also of great public health importance. Several studies[6-8] of AECOPD have been conducted in UK electronic healthcare records (EHR) which are becoming an increasingly important resource for evidence from real life research.

Data from primary care are used by organisations such as Public Health England (PHE) to compare data on AECOPD incidence and management across localities and by clinical commissioning groups to inform delivery of care and design of services. In addition, the recording of AECOPDs is important for clinicians as GPs need an easy and reliable way of accessing information on the timing and severity of previous AECOPD to tailor management programmes for their patients.

The investigation of AECOPD using EHR has so far been limited by the use of non-validated strategies to identify AECOPD events based on clinical experience. Previous studies used different combinations of drug therapy (for example, oral steroids and/or antibiotics)[7] and/or medical diagnosis codes. However, the validity of these approaches is not clear. Antibiotics may not be given if AECOPD are thought to be viral and, therefore, use of prescription of antibiotics alone may lead to misclassification of other diseases for AECOPD, particularly as up to 50% of AECOPD are known to be associated with a virus[9]. In addition, these prescriptions may be rescue packs intended for future use and may not represent individual acute events.

This study aimed to investigate a comprehensive set of pre-specified algorithms for the identification of AECOPD within UK primary care electronic healthcare records.

Methods

Data source

We used the Clinical Practice Research Datalink (CPRD), a large electronic database of UK general practice data that has been widely used for research. The Clinical Research Practice Datalink (CPRD)[10] is a large electronic database of primary care medical records. CPRD contains anonymised records for over 13 million patients, of which 4.4 million are currently registered with a practice that is contributing data to the CPRD, representing about 7% of the UK population. Data held include information on consultations, diagnoses, tests, referrals to secondary care and prescriptions from primary care as well as some lifestyle data. Around 60% of the patients included in the CPRD have been linked to hospital episode statistics data (HES).

Codelist and algorithm development

Codelists (Read codes and product codes) were developed prior to the beginning of the study. Read codes are a hierarchical coding system of clinical terms used in the UK general practice which are entered into the GP software system and uploaded to the CPRD. Prescriptions for drugs are recorded in the CPRD as unique product codes. The codes used to construct AECOPD algorithms are available in the supplementary appendix.

Strategies to ascertain AECOPD, translated into coding algorithms, were developed prior to the beginning of the study. These were based on both previous definitions that have been used in published papers, as well as definitions deemed to show high face validity. Face validity was determined after discussion between respiratory, primary care physicians with experience of UK primary care, and epidemiologists with experience in the design and analysis of studies using large UK primary care EHR databases. We used the August 2013 CPRD build and Read code dictionary. The fifteen algorithms are described in Table 1.

Table 1. Description of the algorithms tested

Algorithm	Notes
1. Oral corticosteroid (OCS) prescription	For 5-14 days
2. Antibiotic prescription	For 5-14 days
3. Oral corticosteroid and antibiotic prescription	For 5-14 days, both on the same day
4. Exacerbation Symptom definition	Codes suggesting increase in two or more of: breathlessness, cough, or sputum volume and/or purulence
5. Exacerbation Symptom definition and oral corticosteroid prescription	Symptom definition the same as 4. Medical codes must have been on the same day as prescription. Duration of prescription was not limited.
6. Exacerbation Symptom definition and antibiotic prescription	Symptom definition the same as 4. Medical codes must have been on the same day as prescription. Duration of prescription was not limited.
7. Exacerbation Symptom definition and oral corticosteroid & antibiotic prescription	Symptom definition the same as 4. Medical codes must have been on the same day as prescription. Duration of prescription was not limited.
8. Lower respiratory tract infection (LRTI) code	Specifically excluding codes for pneumonia
9. LRTI code and oral corticosteroid prescription	Medical codes must have been on the same day as prescription. Duration of prescription was not limited.
10. LRTI code and antibiotic prescription	Medical codes must have been on the same day as prescription. Duration of prescription was not limited.
11. LRTI code and oral corticosteroid & antibiotic prescription	Medical codes must have been on the same day as prescription. Duration of prescription was not limited.
12. AECOPD code	
13. AECOPD code and oral corticosteroid prescription	Medical codes must have been on the same day as prescription. Duration of prescription was not limited.
14. AECOPD code and antibiotic prescription	Medical codes must have been on the same day as prescription. Duration of prescription was not limited.
15. AECOPD code and oral corticosteroid & antibiotic prescription	Medical codes must have been on the same day as prescription. Duration of prescription was not limited.

As prescription of rescue packs and acute codes used at annual reviews may be identified by our algorithms, we developed further codelists to identify consultations during which rescue packs were prescribed or annual reviews occurred.

Study population

COPD patients were identified in the CPRD using a previously validated strategy[11]. For this analysis, we specifically defined COPD patients as having a record for a specific COPD Read code, history of current or past smoking, at least two prescriptions for COPD medicines (one within 4 weeks of the initial COPD Read code) and of age over 35 years at the time of the initial COPD Read code. Inclusion was further restricted to those patients whose GP practice last collection date was four months or less from the end of the study (August 2013) and were alive and registered at the GP practice at the time of the last CPRD data collection.

Patients were followed up from January 2004, date of COPD diagnosis or date of registration with an eligible practice, whichever was later and were followed up until August 2013, date of death, last collection date, or date of transfer out of an eligible GP practice, whichever was earlier. The fifteen pre-specified AECOPD algorithms were used to ascertain any potential AECOPD event which occurred during this time period.

For the validation purposes, potential AECOPD events identified via algorithms were further selected using stratified random sampling. This procedure was designed such that it would 1) select events randomly within algorithms, 2) maximise the amount of information available per questionnaire, and 3) select potential events from rarer algorithms preferentially over events from algorithms which had potential events which were more common. Briefly, 1600 patients were selected such that each algorithm was represented by potential AECOPD events in at least 100 patients. Up to 10 potential AECOPD events (up to 5 from a single algorithm) were then randomly selected from each patient's individual pool of AECOPD events. This procedure ensured that several dates could be enquired about for each patient; that none of the definitions

had no, or very few, potential AECOPD events in the final sample; and that the number of dates enquired about for each patient was not so high as to make response by the GP unlikely.

Questionnaires

We sent a short questionnaire to GPs asking them to confirm whether their patients had AECOPD on the dates identified. GPs were allowed to respond with "Yes", "No" or "Uncertain". We also asked about any dates in the last 12 months on which the patient had an AECOPD, not already listed on the dates specified. Finally, we asked GPs to send copies of any relevant material, such as extracts from patient notes or hospital discharge letters. All material was anonymised by the CPRD before being returned to investigators. We sent two reminders to GP practices who did not initially respond.

Outcome assessment

The reference standard for diagnosis of AECOPD was an independent review of all material from the GP (questionnaire and other relevant material) by two respiratory physicians. Each respiratory physician independently reviewed all available information before discussing disagreements. We calculated Cohen's Kappa to assess inter-rater agreement. Information from CPRD on dates which the GP specified that their patient had an AECOPD, but which were not listed on the questionnaire, were also reviewed by a respiratory physician. These events were included in the analysis if they were judged to be an AECOPD. For potential AECOPD events which the GP responded with "uncertain", we obtained and reviewed anonymised medical notes and information from the CPRD GP "free-text" field records corresponding to the appropriate date.

Sample size

Assuming a conservative minimum of a 50% response rate and only 100 potential events identified per algorithm (50 AECOPD events per algorithm) in the final analytical sample, we

calculated that the confidence intervals around example PPVs would be: 50% (95% CI, 35.5-64.5%); 70% (95% CI, 55.4-82.1%); 90% (95% CI, 78.2-96.7%).

Analysis

The main outcome was positive predictive value (PPV). True positives were defined as events which were identified by the algorithm, sampled from the AECOPD pool and confirmed by the reference standard. False positives were defined as events which were identified by the algorithm, sampled from the AECOPD pool and not confirmed by the reference standard. PPV was calculated as: True positives / (True Positives + False Positives).

To estimate the sensitivity, we used a combination of algorithm and GP identified dates of AECOPD events in the last 12 months. True positives were defined as events (1) which were identified by the algorithm, sampled from the AECOPD pool and confirmed by the reference standard or (2) which were listed as additional events by the GP, which were also identified by algorithm but had not been sampled. False negatives were defined as events which were (1) listed by the GP as additional dates, but which were not identified by the algorithm or (2) as event dates which were identified and confirmed by the reference standard for other algorithm(s) only (i.e. confirmed events which were not in the AECOPD pool for that algorithm, whether sampled or not). For the analysis of sensitivity, events which occurred within two weeks of another event were considered part of the same episode. Sensitivity was calculated as: True Positives / (True Positives + False Negatives).

We used bootstrapping to obtain cluster-robust confidence intervals for PPV and sensitivity. We excluded events which were still "uncertain" after respiratory physician review. Events which occurred on the same day as annual reviews or rescue pack prescriptions were not included in the main analysis.

We repeated the analysis of PPV and sensitivity restricted to those patients for whom GPs sent additional information (patient notes and discharge summaries). In this group of patients, respiratory physicians who were assessing questionnaires would have been able to see information from several sources in order to reach a decision on whether they thought the patient had an AECOPD on the dates in question. We also repeated the analysis of PPV stratified by characteristics identified from the CPRD: age group, sex, smoking status, GOLD 2006 grade of airflow limitation[12], Medical Research Council (MRC) dyspnoea score[13], socioeconomic status[14], WHO Body Mass Index (BMI) category, previous record of asthma diagnosis, previous records of gastro-oesophageal reflux disease (GORD) diagnosis, and previous record of diagnosis for cardiovascular disease (either of myocardial infarction, angina or heart failure).

Finally, we assessed the PPV and sensitivity for several combinations of algorithms to identify AECOPD. Our strategy was to achieve an adequate sensitivity while maintaining a high PPV. Initially we combined algorithms which had the highest PPV (those with PPV>80%). We then added algorithms which had PPV>75% in order to improve sensitivity. We also calculated PPV and sensitivity using all of the algorithms.

Ethics

Ethical approval was obtained from the London School of Hygiene and Tropical Medicine (LSHTM) Observational Research Ethics Committee (approval number 6481) and the Clinical Practice Research Datalink (CPRD) Independent Scientific Advisory Committee (ISAC) (approval number 13_116). Patient records and questionnaires were de-identified and anonymised by CPRD staff before being sent to the investigators.

Results

Patient characteristics

We selected 1600 patients for the study, of whom 215 had GP practices which had left the CPRD and were therefore excluded from the sampling frame (Figure 1). Our final study consisted of questionnaires related to the remaining 1385 patients. Of these 988 (71%) were returned by their GPs, representing 8258 potential AECOPD events. Characteristics of patients included in the study are detailed in table 2. Mean age in our final sample of COPD patients was 62.4 years (SD, 10.6), 49% were male, 38% had severe or very severe airflow limitation (GOLD 2006 grades 3 or 4), 53% reported moderate/severe dyspnoea (MRC score of 3 or more), and 55% were current smokers. Restricting the sample to those dates which did not occur on annual review dates or dates of rescue pack prescriptions reduced the sample to 7136 events in 955 patients. Characteristics of patients whose GPs responded to the questionnaire were similar to those who did not, with the exception of socioeconomic status (supplementary table 1). Patients whose GPs did not respond were on average more deprived than those whose GP responded. Details of the event flow through the study stratified by algorithm are presented in table 3.

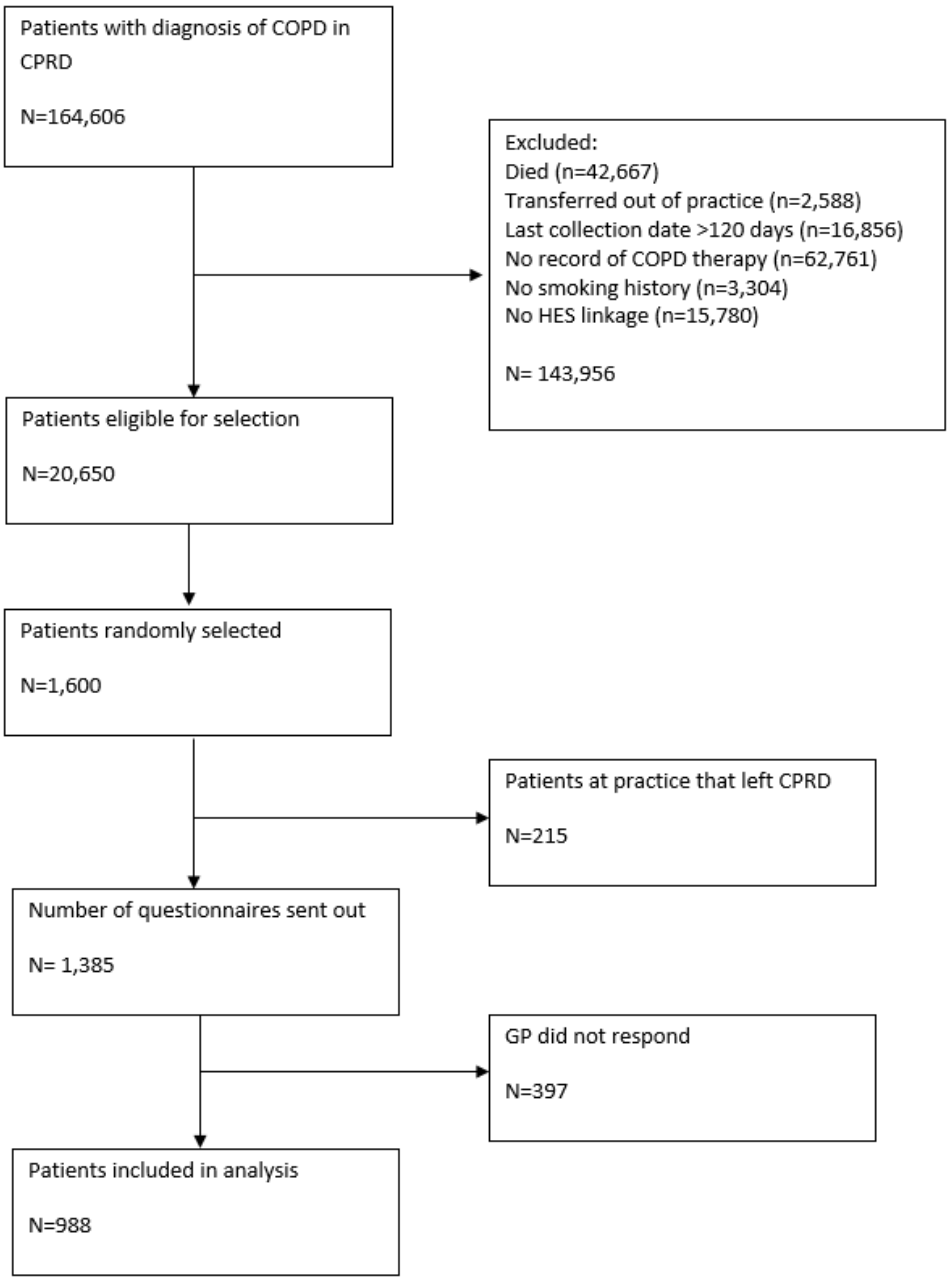

Figure 1 – Patient flow through the study

Table 2 Characteristics of the 988 patients included in the analysis

Characteristic	n	% (N=988)
Age group		
≤55	212	21.5
55 to 64	359	36.3
65 to 74	301	30.5
≥ 75	116	11.7
Sex		
Male	481	48.7
Female	507	51.3
MRC breathlessness scale (N=950)		
≥3	449	47.3
< 3	501	52.7
BMI		
< 19	39	4.0
19 – 25	353	35.7
≥25	596	60.3
Record of cardiovascular disease		
No	731	74.0
Yes	257	26.0
Record of asthma		
No	482	48.8
Yes	506	51.2
Record of GORD		
No	729	73.8
Yes	259	26.2
GOLD 2006 grade (N=592)		
1	76	12.8
2	285	48.1
3	185	31.3
4	46	7.8
Smoking status		
Ex-smoker	447	45.2
Current smoker	541	54.8
Index of multiple deprivation quintile (N=985)		
1 (least deprived)	152	15.4
2	213	21.6
3	188	19.1
4	216	21.9
5 (most deprived)	216	21.9

Table 3. Flow of events through the study

Algorithm	N events identified in the CPRD	N events sampled	N events from returned questionnaires	N events adjudicated for uncertain response	N events uncertain after respiratory physician review (% of those returned questionnaires)
All	261981	11697	8253	914	227 (2.8)
1.OCS prescription for 5-14 days	33898	1956	1285	120	32 (2.5)
2.Antibiotic prescription for 5-14 days	225761	9622	6283	809	208 (3.3)
3.OCS and antibiotic prescription for 5-14 days	22990	1374	919	72	22 (2.4)
4. Symptom definition	1745	462	341	11	2 (0.6)
5. Symptom definition and OCS prescription	553	232	156	6	1 (0.6)
6. Symptom definition and antibiotic prescription	165	132	108	5	0 (0)
7. Symptom definition and OCS & antibiotic prescription	142	112	90	3	0 (0)
8. LRTI code	60099	2753	1809	214	36 (2.0)
9. LRTI code and OCS prescription	53460	2488	1617	200	34 (2.1)
10. LRTI code and antibiotic prescription	9354	600	411	25	2 (0.5)
11. LRTI code and OCS & antibiotic prescription	8770	569	388	25	2 (0.5)
12. AECOPD code	20905	1371	966	21	0 (0)
13. AECOPD code and OCS prescription	15020	992	698	14	0 (0)

14. AECOPD code and antibiotic prescription	8571	674	466	11	0 (0)
15. AECOPD code and OCS & antibiotic prescription	7440	601	418	10	0 (0)

PPV and sensitivity

Inter-rater agreement in outcome assessment was high. The respiratory physicians reviewing the questionnaires agreed for 92.5% of the potential AECOPD dates before discussion, and this resulted in a Cohen's Kappa of 0.844. All disagreements were resolved by discussion between the two respiratory physicians and none were referred to a third physician. The PPVs and sensitivity of each algorithm are presented in table 4. The algorithms with the higher PPVs (>80%) were those that used (1) an LRTI code along with either prescription of an antibiotic or a steroid or antibiotic and a steroid, and (2) AECOPD code either with or without prescription of antibiotics; and (3) the symptom definition with either prescription of OCS or antibiotics. The LRTI code alone (79.6%, 76.9-82.3%) and prescription of both antibiotics and OCS for 5-14 days (79.3%, 75.8-82.9%) had slightly lower PPVs. The symptom definition alone, prescription for 5-14 days of antibiotics and prescription of 5-14 days of OCS had poorer PPVs (60-73%).

Table 4. PPV and sensitivity for the algorithms

Algorithm	N events identified in the CPRD	N events confirmed by reference standard	PPV (95% CI)	N events identified in the CPRD in last year	N extra events identified by other algorithms or GPs in last year	Sensitivity (95% CI)
1.OCS prescription	1152	841	73.0 (69.5 - 76.5)	164	379	30.2 (25.8 - 34.6)
2.Antibiotic prescription	5840	3559	60.9 (59.0 - 62.9)	386	157	71.1 (66.8 - 75.4)
3.OCS and antibiotic prescription	823	653	79.3 (75.8 - 82.9)	133	410	24.5 (20.4 - 28.6)
4. Symptom definition	142	92	64.8 (56.2 - 73.3)	14	529	2.6 (1.1 - 4.0)
5. Symptom definition and OCS prescription	88	79	89.8 (82.9 - 96.7)	12	531	2.2 (0.9 - 3.6)
6. Symptom definition and antibiotic prescription	57	53	93.0 (85.6 - 100.0)	10	533	1.8 (0.6 - 3.1)
7. Symptom definition and OCS & antibiotic prescription	48	47	97.9 (94.5 – 100.0)	9	534	1.7 (0.5 - 2.9)
8. LRTI code	1745	1389	79.6 (76.9 - 82.3)	125	418	23.0 (19.2 - 26.8)
9. LRTI code and OCS prescription	1558	1268	81.4 (78.7 - 84.1)	108	435	19.9 (16.3 - 23.5)

10. LRTI code and antibiotic prescription	393	347	88.3 (84.4 - 92.2)	65	478	12.0 (9.3 - 14.7)
11. LRTI code and OCS & antibiotic prescription	371	327	88.1 (84.1 - 92.1)	62	481	11.4 (8.8 - 14.0)
12. AECOPD code	885	850	96.0 (94.5 - 97.6)	136	407	25.1 (20.9 - 29.2)
13. AECOPD code and OCS prescription	638	618	96.9 (95.4 - 98.3)	99	444	18.2 (14.6 - 21.8)
14. AECOPD code and antibiotic prescription	423	408	96.5 (94.5 - 98.4)	95	448	17.5 (13.8 - 21.2)
15. AECOPD code and OCS & antibiotic prescription	377	365	96.8 (95.0 - 98.6)	87	456	16.0 (12.6 - 19.5)

Antibiotics = selected antibiotics with clinical application in management of AECOPD

OCS = oral corticosteroids specific to AECOPD management

Sensitivity was low (<30%) for all algorithms except for prescription of an antibiotics course for 5-14 days (71.1%, 66.8-75.4%). More restrictive definitions had poorer sensitivity than those without any restriction. Sensitivity was particularly low for all of the algorithms which used respiratory symptoms.

Restricting the analysis to those patients for whom GPs sent supporting information resulted in slight increases in PPV for some algorithms (Table 5). This restriction also reduced the sensitivity for the use of OCS for 5-14 days to 22.7% (95% CI, 16.1-29.2%) from 30.2% (95% CI, 25.8-34.6%); the use of antibiotics for 5-14 days to 63.4% (95% CI, 55.4-71.4%) from 71.1% (95% CI, 66.8-75.4%); and the use of both antibiotics and OCS for 5-14 days to 18.6% (95% CI, 12.4-24.7%) from 24.5% (95% CI, 20.4-28.6%).

Table 5. PPV and sensitivity of the algorithms to identify AECOPD including only patients for whom additional information was available from their GP questionnaire

Algorithm (inclusive definitions)	N events identified in the CPRD	N events confirmed by reference standard	PPV (95% CI)	N events identified in the CPRD in last year	N extra events identified by GPs in last year	Sensitivity (95% CI)
1.OCS prescription	367	265	72.2 (66.5 - 77.9)	44	150	22.7 (16.1 - 29.2)
2.Antibiotic prescription	2245	1376	61.3 (58.3 - 64.3)	123	71	63.4 (55.4 - 71.4)
3.OCS and antibiotic prescription	251	200	79.7 (73.5 - 85.8)	36	158	18.6 (12.4 - 24.7)
4. Symptoms definition	83	53	63.9 (52.7 - 75.0)	4	190	2.1 (0.1 - 4.0)
5. Symptoms definition and OCS Prescription	50	47	94.0 (88.0 - 100.0)	4	190	2.1 (0.1 - 4.0)
6. Symptoms definition and antibiotic prescription	36	34	94.4 (86.8 – 100.0)	3	191	1.6 (0.1 - 3.2)
7. Symptoms definition and OCS & antibiotic prescription	31	31	100.0 (88.8 - 100.0)	3	191	1.6 (0.1 - 3.2)
8. LRTI code	693	574	82.8 (78.8 - 86.9)	48	146	24.7 (18.8 - 30.7)
9. LRTI code and OCS prescription	621	525	84.5 (80.6 - 88.5)	40	154	20.6 (15.2 - 26.0)
10. LRTI code and antibiotic prescription	142	132	93.0 (88.3 - 97.6)	24	170	12.4 (7.8 - 16.9)

11. LRTI code and OCS & antibiotic prescription	129	119	92.2 (87.1 - 97.4)	21	173	10.8 (6.7 - 15.0)
12. AECOPD code	350	344	98.3 (96.9 - 99.6)	52	142	26.8 (19.7 - 33.9)
13. AECOPD code and OCS prescription	236	234	99.2 (98.1 - 100.0)	36	158	18.6 (12.4 - 24.7)
14. AECOPD code and antibiotic prescription	155	152	98.1 (96.0 - 100.0)	33	161	17.0 (10.8 - 23.2)
15. AECOPD code and OCS & antibiotic prescription	140	138	98.6 (96.8 - 100.0)	30	164	15.5 (9.7 - 21.2)

Antibiotics = selected antibiotics with clinical application in management of AECOPD

OCS = oral corticosteroids specific to AECOPD management

The analysis of PPV and sensitivity analyses were repeated for all event date including these dates occurring on annual COPD review and those with prescription for suspected rescue packs of OCS (supplementary material, Table S2). The PPVs stratified by patient demographic and disease severity characteristics are presented in the supplementary material (Supplementary Table S3). Briefly, PPVs for the OCS course for 5-14 days appeared to differ by some of the characteristics. PPV for the OCS course for 5-14 days was higher for patients with no or mild dyspnoea, without CVD co-morbidity, and for women.

The PPV and sensitivity for the composite strategies are presented in Table 6. Combining algorithms with PPV > 80% (5, 6, 8 or 12) resulted in a PPV of 88.1% (95% CI, 85.3-90.8) and a sensitivity of 51.6 (95% CI, 44.1-59.0). Using algorithms with a PPV >75% (3, 5, 6, 8 or 12) resulted a in very high PPV of 85.5% (95%CI, 82.7-88.3%) with a sensitivity of 62.9% (95%CI, 55.4-70.4%). Use of all pre-defined algorithms to identify AECOPD reduced the PPV to 63.8% (95%CI, 61.0-66.6%), but achieved a sensitivity of 88.1% (95%CI, 82.9-93.4%).

Table 6. PPV and sensitivity of composite strategies to identify AECOPD including only patients for whom additional information was available from their GP questionnaire

Strategy	PPV (95% CI)	Sensitivity (95% CI)
Algorithms with PPV > 80% **Algorithms 5, 6, 8 or 12** **Symptom definition with prescription of antibiotic or OCS; or LRTI; or AECOPD code**	88.1 (85.3-90.8)	51.6 (44.1-59.0)
Algorithms with PPV > 75% **Algorithms 3, 5, 6, 8 or 12** **Prescription of antibiotics and OCS for 5-14 days; or Symptom definition with prescription of antibiotic or OCS; or LRTI code; or AECOPD code**	85.5 (82.7-88.3)	62.9 (55.4-70.4)
All algorithms	63.8 (61.0-66.6)	88.1 (82.9-93.4)

Discussion

This is the first study to describe the recording of AECOPD by general practitioners in UK EHRs. Although the definitions used in future studies may depend on the individual needs and potential objectives, particularly with respect to the need for maximising either PPV or sensitivity, our recommendation for identifying AECOPD events in EHR is to use a composite of several of the definitions with higher PPV. To maximise sensitivity over PPV for identifying AECOPD in UK EHR, investigators would need to use prescription of antibiotics, as the PPV was low for this algorithm, this strategy is likely to misclassify many other infections as AECOPD. One recommended approach would be to use the following strategy that resulted in PPV of 86% and sensitivity of 63%: a combination of: (1) a medical diagnosis of LRTI or AECOPD, or (2) a prescription of COPD-specific antibiotic combined with OCS for 5-14 days, or (3) a record of two or more respiratory symptoms of AECOPD along with a prescription of COPD-specific antibiotics and/or OCS on the same day. These combined strategies should be used only after removing any AECOPD events occurring on the same date as codes suggestive of a visit for annual COPD review or provision of rescue packs for COPD-specific antibiotics or OCS. We do not recommend using definitions based on respiratory symptoms without COPD-specific antibiotics or OCS, or COPD-specific antibiotics or OCS without medical diagnosis of LRTI, AECOPD or respiratory symptoms due to mediocre PPVs. This has important implications as previous studies of AECOPD outcomes have used prescription of either antibiotics and or oral steroids to define AECOPD, and our findings suggest that this strategy may lead to a high level of misclassification of AECOPD events. Compared to previous studies, which have attempted to identify AECOPD in EHRs, we used a very specific list of antibiotics and OCS pertaining to management of AECOPD.

Having a validated definition of a COPD outcome, representing a substantial source of burden to patients and health-care providers, such as AECOPD is important. It provides a robust method for deriving statistics on AECOPD which can inform health-care service planning and evaluation of programs over time. In addition, as well as being a resource for "real life"

observational studies, electronic healthcare records have the potential to be used in pragmatic clinical trials. This requires standardised and accurate definitions of exacerbations, and our research provides that.

Our findings illustrate that there are multiple strategies adopted by health care workers when recording AECOPD events in the UK EHR. Only about one half of the AECOPD events were recorded using a medical diagnosis code either for LRTI , AECOPD or respiratory symptoms, whilst the remaining events were recorded only as prescriptions of COPD-specific antibiotics and/or OCS. Even using all pre-defined algorithms, about 12% of AECOPD events failed to be captured (false negatives). We explored medical codes at these dates and did not find any leads allowing derivation of further algorithms. The most frequent events recorded on the AECOPD dates not captured by any algorithm included: "reviewed patient", "home visit" or single symptoms. This heterogeneity makes ascertainment of AECOPD events challenging. We recommend that AECOPD events are recorded consistently by care providers, preferably using medical diagnosis codes stating AECOPD, and that these codes are recorded only at the time of acute events and not to record a historical number of prior episodes. This should be achieved through better education of prescribers, but also by improving health-care information systems to enable health care workers an easy and consistent way to record severity of AECOPD into EHRs, including patient reported AECOPD as milder events and retrieving hospital discharges for AECOPD. Moreover, AECOPD events which are treated by community COPD teams should be reported to GPs via linked health-care information systems to provide an integrated record of critical events. Ideally, GPs should be able to access AECOPD history of their patients with a "one-click" menu given its prognostic value, allowing for individually targeted treatment strategies for COPD patients at high risk of future events. One of the strengths of this study is the robust reference standard used to identify episodes of AECOPD though respiratory physicians independent adjudication of supplementary information from GPs as well as the anonymized "free-text" notes section from the CPRD.

Although we obtained information on AECOPD from GPs, there were still limitations to the available data. To maximize the rigor of the study, we used respiratory physician review of all available information as the reference standard, and we have presented a sensitivity analysis of only those events for which additional information was available. Although we had a reasonable response rate, GPs whose patients were more deprived were less likely to respond to our questionnaire and the extent to which the coding practices differ in association with patient deprivation level could not be determined. In addition, because we needed patients to be alive at the time of the study, our results may not be generalisable to those with the most severe COPD. Another limitation is that by using EHR to identify AECOPD, we will miss events which are self-managed by COPD patients, and therefore this study does not capture the full range of severity. Our results should therefore be interpreted as the accuracy of AECOPD events recorded by primary care clinicians. Our stratified analysis of PPV presented in the supplementary material showed that the algorithms based on symptom definitions and prescription of OCS alone for 5-14 days had different PPV depending on patient characteristics. These differences could potentially cause bias, however we do not recommend that prescription of OCS for 5-14 days alone is used to identify AECOPD, and the symptom-based definitions only contribute to a small number of the AECOPD events. In addition, the PPVs for definitions included in our recommended strategy (based on LRTI codes, AECOPD codes and prescription of both antibiotics and OCS) did not vary significantly depending on patient characteristics. Our recommended strategy for identifying AECOPD achieved a high PPV, however the sensitivity was lower, suggesting that although this strategy is valid it will tend to underestimate the number of events. One option for investigators wishing to assess the burden of AECOPD is to conduct an analysis using both a strategy with high PPV and one with high sensitivity in order to estimate a minimum and maximum number of events per patient. Our study was conducted in the UK, and this may limit generalisability of the results to EHR databases which collect data from other countries. Although we used definitions of AECOPD used in previous studies to develop our algorithms, it may be difficult to relate our findings to the validity of some previously used definitions. This is for two reasons, firstly, in order to

achieve high validity, we used a narrow list of antibiotics in our algorithms. This is likely to have increased the PPV of our algorithms, and studies which used a broader list of antibiotics may have lower PPV for AECOPD identification. Secondly, poor reporting of previously used definitions of AECOPD mean that it is difficult to relate these to our current findings. One further limitation of the analysis presented here is that these results do not include hospital events, however this is the focus of a current study. This limitation should not affect the PPV, however this does mean that our estimates of sensitivity relate to events which are treated/recorded in primary care only and not the total number of AECOPD events.

We have validated strategies to identify AECOPD within electronic healthcare records, however our strategies may underestimate the total number of true AECOPD events. Our results should be used for future research studies and by public health bodies when identifying AECOPD in the UK. We found that some previously used definitions have low PPV. Our results also highlight the lack of standardisation of the recording of AECOPD in EHRs, and efforts should be made to standardise the recording of AECOPD within EHRs.

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7.3 Summary

- AECOPD can be identified in UK primary care EHR with high validity
- The PPV for an algorithm which combines codes for LRTI, AECOPD, antibiotics and oral corticosteroids prescribed on the same day, and symptoms of AECOPD along with either prescription of antibiotics or steroids results in a PPV of over 85% and a sensitivity of almost 63%
- Studies which use prescription of antibiotics or steroids alone are not likely to identify AECOPD with high validity

Chapter 8: Recording of hospitalisations for acute exacerbations of COPD in UK primary and secondary care electronic healthcare records (Research paper VI)

8.1 Preamble

The research paper presented in the previous chapter concluded with recommendations on how AECOPD might be identified in EHR in a valid way. Later in this thesis, in the study investigating the association between AECOPD and risk of MI, it will be necessary to differentiate between moderate AECOPD (GP treated) and severe AECOPD (those resulting in hospitalisation). As hospitalisation for AECOPD is also an important outcome in COPD studies, other researchers would benefit from recommendations on how hospitalisation for AECOPD might be identified in EHR.

The study presented here, therefore, aims to investigate the recording of hospitalisation of AECOPD in UK primary and secondary care EHR, and uses linked data from CPRD and HES. First, a definition of hospitalisation for AECOPD in HES is validated, and then this definition is used as a reference standard to assess the validity of primary care data only definitions of hospitalisation for AECOPD.

As information about hospitalisations should be entered into the primary care EHR by GPs, theoretically, the primary care EHR used on its own, could be a complete source of information for both GP treated and hospitalised AECOPD. This would be advantageous for two reasons. Firstly, as not all of the primary care records are linked to secondary care records, using primary care EHR alone would mean that studies have higher power. Secondly, although monthly CPRD datasets are released, linked HES data is only available in less frequently released builds. As well as a further reduction in power for studies, this is also problematic for studies which require near real time reporting, such as RCTs run within EHR.

However, there are numerous ways in which GPs might enter information on a hospitalisation for AECOPD. Recent studies have suggested that although information on hospitalisations for specific reasons are recorded in primary care EHR, they are not recorded in such a way as to be identifiable by researchers (Crooks et al. 2012, Baker et al. 2015, Millett et al. 2016). Additionally, as there may be a lag in the recording of hospitalisations by GPs (due to the time it takes for discharge letters to reach GPs), information on specific timing of hospitalisation may not be accurate. Accuracy of timing of the event will be of great importance to the study

presented in this thesis which investigates the relationship between AECOPD and risk of MI (Chapter 9).

The research paper presented here has been prepared for publication and is currently under peer-review. The title and current authorship are presented at the beginning of the paper.

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8.2 Research paper

Recording of hospitalisations for acute exacerbations of COPD in UK electronic healthcare records

Authors: Kieran J Rothnie, Hana Müllerová, Sara L Thomas, Joht Chandan, Liam Smeeth, John R Hurst, Kourtney Davis , Jennifer K Quint

Abstract

Background

Accurate identification of hospitalisations for acute exacerbations of COPD (AECOPD) within electronic healthcare records (EHR) is important for research, public health and to inform healthcare utilisation and service provision. We therefore aimed to develop a strategy to identify hospitalisations for AECOPD in secondary care data, and to investigate the validity of strategies to identify hospitalisations for AECOPD in primary care data.

Methods

We identified patients with COPD in the Clinical Practice Research Datalink (CPRD) with linked Hospital Episodes Statistics (HES) data. We used discharge summaries for recent hospitalisations for AECOPD in a sub-sample of these patients to develop a strategy to identify the recording of hospitalisations for AECOPD in HES. We then used the HES strategy as a reference standard to investigate the PPV and sensitivity of strategies for identifying AECOPD using general practice CPRD data. We tested two strategies: 1) codes for hospitalisation for AECOPD; and 2) a code for AECOPD other than hospitalisation on the same day as a code for hospitalisation due to un-specified reason. We also investigated how many hospitalisations for AECOPD were recorded with either an AECOPD code or a hospitalisation code.

Results

In total 27,182 patients with COPD were included in the study. Our strategy to identify hospitalisations for AECOPD in HES had a sensitivity of 87.5%.When compared with HES, using a code suggesting hospitalisation for AECOPD in CPRD resulted in a PPV of 50.2% (95% CI, 48.5-51.8%) and a sensitivity of 4.1% (95% CI, 3.9-4.3%). Using a code for AECOPD on the same day as a code for hospitalisation due to un-specified reason resulted in a PPV of 43.3% (95% CI, 42.3-44.2%) and a sensitivity of 5.4% (95% CI, 5.1-5.7%). Many hospitalisations were recorded with an AECOPD code or a hospitalisation for un-specified reason code only, however using this strategy to identify hospitalisations for AECOPD in CPRD resulted in a very low PPV.

Conclusions

Hospital admission for COPD can be identified with high sensitivity in the HES database. The PPV and sensitivity of strategies to identify hospitalisations for AECOPD in primary care data alone are very poor. Primary care data alone should not be used to identify hospitalisations for AECOPD. Instead, researchers should use data which are linked to data from secondary care.

Introduction

Chronic obstructive pulmonary disease (COPD) is a common, progressive lung disease characterised by airflow obstruction which is not fully reversible. In the UK over 1 million people have been diagnosed with COPD, with an estimated further 2 million undiagnosed[1, 2]. People with COPD often have periods of acute worsening of symptoms beyond normal day to day variation which may require a change in the patient's treatment; these episodes are known as acute exacerbations (AECOPD). On average, people with COPD experience around two AECOPD every year[3] (including mild events) and AECOPD are important drivers of morbidity and mortality[4-6]. Most episodes of AECOPD are managed in primary care or by the patient, however more severe events and or events in patients with more severe disease or significant comorbidities may require admission to hospital. Hospitalisations for AECOPD are serious events with around 8%[7] of those admitted dying in hospital and 23% dying within one year. As well as being important for individuals, as the second most common reason for emergency admission to hospital in the UK[8], they are also of great public health importance. Consequently, hospitalisations for AECOPD are a key outcome in clinical trials and observational studies in people with COPD.

Healthcare in the UK is mainly provided by the NHS, a public healthcare system. Primary healthcare in the NHS is provided by general practitioners (GPs) and over 98% of the UK population are registered with an NHS GP. In the UK, both data from primary care and data related to admissions to hospitals are readily available and are routinely used for research and for health service planning. With potentially very large sample sizes and representative and detailed real life data, electronic healthcare records provide an excellent resource in which to conduct epidemiological studies, including disease epidemiology and comparative safety and effectiveness assessments of interventions. As well as observational studies, an exciting new area in electronic healthcare records research is their use for recruitment and follow up of patients in pragmatic clinical trials[9], and these will require valid definitions of important outcomes. In addition to research, electronic healthcare records can also be used in areas such as national audits of care and by commissioning groups to plan local services.

However, as routine electronic medical or health-care records data are not collected for the purpose of research or audit, one potential limitation of these data is the accuracy and completeness of coded diagnoses. The Clinical Practice Research Datalink (CPRD) is a large database of data from UK primary care. It has been used extensively for research. Many studies have investigated the validity of CPRD diagnoses for use in research, and in general, these have been found to be high[10]. For specific conditions, the validity of research using CPRD data

will depend on both the validity of the algorithm that researchers use to identify the condition and the propensity for the condition to be missed, mis-recorded, or misdiagnosed by GPs.

Our study had two aims: 1) to investigate sensitivity of recording of hospital admissions for AECOPD in UK secondary care electronic health records (HES); and 2) to use linked primary and secondary care data (CPRD-HES) to assess the positive predictive value and sensitivity of strategies to identify hospitalisations for AECOPD using primary care data.

Methods

Data sources

The Clinical Practice Research Datalink (CPRD) is a very large clinical electronic healthcare record database of primary healthcare records in the UK. It contains information on areas such as diagnoses, prescriptions and test results, and some lifestyle data such as smoking status and BMI. Currently, there are data for over 11 million patients in CPRD, with 4.4 million of these active patients (representing around 6.9% of the UK population)[11]. Much of the clinical data recorded in CPRD is in the form of Read codes. Read codes are a clinical classification system used to record diagnoses, symptoms, test results, lifestyle factors such as smoking, and other details of consultations. Some information about patient contacts with secondary care, such as referrals, emergency room visits and hospital admissions may be also captured in CPRD. However as this requires someone in the GP practice to manually enter such encounters, their recording may be incomplete.

Hospital Episodes Statistics (HES) is an administrative database containing information on all episodes of admitted patient care in England requiring overnight stay in hospital these inpatient data used for this study specifically exclude those only seen in A&E. Records for admission to hospital in HES are split up into "finished consultant episodes", these each represent an episode of care under a single consultant. Each admission to hospital may be made up of several finished consultant episodes. Finished consultant episode records contain information on up to 20 diagnoses recorded during that episode and are recorded using ICD-10 codes. As well as recording the reason for hospitalisation, diagnoses recorded in HES may relate to coexistent comorbidities. In addition, there is a financial incentive for hospitals to accurately record comorbidities during each hospitalisation. The diagnostic code in the first position in the first finished consultant episode is commonly taken to be the reason for hospitalisation. Around 60% of the CPRD population are linked to HES [11].

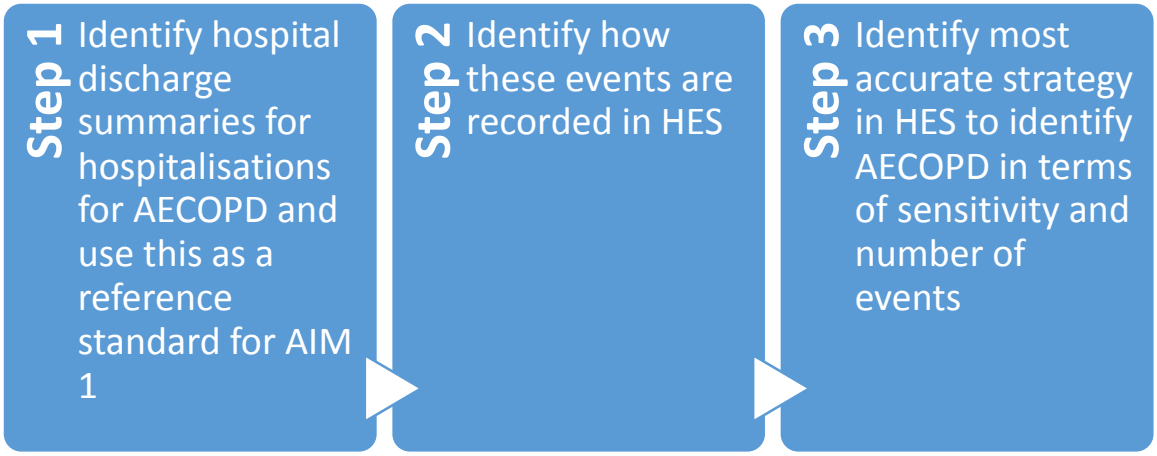
Study population

The total study population consisted of patients in CPRD who had a validated diagnosis of COPD and who were eligible for linkage to HES. Briefly, COPD patients were aged 35 years or older, current or ex-smokers, had a validated diagnostic code suggesting COPD and at least two prescriptions for a COPD medicine, one within four weeks of COPD diagnosis[12]. Patients were followed up from 1 January 2004, their date of COPD diagnosis, 35th birthday, or CPRD practice "up to standard" date whichever was latest; to 31 March 2014, date of death, transfer out of practice or practice last collection date, whichever was earliest.

Recording of hospitalisations for AECOPD in HES

A summary of the analytical approaches for each of the aims is presented in Figure 1. For the first aim, we used hospital discharge summaries to identify how hospitalisations for AECOPD are recorded in HES. Hospital discharge summaries were available for a sub-set of patients (n=40) who were also included in two previous validation studies (one validating the recording of COPD and one validating the recording of AECOPD in CPRD[12, 13]. As part of these studies, GPs were contacted and asked to send material related to their patient's COPD, including hospital discharge - summaries, to investigators. We used these summaries as a reference standard to estimate the sensitivity of the possible HES strategies to identify hospitalisations for AECOPD. Firstly, ICD codes which could be used to record hospitalisations for AECOPD in HES were pre-specified: "J44.0" and "J44.1"as specific AECOPD codes, the code for lower respiratory tract infection "J22" and the code for COPD "J44.9". Next, we visualised the diagnostic position of each of the ICD codes used which might potentially be used to record hospitalisations for AECOPD. Then, we used these codes to create strategies which might relate to hospitalisations for AECOPD based on combinations of these codes being in the first position or any position in of finished consultant episodes (Table 1). We then estimated the sensitivity of each of these strategies in identifying hospitalisations for AECOPD using hospital discharge summaries as the reference standard. Finally, we then calculated the total number of events each of these strategies would identify if they were used in the sample.

AIM 1 – How are hospitalisations for AECOPD recorded in secondary care (HES)?



AIM 2 – How are hospitalisations for AECOPD recorded in primary care (CPRD)?

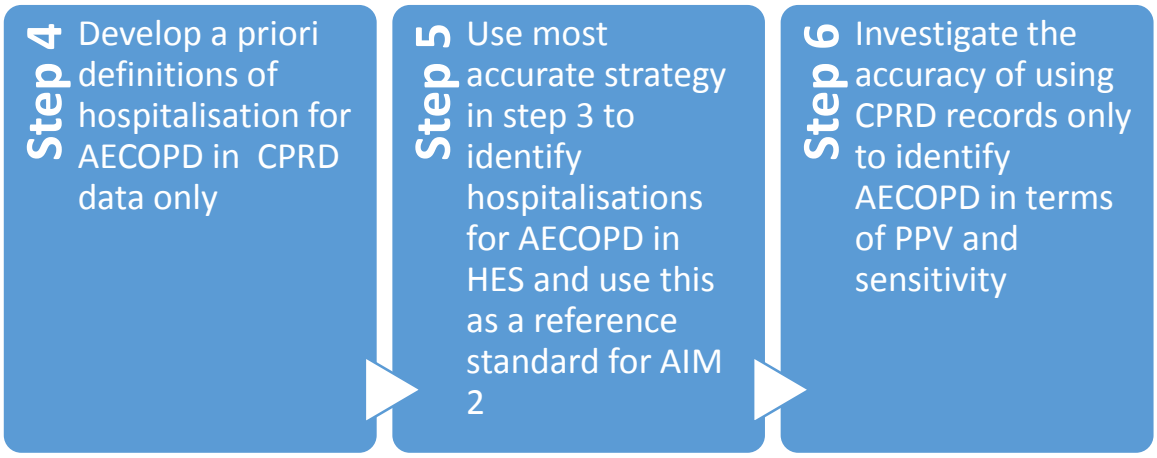


Figure 1. Summary of the methods for each of the aims of the study

Table 1. Possible strategies for identifying hospitalisations for AECOPD using primary care data alone

Definition	**Example**
Diagnostic code or codes suggesting hospitalisation for AECOPD	"Admit COPD emergency"
Diagnostic code(s) suggesting AECOPD (using our previously validated algorithm) and non-specific code(s) suggesting admission to hospital on the same day	"Acute lower respiratory tract infection" and "Admission to hospital" on the same day

Recording of hospitalisations for AECOPD in CPRD

For the second aim, we identified strategies which might be used to identify hospitalisations for AECOPD in stand-alone primary care records. Broadly there were two strategies: 1) Presence of a code which suggested hospitalisation for AECOPD; and 2) presence of a code or codes on the same day which suggested that the patient both had an AECOPD and had been admitted to hospital. In order to identify records for AECOPD in CPRD we used our previously validated algorithm[13]. We did not include codes suggesting pneumonia in either of these strategies, as although AECOPD may be (incorrectly) coded using these codes, they are unlikely to be used in a strategy to identify hospitalisations for AECOPD for research purposes. Further, we searched the Read code dictionary for codes which suggested hospitalisation for AECOPD or for hospitalisation without a specified reason. These strategies are summarised in Table 2. We also removed dates which were coded as COPD "annual review" dates as we have previously demonstrated that AECOPD codes are used at these times despite these not being acute episodes of AECOPD[13]. Details of the Read codes used are available in the supplementary material.

Table 2. Strategies for identifying admissions to hospital for AECOPD in HES – not sure if need this one

HES definition of AECOPD hospitalisation
1. Specific AECOPD code or COPD code in any position in any FCE during spell
2. Specific AECOPD code in any position or COPD code in first position in any FCE during spell
3. Specific AECOPD code in any position in any FCE during spell
4. Specific AECOPD code in any position in or LRTI code or COPD code in first position in any FCE during spell
5. Specific AECOPD code or LRTI code in any position or COPD code in first position in any FCE during spell
6. Specific AECOPD code in first position in first FCE during spell

In order to test the validity of different strategies to identify hospitalisations for AECOPD in primary care data, we calculated the positive predictive value (PPV) and sensitivity of the strategies listed in Table 2 using HES recorded hospitalisation for AECOPD as the reference standard. For the estimation of PPV, we looked backwards in the HES record for 30 days following a potential AECOPD hospitalisation in CPRD; and for sensitivity, we looked forward in the CPRD patient record 30 days after the HES recorded admission to hospital to allow for any delays in recording in the GP surgery. As an additional analysis, we increased this window to 60 days. We repeated these analyses stratified by different pre-defined definitions of HES recorded hospitalisation for AECOPD (definitions 1, 3, and 5 in Table 2).

We conducted an additional analysis to investigate other ways in which hospitalisations for AECOPD may be coded which would not have been picked up by either of the strategies that we developed. To accomplish this goal, we investigated the PPV and sensitivity of just using either a code or codes which suggested the patient had an AECOPD or had been to hospital in identifying hospitalisations for AECOPD (for example "admission to hospital" alone; or "lower respiratory tract infection" alone); i.e. when there was information that the COPD patient had either a) been to hospital for an unspecified reason; or b) had an AECOPD but no code to suggest that the patient had been to hospital. As admission to hospital may also be recorded by GPs using "consultation types" and "referral" types rather than separate Read codes, we also extended the CPRD definition of a AECOPD code on the same day as a hospitalisation code to include these consultation types and referral types, and then assessed this extended definition against our main HES definition of hospitalisation for AECOPD. In addition, we also explored a random sample of 100 Read codes present on days in which there was a record for a hospitalisation for AECOPD in HES and were not associated with codes for AECOPD or hospitalisations. Statistical analysis was conducted in Stata 14.1 MP and R 3.2.3.

Ethics

Ethics approval was obtained from the London School of Hygiene and Tropical Medicine (LSHTM) Observational Research Ethics Committee (approval number 6481) and the Clinical Practice Research Datalink (CPRD) Independent Scientific Advisory Committee (ISAC) (approval number 13_116A). Patient records and questionnaire responses were de-identified and anonymised by CPRD staff before being sent to the investigators. The ISAC protocol is available on request.

Results

In total 27,182 COPD patients with linked HES-CPRD data were included in the initial cohort after fulfilling inclusion criteria. A flow diagram of patient flow into the study is presented in

Figure 2. The characteristics of patients included in the study are summarised in Table 3. Additional questionnaire data were available for 637 patients, of whom 40 had linkable HES data and discharge letters for an admission to hospital for AECOPD. In the total cohort, the mean age was 65.5 years (SD: 11.1), 46.5% were females, and 59.7% current smokers. 54.4% had moderate-severe dyspnoea (MRC>=3) and 36.4% had GOLD grade of airflow limitation 3 or higher.

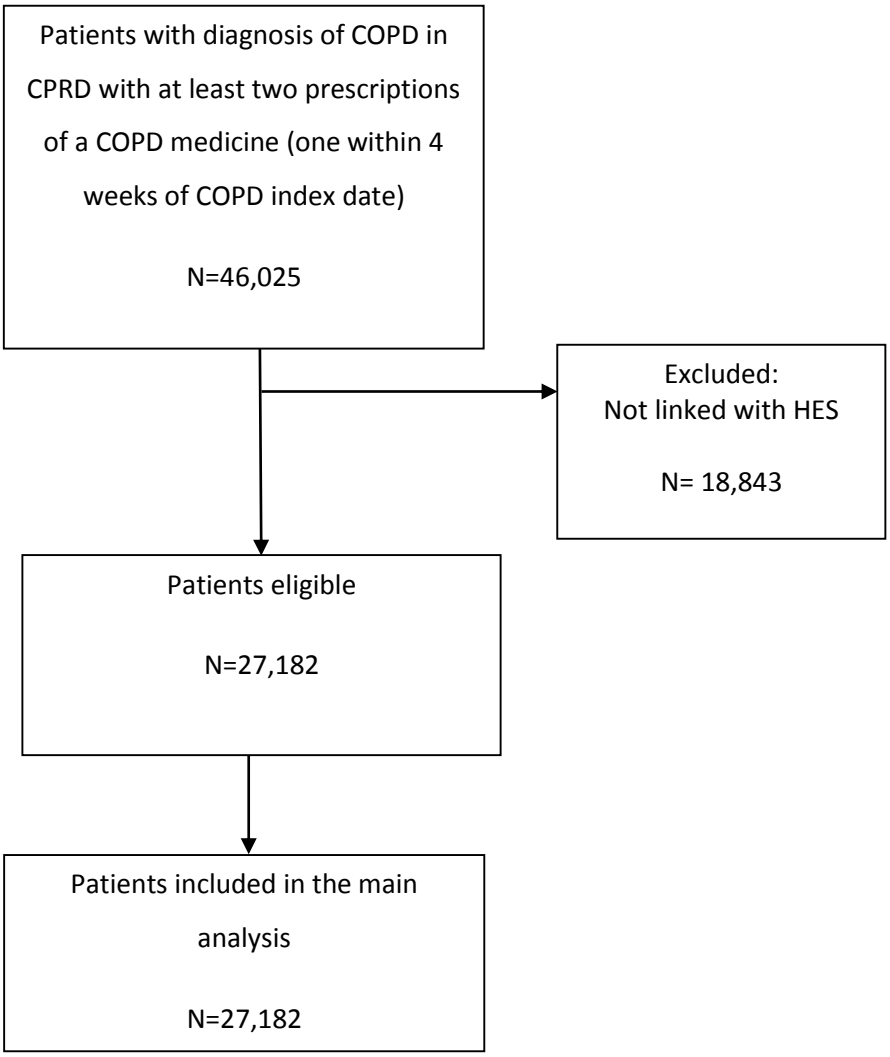


Figure 2. Flow of patients through the study.

Table 3 – Characteristics of patients included in the study

Characteristic	Overall	Those with hospital discharge information
	N % (N=27,182)	N % (N=40)
Age group		
≤55	5003 (18.4)	7 (17.5)
55 to 64	7746 (28.5)	16 (40.0)
65 to 74	8537 (31.4)	12 (30.0)
≥ 75	5896 (21.7)	5 (12.5)
Sex		
Male	14556 (53.6)	18 (45.0)
MRC breathlessness scale (N=21,151)		
<3	9645 (45.6)	21 (46.2)
≥3	11506 (54.4)	18 (46.2)
BMI (N=26,447)		
< 19	1441 (5.5)	1 (2.5)
19 – 25	9568 (36.2)	18 (45.0)
≥25	15438 (58.4)	21 (52.5)
GOLD 2006 grade (N=14,055)		
1	2829 (20.1)	4 (16.7)
2	6116 (43.5)	6 (25.0)
3	4075 (29.0)	10 (41.7)
4	1035 (7.4)	4 (16.7)
Smoking status		
Ex-smoker	10963 (40.3)	19 (47.5)
Current smoker	16219 (59.7)	21 (52.5)
Index of multiple deprivation quintile (N=25,852)		
1 (least deprived)	3632 (14.1)	8 (20.0)
2	5259 (20.3)	7 (17.5)
3	4989 (19.3)	7 (17.5)
4	5794 (22.4)	6 (15.0)
5 (most deprived)	6178 (23.9)	12 (30.0)

Recording of hospitalisations for AECOPD in HES

Graphs demonstrating the diagnostic positions of ICD codes in HES for AECOPD, LRTI and COPD in finished consultant episodes (FCE) for hospitalised COPD patients are shown in Figure 3. These graphs demonstrate that codes for AECOPD and LRTI tend to be used in the first position. The code for COPD, although it is commonly used in the first position, is also often used in subsequent positions.

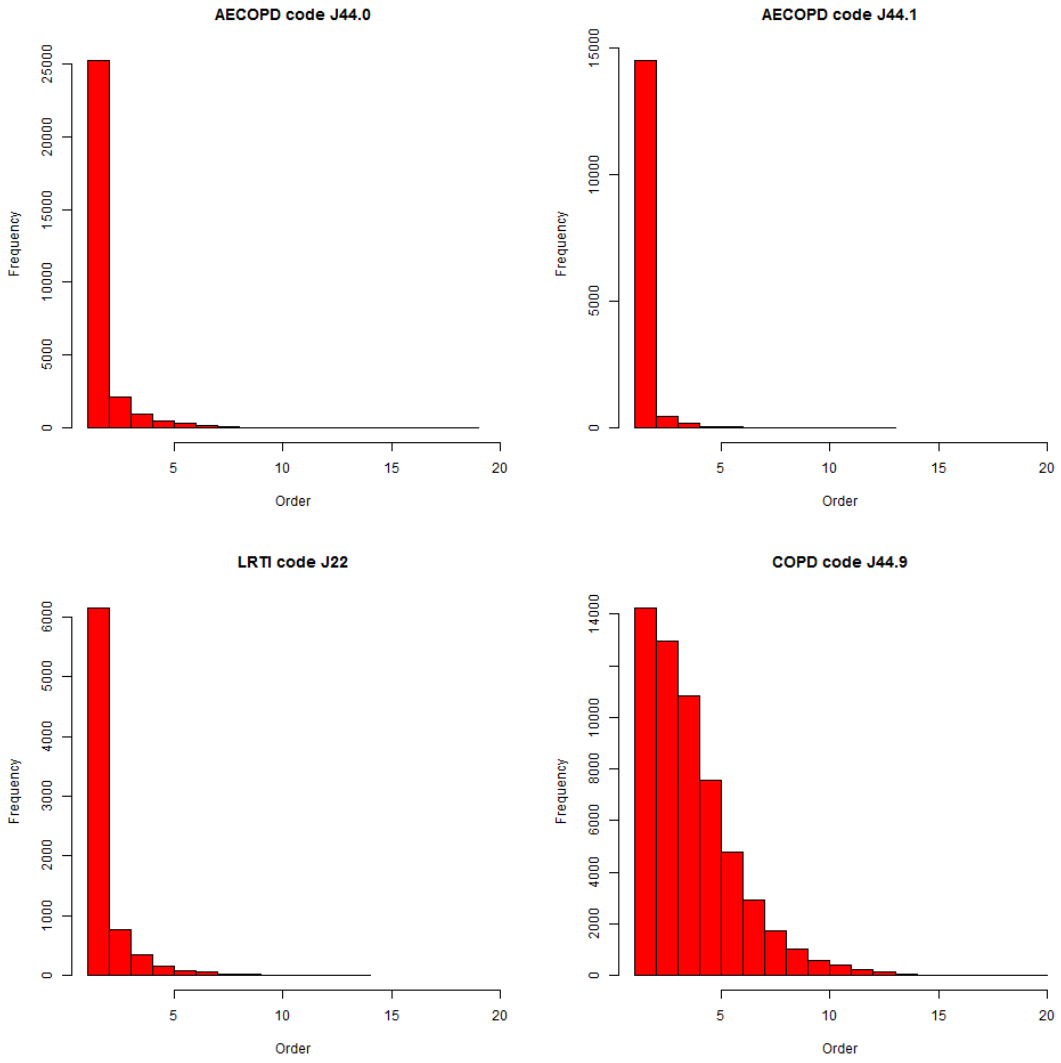


Figure 3. Diagnostic positions of ICD codes for acute exacerbations of COPD, lower respiratory tract infections, and COPD in hospital episodes statistics records for hospitalisations for COPD patients.

The findings for the investigation of the validity of the strategies used to identify hospitalisations for AECOPD are presented in Table 4. For the assessment of sensitivity, 40 discharge letters were available. The lowest estimated sensitivity was definition 6, using only a

specific AECOPD code in the first position in the first finished consultant episode for a hospitalisation (sensitivity 65.0%, 95% CI 45.8-78.6%). The highest estimated sensitivity was definition 5, using either a specific AECOPD code or an LRTI code in any position or a COPD code in first position in any FCE during a hospitalisation (sensitivity 87.5%, 95% CI 72.4-94.9%).

Table 4. Validity of HES definitions of AECOPD hospitalisation

	Discharge summary analysis	Full HES sample analysis	
HES definition of AECOPD hospitalisation	**Number of discharge summary confirmed AECOPD hospitalisations identified using strategy (N=40 events from discharge letters)**	**Sensitivity (95% CI) (% of discharge summary confirmed AECOPD hospitalisations picked up)**	**Number of potential AECOPD hospitalisation events in total sample identified using strategy (full HES sample for all COPD patients included in the study) ***
Specific AECOPD code or LRTI code in any position or COPD code in 1st position in any FCE during spell	35/40	87.5% (72.4-94.9%)	40,174
Specific AECOPD code or COPD code in any position in any FCE during spell	34/40	85.0% (69.6-93.3%)	74,590
Specific AECOPD code in any position in or LRTI code or COPD code in 1st position in any FCE during spell	34/40	85.0% (69.6-93.3%)	37,966
Specific AECOPD code in any position or COPD code in 1st position in any FCE during spell	31/40	77.5% (61.3-88.2%)	35,793
Specific AECOPD code in any position in any FCE during spell	31/40	77.5% (61.3-88.2%)	33,933
Specific AECOPD code in first position in first FCE during spell	26/40	65.0% (48.5-78.6%)	21,387

* These potential events will represent both true and false positives; FCE, finished consultant episode.

Recording of hospitalisations for AECOPD in primary care records

Using the most sensitive definition of AECOPD hospitalisation identified in HES as the reference standard, the PPV for the specific AECOPD hospitalisation code in CPRD was 50.2% (95% CI, 48.5-51.8%) and the sensitivity was 4.1% (95% CI, 3.9-4.3%) (Table 5). Using AECOPD identified using the previously validated algorithm on the same day as a Read code suggesting hospitalisation for un-specified reason in the primary care record resulted in a PPV of 43.3% (95% CI, 42.3-44.2%) and a sensitivity of 5.4% (95% CI, 5.1-5.7%). The use of different HES definitions of hospitalisation for AECOPD did not result in markedly different results (Table 5). The results of the additional analysis repeated using only the day of the HES recorded event, and using a 60 day window rather than a 30 day window following the HES recorded event are presented in the supplementary material. With the exception of an increase in the sensitivity of use of AECOPD code alone or non-specific hospitalisation code alone as the window was increased, these results did not differ significantly from the analysis using a 30 day window.

Table 5. PPV and sensitivity of CPRD strategies to identify hospitalisations for AECOPD using different HES definitions as reference standard allowing 30 days after HES record of hospitalisation for AECOPD

HES AECOPD definition	**CPRD strategy**	**PPV (95% CI)**	**Sensitivity (95% CI)**
AECOPD hospitalisation or LRTI code in any position or COPD in first position in any FCE	**AECOPD hospitalisation code**	50.2% (48.5-51.8%)	4.1% (3.9-4.3%)
	AECOPD identified using validated algorithm & hospitalisation code	43.3% (42.3-44.2%)	5.4% (5.1-5.7%)
Either specific AECOPD code in any position or COPD code in 1st position	**AECOPD hospitalisation code**	49.0% (47.3-50.6%)	4.6% (4.5-4.9%)
	AECOPD identified using validated algorithm & hospitalisation code	38.5% (37.6-39.4%)	5.5% (5.2-5.9%)
Either specific AECOPD code in first position in any finished consultant episode	**AECOPD hospitalisation code**	45.9% (44.2-47.6%)	4.7% (4.4-4.9%)
	AECOPD identified using validated algorithm & hospitalisation code	37.2% (36.3-38.1%)	5.7% (5.4-6.0%)

When the definition using AECOPD codes on the same day as hospitalisation codes was extended to use consultation or referral types indicating hospitalisation, this reduced the PPV to 14.6% (95% CI, 14.2-14.9%), and increased the sensitivity to 6.0% (95% CI, 5.7-6.3%). In the additional analysis to investigate the use of either a code or codes suggesting AECOPD or hospitalisation for any reason, the use of the AECOPD algorithm alone resulted in a PPV of 1.8% (95% CI, 1.7-1.8%) and a sensitivity of 34.2% (95% CI, 33.7-34.6%). The use of a code suggesting hospitalisation alone resulted in a PPV of 14.5% (95% CI, 14.3-14.6%) and a sensitivity of 53.5% (95% CI, 53.0-54.0%). These results repeated using different HES definitions for hospitalisation due to AECOPD are presented in the supplementary material.

When assessing a random sample of 100 Read codes on the day of admission on which patients had a HES hospitalisation for AECOPD (after excluding codes which either suggested AECOPD according to our algorithm, or hospitalisation for any reason), we found many of these related to non-specific Read Terms suggesting patient contact such as "Had a chat to patient", "Patient reviewed", and "Seen in out of hours centre" (N=41); several related to recording of either heart rate or blood pressure (N=16); some related to contact with secondary care (but not necessarily suggesting admission to hospital), such as "seen by respiratory physician" or "letter from specialist" (N=10); few related to symptoms of an AECOPD such as "Cough" (N=5); the remaining (N=28) were not specific for AECOPD.

Discussion

We developed a valid strategy to identify hospitalisations for AECOPD using HES linked CPRD data. Using this definition as a reference standard, we found that using information from primary care data alone resulted in low PPV and sensitivity for identifying hospitalisations for AECOPD.

When we assessed the validity of the recording of hospitalisations for AECOPD in HES, we found that the most sensitive strategy was the use of a specific AECOPD or LRTI ICD-10 code in any position in any finished consultant episode; or the COPD ICD-10 code in first position only in any finished consultant episode in a hospitalisation (sensitivity 87.5%). The use of the COPD ICD-10 code in any position results in a very large number of events and this likely represents it being used to record COPD as a co-morbidity not as a reason for hospitalisation. Although the exact definition used in future studies may differ depending on the needs of the study, this definition is likely to represent the "optimal" way to identify hospitalisations for AECOPD in HES. Restricting the definition to the specific AECOPD codes in the first position only in the first finished consultant episode reduced the sensitivity to around 65%. The failure to recognise the remaining patients is likely to represent COPD

patients receiving a non-specific ICD-10 code such as "shortness of breath" on an assessment ward before being moved to a specialist ward.

For the analysis of the accuracy of using primary care data only to identify hospitalised AECOPD, using the most sensitive HES definition of AECOPD as the reference standard, the maximum PPV achievable was 50.2% and the maximum sensitivity achievable was only 5.4%. The use of such strategies to identify hospitalisations for AECOPD would mean that the vast majority of "true" events would not be picked up, and that of those events which were picked up, only half would be "true" events. The findings from our additional analysis suggest that GPs are recording the majority of AECOPD hospitalisations simply by using generic hospitalisation codes and/or AECOPD codes alone. The use of consultation and referral type data increased the sensitivity very slightly, however resulted in a large decrease in PPV. Although use of non-specific hospitalisation codes or AECOPD codes alone had a higher sensitivity, particularly when the window was extended to 60 days, the PPV were very low and it is unclear if these relate to the index HES recorded event or further moderate AECOPD or hospitalisations. For the other CPRD definitions of AECOPD hospitalisation, increasing the window beyond 60 days may have improved performance, but it would become difficult to differentiate multiple hospitalisations from each other. The findings from the examination of Read codes on days on which AECOPD hospitalisations occurred but were not identified by any of the CPRD strategies suggest that on the day of hospitalisation, many AECOPD hospitalisations are also recorded using even less specific codes than a generic hospitalisation code. This is of clinical concern given the impact of prognosis for patients admitted to hospital with first, and subsequent exacerbations of COPD[14].

Our finding that validity of primary care recorded hospitalisations for AECOPD is low is certainly striking, but perhaps not surprising. Previous work in cause-specific hospitalisation in other disease areas have produced similar results. Recent studies investigating the validity and completeness of UK primary care recording of admission to hospital for acute myocardial infarction[15], poisonings, fractures and burns[16], and gastrointestinal bleeding[17] have all found that strategies to identify these events in primary care tend to have low-moderate sensitivity, and varying levels of PPV. In addition, a recent study showed that using HES-linked CPRD data, rather than CPRD data alone, resulted in a doubling of incidence of community acquired pneumonia and that this could be attributable to patients presenting directly to hospital without first consulting their GP[18]. These findings are consistent with our results. A recent study did find a high PPV for codes suggesting hospital admission for community acquired pneumonia in the general population, but this was only after restricting to those with a recent non-specific respiratory infection code, and this study did not assess sensitivity[19].

Interestingly, another study in UK primary care records found an increasing trend towards coding episodes of influenza-like-illness (ILI) using non-specific codes rather than definite ILI codes, and a tendency not to use definite ILI codes in populations in whom there was more likely to be diagnostic uncertainty[20]. These findings are reflected in our results. The reasons that the PPV and sensitivity of the recording in primary care of hospitalisations for AECOPD is particularly low are likely to be: the use of non-specific codes, diagnostic uncertainty, and the use of apparently acute codes to record historical events. Our findings from this analysis are in stark contrast to our validation of the recording of AECOPD treated in general practice, where we found high PPV and adequate sensitivity[13].

Electronic healthcare records are becoming increasingly used both for research and for audit and service planning. Due to its universal public healthcare system the UK is an attractive setting to use electronic healthcare records to study diseases and medical interventions. Although GPs should be informed when their patients are admitted to hospital, this may not be recorded in such a way that is useful for researchers. Just as details such as comorbidities, prior medicine use and sociodemographic details might be missing from secondary care records, detailed information about hospital admissions may be missing from primary care records. The present study underlines previous findings that hospital admission diagnoses and procedures are not consistently recorded in primary care. Although this may reduce sample sizes, and result in a lag in available linked data, it seems that, for some conditions, use of primary care data alone may not result in valid definitions when used to study events which may result in admission to hospital. Although the validity of definitions will likely differ between different conditions, researchers should be cautious about using primary care data alone to define cause-specific hospitalisations.

The major strength of this study is the size and representativeness of the sample. We used data for over 27,182 COPD patients. Our assessment of the validity of the HES definitions of AECOPD hospitalisation was only based on 40 patients, however, which may have affected the precision of the sensitivity estimates for the HES definitions. We also made use of a validated strategy to identify patients with COPD in the CPRD. Although there is some uncertainty in the best definition of hospitalisation for AECOPD in HES to use as the reference standard, we used hospital discharge summaries to validate how these were recorded in HES. In addition, we repeated our main analysis using several different HES definitions of hospitalisation for AECOPD and these did not change our conclusions. One weakness of the study is that the HES strategy did not identify all of the hospitalisations for AECOPD, however in the main analysis, we used a strategy with a sensitivity of 87.5%, and this is unlikely to have impacted on the conclusions of the study. In addition, although we were able to assess the sensitivity of the

strategies to identify hospitalisations for AECOPD in HES, we were unable to assess their PPV. The impact of this limitation is likely to be small, however. Imperfect PPV of the definition of hospitalisations for AECOPD in HES would have the effect of underestimating the sensitivity of CPRD algorithms. Using a range of hypothetical PPVs, we can estimate the potential effect of lower PPV of the HES definitions by multiplying the estimated sensitivity of the CPRD definitions by the inverse of the PPV (1/hypothetical PPV). For example, if the PPV of our main HES definition were only 80%, the sensitivity of the CPRD definition using AECOPD hospitalisation codes would only rise from 4.1% to 5.1%; and the algorithm using an AECOPD code and a hospitalisation code on the same day would rise to 6.8%. Even in the unlikely situation that the PPV of our main HES algorithm was as low as 60%, the respective sensitivities would only increase to 6.8% for an AECOPD hospitalisation code and 9.0% for an AECOPD code and hospitalisation code on the same day. We also assessed the CPRD definitions of hospitalisation for AECOPD using several definitions of AECOPD hospitalisations in HES, and the findings did not change when we used definitions with varying sensitivities.

Conclusions

In the UK, primary care electronic health records data should not be used alone to identify hospitalisations for exacerbations of COPD. In order to accurately identify hospitalisations for AECOPD, and to correctly classify AECOPD either as those treated in primary care or resulting in hospitalisation, researchers should use linked primary care data linked with secondary care data on hospitalisations.

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8.3 Summary

- Hospitalisations for AECOPD can be identified in HES with a high sensitivity, however the PPV is unclear
- Primary care data alone (that is not linked to secondary care EHR) cannot be used to reliably identify hospitalisation for AECOPD due to both low PPV and sensitivity
- Researchers should use linked primary and secondary care EHR to identify AECOPD which result in hospitalisation

Chapter 9: Risk of myocardial infarction associated with acute exacerbations of COPD: A self-controlled case series (Research paper VII)

9.1 Preamble

The research paper presented in this chapter aims to answer the ultimate aim of this thesis by investigating the relationship between AECOPD and the risk of MI.

The findings of the previously presented research papers have provided important information for the rationale for and design of this study. Firstly, findings from the systematic review highlighted the higher risk of MI in people with COPD, and that this higher risk of MI could not entirely be explained by smoking. Findings from the two studies in the MINAP database along with the review paper indicated the higher risk of death following MI for people with COPD, the delay in diagnosis of MI in people with COPD (which is consistent with co-occurrence or misclassification with another condition, such as AECOPD), the higher risk of and impact from non-STEMI in people with COPD, the importance of age (which is a major driver of the GRACE score) as an effect modifier for the increased risk of MI and impact of MI on risk of death in people with COPD, and the importance of cardiovascular medicines, and other therapies for modifying cardiovascular risk in people with COPD. The previous analysis has also provided validated definitions of AECOPD and hospitalisation for AECOPD.

The definitions of AECOPD and hospitalisation for AECOPD which were validated in previous chapters will be used in this study. The results of the AECOPD validation study can also be used to re-examine the results of Donaldson et al. (Donaldson et al. 2010), who also investigated the relationship between AECOPD and MI. Donaldson et al. used three definitions of AECOPD (1 prescription of antibiotics alone; 2 prescription of oral corticosteroids alone; and 3 prescription of antibiotics and oral corticosteroids) in a self-controlled case series analysis which investigated the risk of MI in the days and weeks following AECOPD. The results of this analysis are presented below next to an estimated PPV obtained from the AECOPD validation study in this thesis:

		Estimated PPV*
Antibiotics:	IRR 1.14 (95% CI, 0.7-1.8)	~60%
Oral steroids:	IRR 1.55 (95% CI, 0.9-2.8)	~70%
Antibiotics and oral steroids:	IRR 2.27 (95% CI, 1.1-4.7)	~80%

* Based on Rothnie et al. 2016

Although not all of the definitions of AECOPD were associated with an increased risk of MI, there was an association when a definition with the highest validity was used, and the effect size increased with increasing PPV. This suggests that the analysis which did find an association between AECOPD and risk of MI was the most robust in terms of validity of the exposure definition.

The study presented here aims to use a larger sample and a validated AECOPD definition to confirm the association between AECOPD and MI, quantify the magnitude and duration of the increased risk, and to stratify the analysis by important characteristics. Stratified analysis is important as this will inform future studies into possible interventions to mitigate the risk of MI associated with AECOPD.

The study design used in this research paper is the self-controlled case series. The self-controlled case series is a within person design which can be used to investigate the effect of a transient exposure on an outcome (Whitaker et al. 2006). The self-controlled case series is based on the cohort model, in the sense that exposures are fixed and outcomes are random. The key feature of the self-controlled case series is that the comparisons are made within person: exposed periods are compared to individual's own baseline periods. A diagram representing the study design is displayed in Figure 9. The advantage of this design is that fixed between-person confounding, due to factors such as genetics, socioeconomic status or long term medicine use, are completely and implicitly controlled for. The design does not implicitly control for the effect of within-person time varying confounders, however. Confounding may arise in this situation if change in confounder levels temporally associates closely with the exposure, or if the probability of experiencing the exposure and the confounder increases or decreases over time. In order to deal with this source of confounding, age-bands are often constructed and statistically controlled for (Figure 10). The age bands not only control for the effects of age, but also control for the effects of time varying confounders. The age bands, however, must be sufficiently small such that important confounders will not vary significantly within bands.

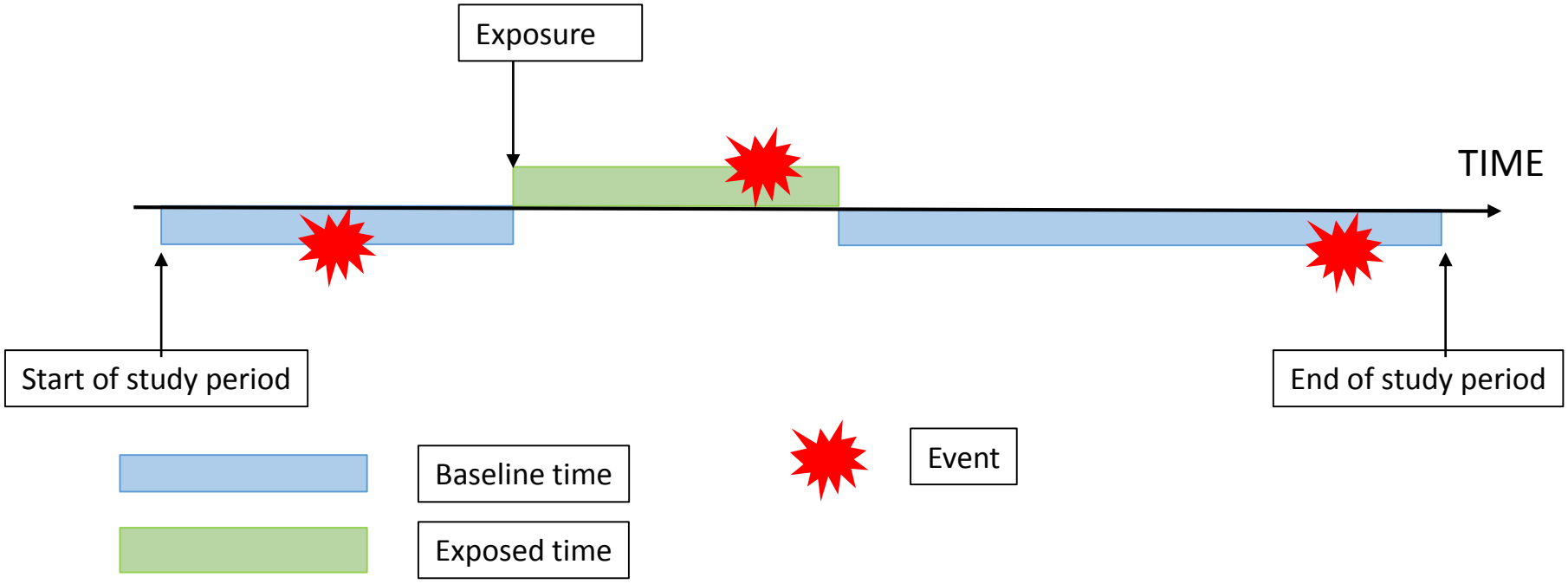

Figure 9. Diagram representing the self-controlled case series design

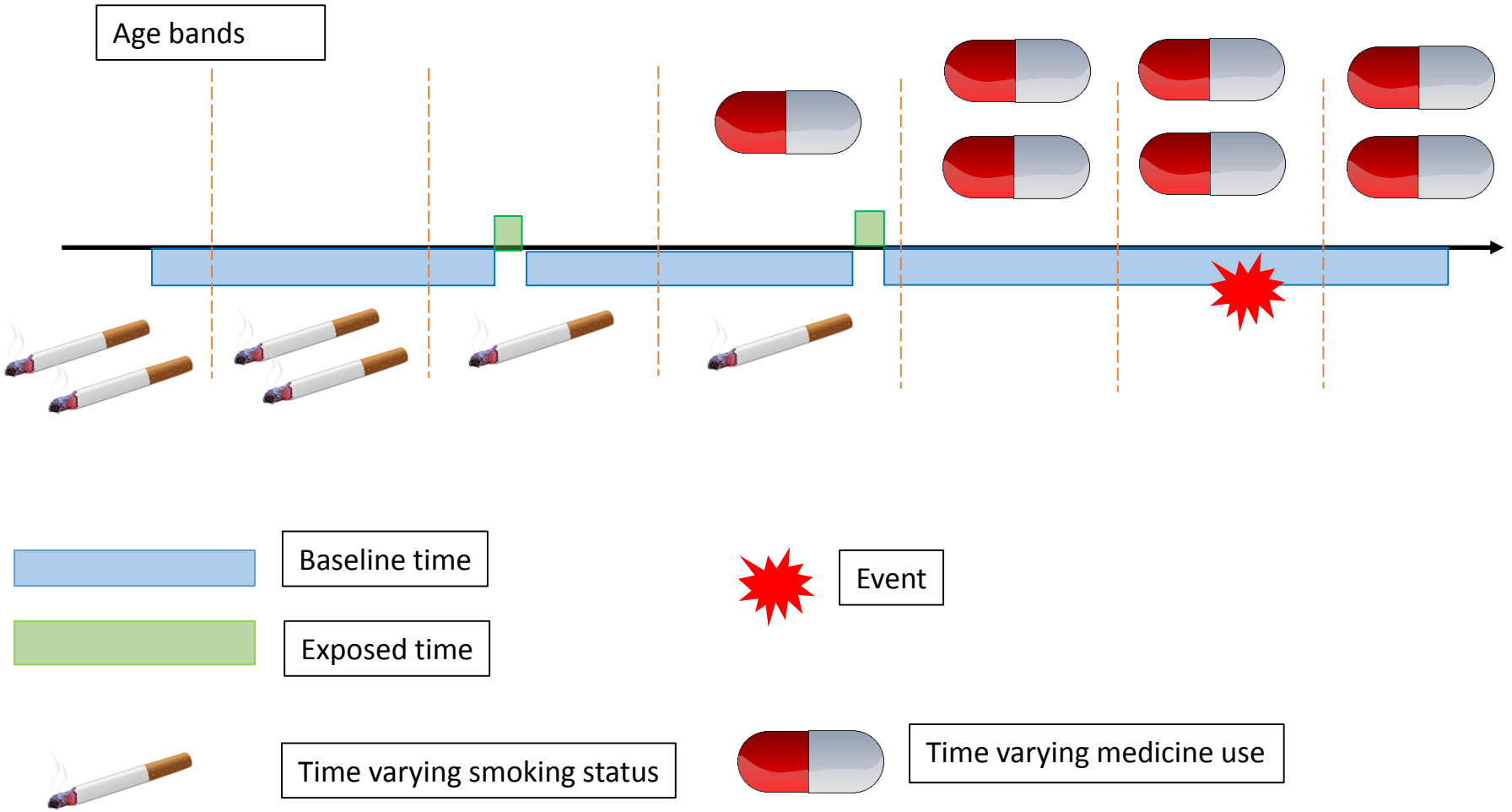

Figure 10. Diagram representing the use of age bands to control for time varying confounders in the self-controlled case series

The self-controlled case series method was originally designed to be used to investigate adverse effects of vaccines (Farrington 1995). Since then, it has been used extensively in pharmacoepidemiology (Tata et al. 2005, Gribbin et al. 2011, Douglas et al. 2013, Brauer et al. 2015), and more recently in investigating the effects of infections, viral reactivation, and other inflammatory events on the risk of vascular outcomes (Smeeth et al. 2004, Minassian et al. 2010, Langan et al. 2014).

There were two main reasons for selecting the self-controlled case series as the method for investigating the relationship between AECOPD and MI for this thesis. Firstly, there are many potential sources of confounding in the relationship between AECOPD and MI, such as socioeconomic status, genetics and co-morbidities, which are likely to be difficult to describe in EHR, which would be controlled for implicitly using the self-controlled case series. Secondly, the transient nature of the exposure lends itself to this study design, and would allow duration of the increased risk to be studied. An alternative study design might have been a cohort study, however this would have introduced confounding. Another within-person design which would have also have eliminated between-person confounding and would have been computationally simpler is a case-crossover design (Maclure 1991). However this would have relied on the assumption that the probability distribution of experiencing the exposure is exchangeable within-persons in successive time periods (Vines and Farrington 2001), which is not likely to be the case with AECOPD.

There are some limitations to the self-controlled case series study design. Firstly, due to the way individuals are sampled, it is not possible to produce absolute measures of effect. Secondly, although the method implicitly accounts for fixed confounders, time varying confounders are not implicitly controlled for, but their effect can be minimised by using age bands. Finally, the method relies on several assumptions (Whitaker et al. 2006).

The assumptions of the self-controlled case series are:

1. **The probability of experiencing future exposures (AECOPD) is not influenced by occurrence of the outcome event (MI).**

It is unlikely that this assumption will be violated, and no studies have suggested that MI would modify the natural history of AECOPD.

2. **Outcomes (MI) are independent (that is, occurrence of the outcome does not influence the probability of experience subsequent outcome events (MIs)).**

Since having an MI increases the risk of future MIs (Smolina et al. 2012), this assumption may be violated if recurrent events are included. To overcome this problem, this analysis will only look at first events.

3. **The outcome event (MI) does not lead to observation censoring (notably due to death).**

As MIs increase the risk of death, this assumption could be violated in this analysis. The analysis presented in chapter 4 indicated that during this time period in the UK, the mortality after MI is around 4.6% in-hospital, and 12.8% at 180 days after MI for those with COPD. Sensitivity analyses will be used in order to assess the potential impact of violation of this assumption.

The research paper presented in this chapter has been prepared for publication, however has not yet been submitted for peer review. The reason for this is that I would like to extend the analysis to also investigate pneumonias as exposures in addition to AECOPD, and also to investigate potential effect modification by COPD medicines. I am currently arranging the necessary approvals to do this. The working title and current authorship is presented at the beginning of the research paper.

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9.2 Research paper

Risk of myocardial infarction associated with acute exacerbations of COPD: A self-controlled case series

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Abstract

Background

People with COPD are at higher risk of MI compared to people without COPD, and this increased risk is independent of smoking status. Cardiovascular disease is also a common cause of death for those with COPD. Previous studies have suggested that acute exacerbations of COPD (AECOPD) may be temporally associated with increased MI risk. Using a large dataset, we precisely quantified the size and duration of the increased MI risk associated with AECOPD, and investigated factors which may modify that risk.

Methods

We used linked data from the Clinical Practice Research Datalink and Hospital Episodes statistics to conduct a self-controlled case series on COPD patients with at least one AECOPD and a first MI between January 2004-March 2015. We used conditional Poisson regression to compare the rate of MI in the 91 days following AECOPD to patient's own stable periods, adjusting for age (in 2 year bands) and season. We then stratified the analysis by patient characteristics.

Results

We included 2,745 COPD patients in the analysis. The 91 days following AECOPD were associated with increased risk of MI for people with COPD (IRR 1.65, 95% CI 1.50-1.81). This peaked in the first 3 days following AECOPD onset (IRR 2.80, 2.26-3.49), and returned to baseline within 4 weeks of AECOPD. Risk of MI associated with AECOPD was higher for hospitalised events compared to GP treated events (GP treated days 1-3 IRR 1.96, 1.52-2.52; hospital treated IRR 8.00, 5.81-11.01; p-value for interaction <0.001). Risk of MI associated with AECOPD was higher for infrequent exacerbators (Days 1-3 IRR 4.28, 2.94-6.24; p-value for interaction p=0.009), those with more severe airflow limitation (Days 1-3 IRR 4.67, 3.11-7.01; p-value for interaction=0.007), and for non-STEMIs compared to STEMIs (Days 1-3 IRR 3.15, 2.30-4.33; p-value for interaction<0.001).The risk of MI associated with AECOPD was not modified by age, sex, use of cardiovascular medicines at baseline or previous cardiovascular disease.

Conclusions

People with COPD are at higher risk of MI in the weeks following an AECOPD compared to stable periods. In the first 3 days following AECOPD onset, the increased risk of MI peaks at around a doubling of risk for primary care treated AECOPD, and an eight-fold increased risk

for severe AECOPD. The relative effect of AECOPD on risk of MI is higher for infrequent exacerbators, for those with more severe airflow limitation, and following a non-STEMI.

Introduction

Chronic obstructive pulmonary disease (COPD) is a common progressive lung disease characterised by airflow obstruction which is not fully reversible. People with COPD are at increased risk of MI compared to the general population[1]. This increased risk cannot be completely explained by smoking[2] and has been attributed to increased systemic inflammation[3]. Not only is the incidence of MI greater in people with COPD compared to the general population, up to one third of COPD patients die from cardiovascular disease[4]. Therefore, targeting cardiovascular disease in people with COPD is an important step in reducing their mortality and understanding the reasons for increased risk of MI in people with COPD is important for reducing cardiovascular morbidity.

Acute exacerbations of COPD (AECOPD) have been defined as increases in a patient's breathlessness, cough, or sputum volume and/or purulence which is beyond normal day-to-day variation and may require a change in treatment[5] . AECOPD normally last several days and most are thought to be triggered by infection (bacterial or viral)[6,7] and are associated with increased systemic inflammation[8,9]. People with COPD can be classified as either frequent or infrequent exacerbators, based on the number of exacerbations they have in a given one year period. The frequent exacerbator phenotype has previously been well characterised, and has been defined as individuals who have two or more treated exacerbations per year[10]. This phenotype appears to be stable over time[11], and is associated with faster FEV_1 decline[12], poorer quality of life[5], and higher levels of systematic inflammation, even during stable periods[10].

Previous work has shown that lower respiratory tract infections (LRTI) are associated with increased risk of MI in the general population[13]. In addition, it has been suggested that there might be an increased risk of MI following periods of AECOPD compared to stable periods[14,15] . Also, frequent exacerbators seem to have a higher risk of MI than infrequent exacerbators[14]. Recent improvements in the methods to identify AECOPD in electronic health records (EHR) means that more AECOPD can now be identified than ever before, and with greater sensitivity and precision [16].

Further studies into the relationship between AECOPD and MI which have both a validated exposure definition and sufficient power are therefore required. We used a self-controlled case series to investigate the effect of AECOPD on risk of MI. In addition, we investigated potential effect modification by: severity of AECOPD; exacerbator phenotype; GOLD stage of airflow limitation; previous non-MI cardiovascular disease; use of cardiovascular medicines, age, and sex.

Methods

Data Sources

We used data from the Clinical Practice Research Datalink (CPRD) linked with Hospital Episodes Statistics (HES) data. The CPRD is a very large data base of primary care data. It contains details on more than 11 million patients in the UK, with over 4 million of these active patients (around 7% of the UK population)[17]. Data includes details on symptoms, diagnoses, tests, prescriptions, details on patient demographics and health behaviours, and referrals to secondary care. Details in CPRD are mainly recorded using a system of Read codes, which is a hierarchical classification system. HES is an administrative database containing details of all episodes of admitted patient care in England and Wales. Data are structured into episodes of care by single consultants "finished consultant episodes", such that each hospitalisation may be made up from several finished consultant episodes. Data are recorded using ICD-10 codes. Each finished consultant episode may be associated with up to 20 ICD-10 codes, with the first code generally representing the reason for hospitalisation. The remaining codes may represent other acute problems, or co-morbidities. Data for around 60% of CPRD patients are linked to HES. CPRD-HES data were also linked to office of national statistics (ONS) data to determine exact date of death.

Study design

The self-controlled case series is a within-person design developed to account for confounding between individuals by comparing the incidence rate of an outcome following an exposure within the same individual using only those who have the outcome[18]. We used this design to estimate the incidence of MI following periods of AECOPD compared to stable periods. As well as being able to estimate the transient effect of an exposure, the major advantage of this design is that since inference is made within-person, it implicitly controls for the effects of fixed confounders such as sex, socioeconomic status and genetic factors. The effects of transient confounders can be controlled by adjusting for age-bands.

Following a previous study[13] we made an *a priori* decision to include the 91 days following the onset of AECOPD as the exposure period. Additionally, we segmented the 91 day exposure period into periods of 1-3, 4-7, 8-14, 15-28, and 29-91 days. As is common practice for this design, and to reduce misclassification of AECOPD with MI, we created a 14 window of pre-exposure time including the first day of the AECOPD. A diagram representing the study design is shown in Figure 1.

Patients were followed up between 1 January 2004, date of COPD diagnosis, 35th birthdate, or CPRD practice "up to standard" date whichever was later; and 31 March 2015, date of death, transfer out of practice or practice last collection date, whichever was earlier.

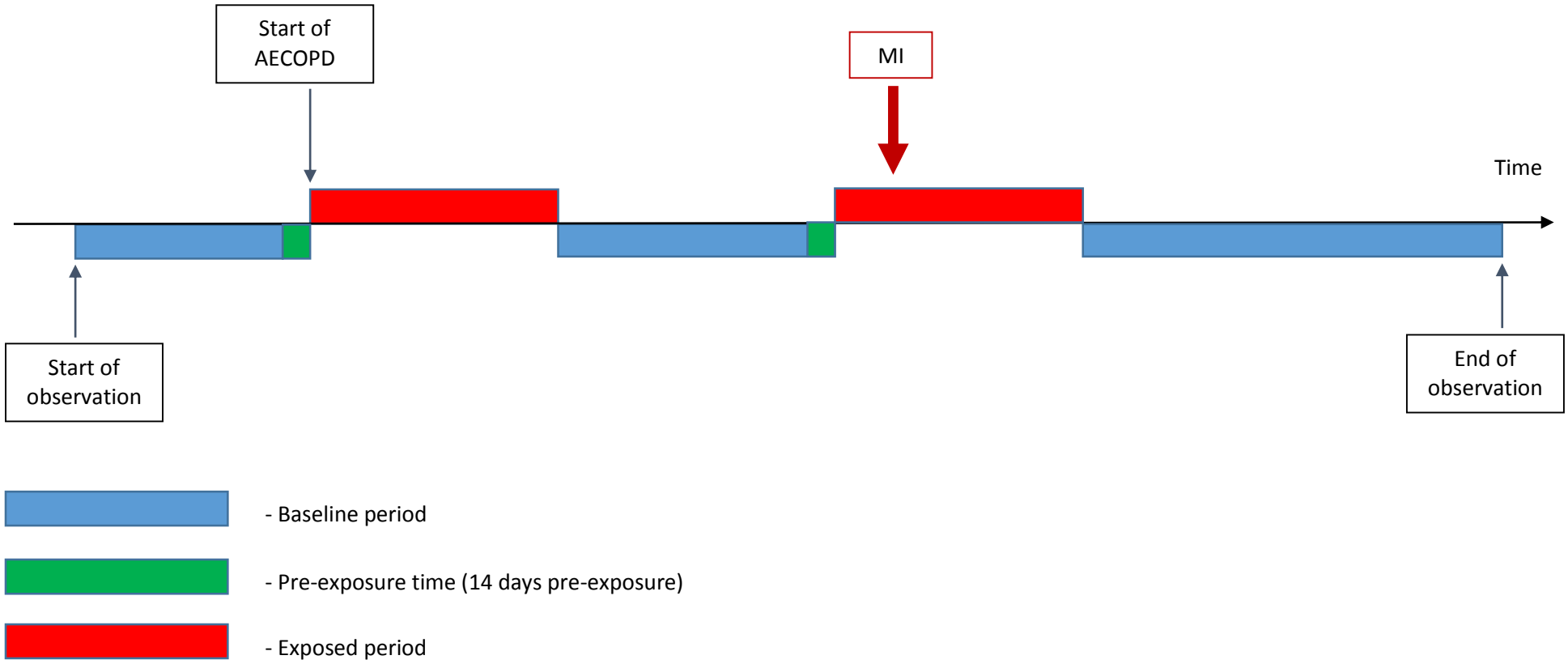

Figure 1. Diagram representing the study design. In this hypothetical example the patient has two AECOPD during follow up and a first MI within 91 days of the start of the second AECOPD.

Population, exposure, co-variates, and outcomes

The population included were COPD patients who had at least one AECOPD and a first MI during the study period. COPD patients were identified using a previously validated algorithm[19], and had a diagnostic Read code for COPD, a smoking history (ex or current smoker), and were aged over 35. Patients were also excluded if their CPRD records could not be linked to HES or ONS.

AECOPD (exposures) were defined using a previously validated algorithm [16]. Briefly, AECOPD were defined in CPRD as one of: 1) an AECOPD code; 2) an LRTI code; 3) prescription of both antibiotics or oral steroids from a pre-defined list for 5-14 days; or 4) symptoms of AECOPD (two of cough, sputum, or breathlessness) and either prescription of antibiotics or oral steroids on the same day. Hospitalisations for AECOPD were defined using linked HES data, we have also previously validated the recording of AECOPD in HES [Chapter 8]. Briefly, hospitalisation for AECOPD was defined as 1) an ICD-10 code for AECOPD or LRTI in any position in a hospitalisation record in a patient with a diagnosis of COPD in their CPRD record; or 2) an ICD-10 code for COPD in the first diagnostic position in any finished consultant episode in a hospitalisation record in a patient with a diagnosis of COPD in their CPRD record. We characterised AECOPD severity according to health care utilisation, with those requiring treatment from the general practitioner (GP) as moderate events, and those requiring hospitalisation as severe events. AECOPD which occurred within two weeks of the onset of a previous AECOPD were taken to be a continuing event.

Apart from age, sex and type of MI, all potential effect modifiers were defined at baseline using CPRD data. Cardiovascular drug (β-blocker, aspirin, and statins) use was defined as at least one prescription during the pre-baseline year. Previous cardiovascular disease (stroke, heart failure, and angina) was defined as any code suggesting one of these conditions at any time prior to follow up. GOLD status was defined using pre-baseline spirometry results. Patients were phenotyped as frequent or infrequent exacerbators depending on the number of exacerbations in the pre-baseline year. When assessing for effect modification, age was stratified into three groups: <61, 61-83, and ≥ 83.

MI events (outcomes) were defined using both primary care (CPRD) and hospital data (HES). Read codes were used to define MI in CPRD. In HES, MI was defined as an ICD-10 code for MI in the first position of a finished consultant episode. The date of MI was taken as the date of the start of the finished consultant episode, rather than the date of admission to hospital. ICD-10 codes I21.0, I21.1, I21.2, I21.3, and I21.4 were used to identify MI in HES.

Statistical analysis

We used conditional Poisson regression to estimate the incidence rate ratio (IRR) of first MI in the 91 days following AECOPD compared to stable periods.

To account for time-varying confounders, we adjusted for age, initially in five year bands, and then in two year bands. In addition, as weather may be associated with both AECOPD [20] and MI[21], and because season varies within the age bands, we adjusted for the effects of season (split into October-March and April-September).

One of the assumptions of the self-controlled case series analysis is that the outcomes do not alter the probability of future exposure or result in censoring of the observation time. As MI is associated with death, which would decrease the probability of further AECOPD and result in censoring, we conducted a sensitivity analysis to assess the potential impact of breaking this assumption. To do this, we repeated the main analysis in those whose follow up was not censored first for at least 6 months following MI, and also in those whose follow up was not censored for at least 12 months following MI.

As occurrence of both MI and at least one AECOPD during the study period were necessary criteria for entry into the study, those who had a fatal MI before their first recorded AECOPD would not enter into the study. This might result in a spuriously low rate of MI in the stable period between study entry and first AECOPD, which would bias the effect of AECOPD on MI towards the null. To assess the impact of this potential bias, we carried out another sensitivity analysis excluding the first period of baseline time between study entry and first AECOPD.

Analysis was conducted using Stata 14.1MP.

Ethical approval

Ethical approval was obtained from the LSHTM Observational Research Ethics Committee, CPRD's Independent Scientific Advisory Committee and the GSK protocol review forum. The protocol is available on request.

Results

We identified 2,475 individuals with COPD who had a first MI and at least one AECOPD during the study period (Figure 2). The characteristics are summarised in Table 1. Briefly, the median age was 73.3 years (IQR, 66.0-80.3). Around half of the patients had an AECOPD

requiring hospitalisation during the study and about 60% were frequent exacerbators. Of the index MIs for which patients were included, almost two-thirds were non-STEMIs.

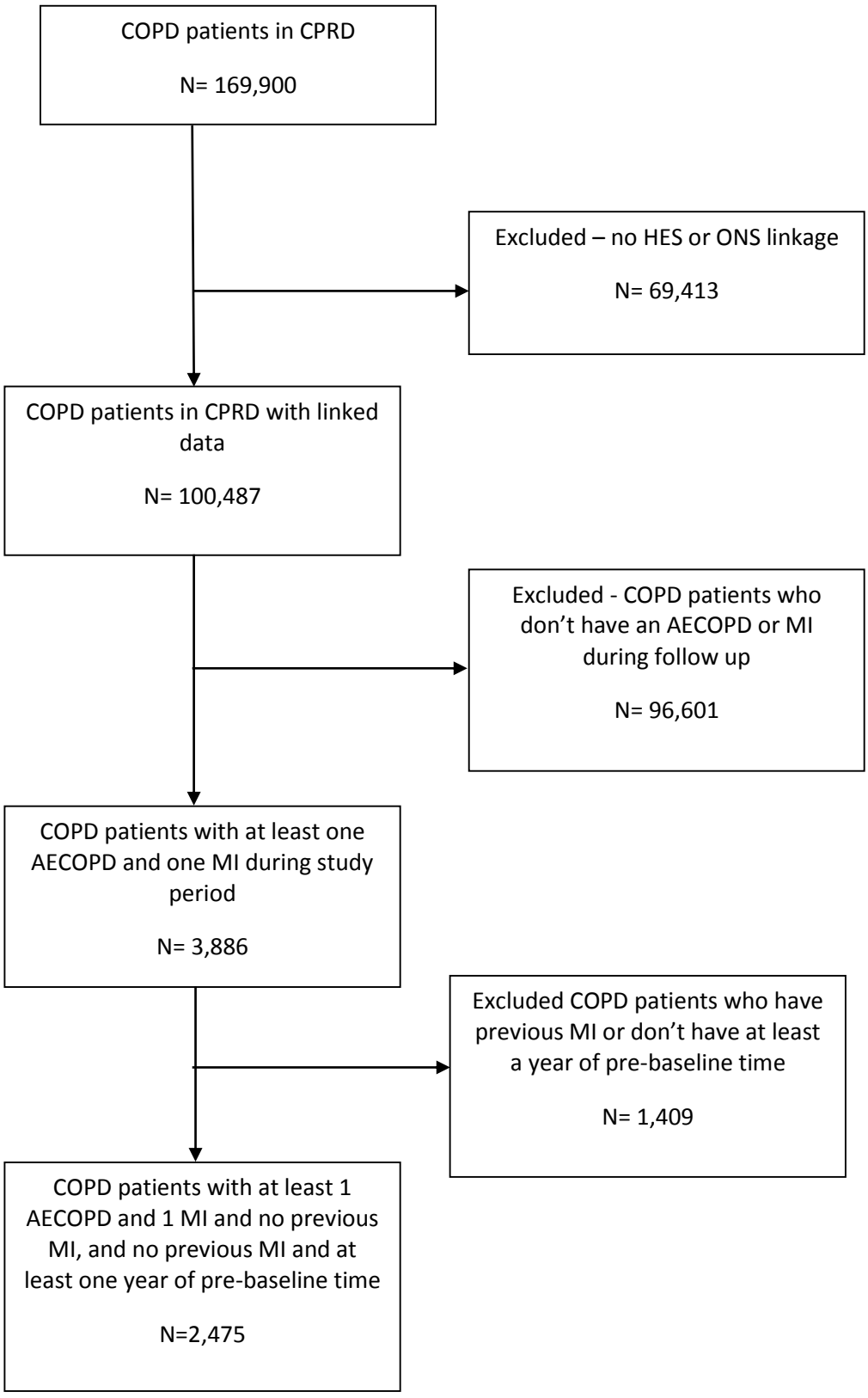

Figure 2. Patient flow in the study.

Table 1. Characteristics of 2,745 eligible COPD patients with myocardial infarction and acute exacerbation of COPD during the study period

Characteristic	
Age at index myocardial infarction, median (IQR)	73.3 years (66.0-80.3)
Average observation time, median (IQR)	8.2 years (6.0-10.3)
Male sex, n (%)	1,631 (59.4%)
Number with at least one severe event (requiring hospitalisation), n (%)	1,400 (51.0%)
Frequent exacerbators, n (%)	1,629 (59.3%)
Non-MI cardiovascular disease	
Total, n (%)	716 (26.1%)
Angina, n (%)	493 (18.0%)
Heart failure, n (%)	211 (7.7%)
Stroke, n (%)	153 (5.6%)
Prescribed cardiovascular drug during follow up	
Total, n (%)	1,336 (48.7%)
Statin, n (%)	804 (29.3%)
Aspirin, n (%)	791 (28.8%)
Beta-blocker, n (%)	671 (24.4%)
GOLD stage of airflow limitation (N=1476)	
Stages I-II, n (%)	945 (64.0%)
Stages III-IV, n (%)	531 (36.0%)
Type of MI (N=1872)	
STEMI, n (%)	667 (35.6%)
Non-STEMI, n (%)	1,205 (64.4%)

Results for the main analysis including all AECOPD events, and by severity of AECOPD are presented in Table 2. Compared to stable periods, the 91 days following the onset of AECOPD were associated with a 65% increased risk of MI (IRR 1.65, 95% CI 1.50-1.81). During the first 3 days following AECOPD, the rate of MI was almost three times as high as stable periods, the risk gradually fell back to baseline level after 28 days. The effect of AECOPD on risk of MI was modified by severity of AECOPD (p-value for interaction <0.001), with the risk of MI over 2.5 times that of stable periods in the 91 days following a severe AECOPD, compared to 1.4 times that of stable periods for moderate events. The first three days following a severe AECOPD were associated with an 8 fold increase in risk of MI, compared to a doubling of risk for moderate events. The risk of MI gradually decreased to baseline levels following a severe AECOPD. However, there was a noticeable second peak in risk of MI following moderate AECOPD at 8-14 days following onset before decrease to almost baseline levels at 29-91 days.

Table 2. Incidence rate ratios of first myocardial infarction in risk periods after an acute exacerbation of COPD (AECOPD) relative to stable periods and stratified by AECOPD severity

			AECOPD severity			
	All AECOPD (moderate and severe events)		Moderate AECOPD (not resulting in hospitalisation)		Severe AECOPD (resulting in hospitalisation)	
Risk period	**N outcome events (MI)**	**IRR (95% CI)**	**N outcome events (MI)**	**IRR (95% CI)**	**N outcome events (MI)**	**IRR (95% CI)**
Total risk period (91days)	883	1.65 (1.50-1.81)	619	1.44 (1.33-1.57)	264	2.58 (2.26-2.95)
1-3 days	90	2.80 (2.26-3.49)	51	1.96 (1.52-2.52)	39	8.00 (5.81-11.01)
4-7 days	97	2.38 (1.93-2.93)	49	1.53 (1.19-1.97)	48	7.78 (5.82-10.59)
8-14 days	159	2.36 (1.99-2.80)	112	1.98 (1.67-2.36)	47	4.78 (3.57-6.40)
15-28 days	213	1.91 (1.64-2.21)	143	1.64 (1.41-1.91)	70	4.00 (3.14-5.09)
29-91 days	324	1.17 (1.04-1.33)	264	1.15 (1.02-1.29)	60	1.01 (0.78-1.31)
						p for interaction <0.001

AECOPD – acute exacerbation of COPD; MI – myocardial infarction; IRR – incidence rate ratio.

The effect of AECOPD on risk of MI was higher for infrequent exacerbators compared to frequent exacerbators (p-value for interaction=0.0085), with infrequent exacerbators having a 78% higher rate of MI in the 91 days following onset of AECOPD compared to their stable periods; and frequent exacerbators having a 57% higher rate of MI compared to their stable periods (Table 3).

Table 3: Incidence rate ratios of first myocardial infarction in risk periods after an acute exacerbation of COPD (AECOPD) relative to stable periods stratified by exacerbator phenotype

	Exacerbator phenotype			
	Frequent exacerbators (≥2 AECOPD per year)		**Infrequent exacerbators (<2 events per year)**	
Risk period	**N outcome events (MI)**	**IRR (95% CI)**	**N outcome events (MI)**	**IRR (95% CI)**
Total risk period (91 days)	635	1.57 (1.40-1.76)	248	1.78 (1.53-2.07)
1-3 days	61	2.32 (1.78-3.03)	29	4.28 (2.94-6.24)
4-7 days	70	2.11 (1.64-2.71)	27	3.08 (2.09-4.54)
8-14 days	112	2.05 (1.67-2.52)	47	3.20 (2.37-4.33)
15-28 days	158	1.79 (1.50-2.14)	55	2.11 (1.59-2.79)
29-91 days	234	1.18 (1.02-1.38)	90	1.10 (0.87-1.37)

p for interaction =0.009

AECOPD – acute exacerbation of COPD; MI – myocardial infarction; IRR – incidence rate ratio.

The effect of AECOPD on risk of MI was also higher for those with more severe airflow limitation (GOLD stage 1-2 IRR 1.69, 95% CI 1.45-1.98; GOLD stage 3-4 IRR 1.98, 95% CI 1.61-2.05; p-value for interaction=0.007) (Table 4).

Table 4: Incidence rate ratios of first myocardial infarction in risk periods after an acute exacerbation of COPD (AECOPD) relative to stable periods stratified by GOLD stage of airflow limitation

	Degree of airflow limitation			
	GOLD stage 1-2		**GOLD stage 3-4**	
Risk period	**N outcome events (MI)**	**IRR (95% CI)**	**N outcome events (MI)**	**IRR (95% CI)**
Total risk period (91 days)	305	1.69 (1.45-1.98)	192	1.98 (1.61-2.05)
1-3 days	23	2.22 (1.45-3.39)	28	4.67 (3.11-7.01)
4-7 days	43	3.25 (2.36-4.48)	24	3.17 (2.05-4.89)
8-14 days	56	2.54 (1.91-3.39)	35	2.83 (1.95-4.09)
15-28 days	78	2.10 (1.64-2.69)	49	2.42 (1.75-3.34)
29-91 days	105	1.11 (0.90-1.38)	56	1.16 (0.86-1.57)

p for interaction=0.007

When we stratified the analysis by the type of MI which occurred, we found that the effect of AECOPD on risk of MI in the 91 days following AECOPD was higher for non-STEMIs (IRR 1.80, 95% CI 1.56-2.06) than for STEMIs (IRR 1.39, 95% CI 1.16-1.68), p-value for interaction<0.001 (Table 5).

Table 5: Incidence rate ratios of first myocardial infarction in risk periods after a acute exacerbation of COPD (AECOPD) relative to stable periods stratified by MI phenotype (STEMI or non-STEMI)

	Type of MI			
	STEMI		**Non-STEMI**	
Risk period	**N outcome events (MI)**	**IRR (95% CI)**	**N outcome events (MI)**	**IRR (95% CI)**
Total risk period (91 days)	195	1.39 (1.16-1.68)	407	1.80 (1.56-2.06)
1-3 days	24	2.87 (1.89-4.39)	43	3.15 (2.30-4.33)
4-7 days	15	1.42 (0.84-2.39)	51	2.96 (2.20-3.97)
8-14 days	37	2.09 (1.47-2.96)	70	2.46 (1.90-3.18)
15-28 days	41	1.39 (0.99-1.94)	111	2.36 (1.91-2.91)
29-91 days	78	1.08 (0.84-1.39)	132	1.14 (0.94-1.39)

p for interaction<0.001

There was no modification of effect of AECOPD on risk of MI by either previous cardiovascular disease or use of cardiovascular drugs in the baseline period (Tables 6 and 7), or by age or sex.

Following MI, 517 COPD patients were censored within 6 months, and 832 were censored within 12 months. In the sensitivity analysis on individuals whose observation time was not censored significantly following MI, results were similar to, but slightly smaller in magnitude than the main analysis (supplementary material). In the sensitivity analysis which excluded the period of stable time prior to the initial AECOPD in each patients' observation period, the 91 day period following AECOPD was associated with a slightly higher risk of MI compared to the main analysis (supplementary material).

Table 6: Incidence rate ratios of first myocardial infarction in risk periods after a acute exacerbation of COPD (AECOPD) relative to stable periods and interactions with cardiovascular drugs

			Cardiovascular drug					
	All time periods (same as table 1 column 1)		Statin		Aspirin		Beta-blocker	
Risk period	**N outcome events (MI)**	**IRR (95% CI)**	**N outcome events (MI)**	**IRR (95% CI)**	**N outcome events (MI)**	**IRR (95% CI)**	**N outcome events (MI)**	**IRR (95% CI)**
Total risk period (91 days)	883	1.65 (1.50-1.81)	261	1.60 (1.35-1.89)	250	1.72 (1.45-2.04)	204	1.64 (1.36-1.98)
1-3 days	90	2.80 (2.26-3.49)	27	2.77 (1.86-4.12)	29	3.40 (2.32-5.00)	26	3.62 (2.41-5.44)
4-7 days	97	2.38 (1.93-2.93)	27	2.19 (1.47-3.26)	24	2.22 (1.49-3.38)	26	2.85 (1.90-4.29)
8-14 days	159	2.36 (1.99-2.80)	55	2.70 (2.02-3.62)	49	2.75 (2.02-3.73)	36	2.39 (1.68-3.40)
15-28 days	213	1.91 (1.64-2.21)	57	1.68 (1.26-2.24)	59	1.97 (1.49-2.62)	43	1.70 (1.23-2.36)
29-91 days	324	1.17 (1.04-1.33)	95	1.13 (0.89-1.42)	89	1.17 (0.92-1.48)	73	1.11 (0.86-1.44)

p-value for interaction statin = 0.671
p-value for interaction aspirin = 0.454
p-value for interaction β-blocker = 0.579

Table 3: Incidence rate ratios of first myocardial infarction in risk periods after an acute exacerbation of COPD (AECOPD) relative to stable periods stratified by previous non-MI cardiovascular disease

	Previous non-MI cardiovascular disease													
	Any		**None**		**Heart failure**		**No heart failure**		**Angina**		**No angina**		**Stroke**		**No stroke**	
Risk period	**N outcome events (MI)**	**IRR (95% CI)**	**N outcome events (MI)**	**IRR (95% CI)**	**N outcome events (MI)**	**IRR (95% CI)**	**N outcome events (MI)**	**IRR (95% CI)**	**N outcome events (MI)**	**IRR (95% CI)**	**N outcome events (MI)**	**IRR (95% CI)**	**N outcome events (MI)**	**IRR (95% CI)**	**N outcome events (MI)**	**IRR (95% CI)**
Total risk period (91 days)	207	1.18 (1.02-1.36)	676	1.36 (1.23-1.49)	56	1.22 (0.92-1.61)	827	1.31 (1.20-1.42)	149	1.13 (0.96-1.34)	734	1.35 (1.23-1.48)	42	1.39 (0.99-1.96)	841	1.29 (1.19-1.40)
1-3 days	21	1.98 (1.37-2.86)	69	2.14 (1.67-2.74)	8	2.18 (1.13-4.18)	82	2.08 (1.68-2.59)	11	2.34 (1.86-2.92)	79	1.38 (0.85-2.26)	9	4.39 (1.31-8.34)	81	1.97 (1.58-2.44)
4-7 days	22	1.40 (0.95-2.06)	75	1.85 (1.46-2.34)	5	1.36 (0.66-2.79)	92	1.74 (1.41-2.14)	17	1.78 (1.42-2.24)	80	1.46 (0.95-2.23)	4	0.94 (0.30-3.00)	93	1.75 (1.42-2.14)
8-14 days	32	1.71 (1.29-2.27)	127	1.81 (1.50-2.19)	9	2.04 (1.26-3.31)	150	1.75 (1.48-2.07)	24	1.77 (1.48-2.12)	135	1.80 (1.32-2.44)	6	1.88 (0.97-3.67)	153	1.78 (1.51-2.09)
15-28 days	52	1.34 (1.05-1.72)	161	1.56 (1.32-1.83)	14	1.11 (0.67-1.83)	199	1.53 (1.33-1.76)	38	1.56 (1.34-1.82)	175	1.26 (0.95-1.69)	11	1.94 (1.14-3.30)	202	1.46 (1.27-1.68)
29-91 days	80	0.86 (0.70-1.06)	244	1.02 (0.89-1.16)	20	0.94 (0.64-1.37)	304	0.97 (0.87-1.09)	59	1.01 (0.89-1.15)	265	0.85 (0.67-1.07)	12	0.49 (0.43-1.37)	312	0.98 (0.87-1.10)

Any CVD p for interaction= 0.671
Angina p for interaction = 0.162
HF p for interaction = 0.793
Stroke p for interaction = 0.679

Discussion

We have demonstrated that the weeks following AECOPD represent an increased risk of MI for those with COPD. In the days following AECOPD the risk of MI is almost three times as high as baseline, and falls down to the baseline level after around four weeks. The increased risk is higher for those AECOPD which result in hospitalisation. We also found that the relative increased risk of MI following AECOPD is higher for infrequent exacerbators, those with greater airflow limitation, and is higher following a non-STEMI than STEMI.

Our finding that AECOPD is associated with a transient increased risk of MI confirms previous work which has suggested that AECOPD are associated with MI[14,15] and myocardial injury[22]. In an analysis of 426 COPD patients and using prescription of antibiotics and oral steroids as a definition of AECOPD, Donaldson et al. also found an increased risk of MI associated with AECOPD, but this was limited to the first 5 days following AECOPD onset. Our large study size and validated exposure measures meant that we could estimate a more precise effect size and length of increased risk. Broadly, our results are comparable with those from Smeeth et al.[13], who investigated the relationship between lower respiratory tract infection (LRTI) and risk of MI in 20,921 people from the general population. Smeeth et al. found a five-fold increased risk of MI in the 3 days following LRTI, which declined towards baseline over time, but lasted over 4 weeks. The higher risk of MI following LRTI in the general population compared to AECOPD may be due to a smaller relative difference in inflammation between AECOPD/LRTI and stable periods for those with COPD. Alternatively, those with COPD may attend their GP with milder LRTI (in terms of inflammatory burden) than would those from the general population. Compared to previous work, this study was able to provide much more precise information on the magnitude and duration of increased risk of MI associated with AECOPD, investigate the effect of severe AECOPD compared to moderate events. In addition this study had the necessary power to stratify the analysis to identify important effect modifiers which should inform future work on the pathophysiology of increased risk of MI associated with AECOPD and potential interventions to mitigate this risk.

We found an eight-fold increased risk of MI in the first 3 days following hospitalised AECOPD, compared to a two-fold increased risk for moderate events, suggesting a dose-response relationship to severity of AECOPD. Additionally, our results suggest that risk of MI increases again at around 8-14 days after falling for the first 7 days following moderate but not severe AECOPD. This could be a chance finding, however the timing may correspond to secondary bacterial infection in those with a viral exacerbation[23].

Previous studies have suggested that frequent exacerbators have higher risk of MI[14]. Our study found that the effect of AECOPD in risk of MI was lower for infrequent exacerbators. Crucially, our study compared relative risk of MI during AECOPD to participant's own stable periods, not risk of MI between people. One explanation could be that frequent exacerbators have a higher risk of MI during stable periods (due to perhaps increased baseline inflammation), and thus there is less of a relative difference between stable and exacerbation periods for them. Indeed, as most of this sample of COPD patients with a first MI and at least one AECOPD were frequent exacerbators, this suggests that overall, frequent exacerbators do have a higher risk of MI than infrequent exacerbators.

Previous studies have found that increased airflow limitation is associated with increased risk of MI [24]. This is reflected in our finding that COPD patients with worse airflow limitation are more susceptible to the effects of AECOPD on risk of MI than those with lesser limitation. Although there may be other differences between these patients, this finding points to the possibility that acutely worsening airflow limitation during AECOPD may be involved in the increased risk of MI associated with AECOPD. This finding lends support to the idea that AECOPD may be a risk factor for type-2 MI; which are a result of mismatch of myocardial supply and demand of oxygen, but not due to plaque rupture[25].

We have previously demonstrated that after adjusting for age, sex, smoking status, and co-morbidities, people with COPD and acute MI are more likely to have a non-STEMI than a STEMI, compared to people without COPD with acute MI [26]. Our finding that the effect of AECOPD on MI is higher for non-STEMIs may go some way in explaining these excess non-STEMIs in those with COPD.

We did not find that aspirin, beta-blockers, or statins modified the effect of AECOPD on risk of first MI. This is not evidence that these medicines do not prevent MI associated with AECOPD, but suggests that the particular risk of MI associated with AECOPD may not be mitigated by use of these medicine. However, this finding might be explained by the definition of medicine use.We defined medicine use at baseline rather than as a time-varying effect modifier as prescription of these drugs are very much more likely after acute MI. Since we only included first MIs in the analysis, this period would be associated with an apparent rate of MI of zero, and as such would have resulted in bias had we used a time-varying definition of cardiovascular medicines. This approach, however, may have resulted in underestimation of any effect modification by these medicines. We also did not find evidence that previous non-MI cardiovascular disease modified the risk of MI associated with AECOPD.

Our study has several implications, firstly, our findings suggest that AECOPD may explain some of the increased cardiovascular risk in those with COPD, particularly the increased risk of non-STEMI. AECOPD are known to drive mortality in those with COPD, and our findings are another reason that clinicians should focus on preventing AECOPD. However, the recently reported SUMMIT trial[27], which investigated the effects of vilanterol and fluticasone furoate did not find a reduction in cardiovascular events despite a reduction in AECOPD. However, most of the SUMMIT population had previous coronary artery disease. It is difficult to disentangle the effects of treatment of AECOPD on MI from the effects of AECOPD itself. In order to investigate this, future studies should collect detailed information on the use of medicines during AECOPD. Further analyses should also investigate the relationship between AECOPD and risk of stroke, and the effect of pneumonia in people with COPD on risk of MI. Finally, clinicians should be aware that COPD patients are at higher risk of MI in the weeks following an AECOPD.

Our study had several strengths. Firstly, the within person nature of the study design meant that there was no confounding between individuals included in the study, such as the effects of sex, genetics, long term medicine use and socioeconomic status. In addition, compared to previous studies, we used a validated definition of AECOPD in EHR which allowed us to accurately identify AECOPD and we used linked secondary care HES data to categorise them as moderate (GP treated) or severe (hospital treated). In addition, we obtained data on MI events from both primary and linked HES data which allowed us to identify more MI[28]. Previous work has shown that data from both primary and secondary care are necessary to identify adequate numbers of MI. Another strength of our study was the size, compared to previous work in similar populations, our study was significantly larger. This increased power allowed us to confirm previous findings in a larger sample, and to give a more precise estimate of both the size and duration of the effect.

Our study also has some weaknesses. Although our study is without between-person confounding, there is still potential for within-person confounding by factors which vary over time. In order to deal with time-varying confounders, we split time up into two year age bands and adjusted for these. In addition, we specifically adjusted for the effects of season. However, our study could still be susceptible to time-varying confounders if these correlated very closely in time with AECOPD, such as the use of treatments for AECOPD. Additionally, our study may have been susceptible to misclassification of AECOPD and MI. We have previously demonstrated that people with COPD have delayed diagnosis of MI[26], if these events are originally diagnosed as AECOPD, this may result in a spurious association between AECOPD and MI. However, to reduce the impact of this bias we excluded the first day of AECOPD

from the analysis, and used a validated algorithm for identifying AECOPD[16]. Such a bias is very unlikely to explain a substantial proportion of the effect however, as the effect of AECOPD in the risk of MI lasted for several weeks. Finally, due to the case-only nature of the study design, it was not possible to examine absolute measures of effect.

Conclusions

Compared to stable periods, people with COPD are at higher risk of MI in the weeks following AECOPD. In the first 3 days following AECOPD onset, the increased risk of MI peaks at around a doubling of risk for primary care treated AECOPD, and an eight-fold increased risk for severe AECOPD. The relative effect of AECOPD on risk of MI is higher for infrequent exacerbators, and for those with more severe airflow limitation.

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9.3 Summary

- AECOPD represent a period of increased risk of MI for those with COPD
- The increased risk of MI peaks during the first three days following AECOPD onset and falls back to baseline levels after four weeks
- The effect of AECOPD on risk of MI is higher for: AECOPD which result in hospitalisation, infrequent exacerbators, those with more severe airflow limitation, and for non-STEMIs compared to STEMIs
- The increased risk of MI associated with AECOPD does not appear to explain the effect modification of the risk of MI associated with COPD by age
- Cardiovascular medicines (at least those used at baseline) do not appear to modify the effect of AECOPD on the risk of MI

Chapter 10 Overall Discussion

This chapter provides an overall summary of the findings for each of the aims of this thesis, highlights some of the important strengths and limitations of each of the studies and provides recommendations, both for practice and future research.

10.1 Aim 1: Understanding MI and outcomes after MI in those with COPD:

10.1.1 Systematic review of the risk of MI associated with COPD and AECOPD and risk of death after MI for those with COPD (Research paper I)

The systematic review and meta-analysis presented in Chapter 3 aimed to investigate 1) the risk of MI associated with COPD; 2) the risk of MI associated with AECOPD; and 3) the risk of death following MI in COPD patients compared to people without COPD.

The findings from the first aim, investigating the risk of MI associated with COPD, demonstrated that people with COPD have a higher risk of MI compared to those who do not have COPD, and this was evident even after adjusting for smoking status. Compared to previous systematic reviews on similar areas (Chen et al. 2015, Müllerova et al. 2013), the systematic review presented here focussed on incident MI, rather than both incident and prevalent MI. Thus, inferences could be drawn about risk of MI associated with COPD. One limitation of this study was that only one study (Feary et al. 2010) reported risk of MI associated with COPD after adjusting for smoking status, and there is the possibility of residual confounding by smoking. Results from those studies which did not adjust for smoking status could not be pooled due to high levels of statistical heterogeneity.

For the second aim of the systematic review, investigating the risk of MI associated with AECOPD, only two studies (Donaldson et al. 2010, Halpin et al. 2011) were found which investigated the risk of MI associated with AECOPD. Both of these studies used within person designs to investigate the risk of MI during AECOPD compared to participant's own stable periods. Although both studies demonstrated a higher risk of MI associated with AECOPD, conclusions were limited as both studies included a small number of participants, and uncertainly about the validity of exposure definitions (Donaldson et al. 2010). Due to heterogeneity in study designs, a meta-analysis of these results was not possible.

For the third aim of the systematic review, investigating the risk of death following MI for those with COPD, following meta-analysis, there was weak evidence that those with COPD have higher in-hospital mortality following MI compared to non-COPD patients. There was strong

evidence that those with COPD had higher levels of mortality in longer term following MI. However, both of these associations were modest in size. Although an increased risk of death following MI for those with COPD was demonstrated, the cause was uncertain. The increased risk could have been due to factors relating to the MI, for example COPD patients having more severe events; factors relating to COPD or associated characteristics, such as death from COPD or lung cancer; or factors relating to the differences in care after MI which others have demonstrated (Stefan et al. 2012).

10.1.2 Closing the mortality gap after a myocardial infarction in people with and without Chronic Obstructive Pulmonary Disease (Research paper II)

Following the findings of aim 3 of the systematic review, the study presented in chapter 4 aimed to 1) investigate the risk of death following MI for COPD patients compared to people without COPD; 2) to investigate any differences in recognition and management following MI between people with and without COPD; and 3) to investigate the extent that any difference may be explained by differences in recognition and management of MI at the population level.

The findings demonstrated that both in-hospital and 180-day mortality were higher for COPD patients compared to people without COPD. The effect of COPD on risk of death remained after adjustment for age, sex, smoking status and other co-morbidites, and was higher for non-STEMIs than STEMIs.

For both STEMIs and non-STEMIS, people with COPD had a delay in diagnosis of MI. For those with a delay in diagnosis following a STEMI, people with COPD had a longer time to reperfusion. COPD patients were less likely to have angiography in hospital following a non-STEMI or reperfusion following a STEMI. COPD patients were less likely to be prescribed secondary prevention medicines at discharge following an MI, notably for β-blockers.

Delay in diagnosis, and timing and use of reperfusion after a STEMI explained some of the in-hospital mortality difference between people with and without COPD. A larger proportion of the difference in 180-day mortality was explained by the use of secondary prevention drugs at discharge.

Delay in diagnosis and use of angiography after a non-STEMI explained some of the mortality difference between people with and without COPD. For 180-day mortality, delay in diagnosis, use of angiography in-hospital, and use of secondary prevention medicines at discharge all explained some of the difference in mortality between people with and without COPD. .

The strengths of this study were the large size and the representative nature of the data. In addition, information on patient care during admission was available, which is not true of other hospital based EHR datasets, such as HES. The findings presented on the effects of treatment are however observational, and may be susceptible to residual confounding.

10.1.3 Chronic obstructive pulmonary disease and acute myocardial infarction: effects on presentation, management, and outcomes (Research paper III)

The research paper presented in Chapter 5 aimed to review the evidence for differences in presentation, management and outcomes between people with and without COPD following MI.

There is good evidence that COPD patients have atypical presentation of MI, and on average have lower peak levels of troponin after acute MI compared to people without COPD.

Several studies found that the increased risk of death following MI associated with COPD was higher for younger people than older people with COPD. Other studies have found an increased risk of incident heart failure following MI for COPD patients compared to people without COPD. This is one possible mechanism behind the increased risk of death for those with COPD. No studies found evidence of an increased risk of re-current MI, stroke, or angina for those with COPD compared to non-COPD patients.

10.1.4 Predicting mortality after acute coronary syndromes in people with chronic obstructive pulmonary disease (Research paper IV)

The study presented in chapter 6 aimed to: 1) investigate whether the GRACE score performs as well at predicting the risk of death at 6 months following admission to hospital for ACS in people with COPD compared to those without; and 2) to investigate if the GRACE score could be amended to perform better for those with COPD.

For aim 1, it was found that the GRACE score does not perform as well in COPD patients as it does in people without COPD, and tends to underestimate risk of death for those with COPD. COPD patients with the same GRACE score as people without COPD had a 30% higher risk of dying at 6 months following admission for ACS.

For aim 2, both re-specifying the GRACE score model including a variable for COPD and multiplying the risk of death following ACS by 1.3 resulted in better performance of the GRACE score for those with COPD.

The strengths of this study, again, like the previous study using this data, were the large size and representativeness. In addition, the results of the study are presented in a way which can be easily implemented.

The limitations of this study were that a measure of severity of acute heart failure was not available in the MINAP dataset, and a proxy for this had to be used. In addition, although internal validation was conducted, findings were not validated externally.

10.1.5 Recommendations for practice

Clinicians should be aware that people with COPD are at higher risk of MI, and this risk is independent of smoking status.

Clinicians should also be aware that people with COPD are more likely to have an atypical presentation of MI, and that this may lead to a delay in diagnosis of MI. Delay in diagnosis of MI, reduced use of reperfusion and angiography in-hospital, and secondary prevention drugs (particularly) beta-blockers seem to contribute to the increased risk of death following MI for those with COPD. Efforts should be made to ensure that COPD patients receive guideline recommended investigation and treatment, where appropriate.

When calculating the predicted risk of death at 6 months following MI using the GRACE score, clinicians should multiply the risk of death by 1.3 for COPD patients to ensure that risk of death for COPD patients is not underestimated. As this predicted risk of death is used to determine eligibility for more early aggressive treatment following non-STEMI or UA (NICE 2010), accurate risk stratification is important to ensure that COPD patients receive guideline recommended treatment. Current guidelines recommend that after a non-STEMI or UA those with a moderate or higher risk of death at 6 months (higher than 3%) should receive more early aggressive treatment. Multiplying that risk of death by 1.3 for those with COPD would result in one third of those previously categorised as low risk being re-categorised as moderate risk, and therefore should be considered for more aggressive treatment.

10.1.6 Recommendations for research

It is currently unclear why COPD patients have an increased risk of MI compared to people without COPD, and further work is needed to investigate this. Researchers should also investigate which COPD patients are at particular risk of MI, and if this risk can be modified. The relationship between AECOPD and MI should be investigated further, using validated exposure measures, and this is the subject of a subsequent chapter of this thesis.

As well as delay in diagnosis of MI for people with COPD, it is possible that MIs might be completely missed for some of these patients, and this should be investigated. As the MINAP data used for the studies presented here is now three years old, some practices may have improved since then, and differences in management between people with and without COPD should be re-visited in the future. Future studies may also wish to relate differences in management to outcomes other than death, such as development of heart failure.

Although differences in the performance of the GRACE score may explain some of the difference in treatment after MI for people with and without, there may be other reasons.

10.2 Aim 2: Improving the definitions of AECOPD in EHR

10.2.1 Validation of the recording of acute exacerbations of COPD in UK primary care electronic healthcare records (Research paper V)

The aim of the study presented in chapter 7 was to validate the recording of AECOPD in UK primary care EHR. For this study, 15 different EHR algorithms were tested against a reference standard of respiratory physician review of questionnaires, additional material sent by GPs, and free-text information.

The findings indicated that only those algorithms which used code for LRTI, AECOPD, prescription of antibiotics and steroids for 5-14 days, and a symptom definition of AECOPD when combined with prescription of either antibiotics or steroids had an acceptable PPV (>75%). When these algorithms were combined, this resulted in an AECOPD definition which had a PPV of 85.5%, and a sensitivity of 62.9%.

The strengths of this study were the size of the sample, and the detailed information which was obtained from GP records, including free-text information, which was used by respiratory physicians when reviewing events. However, as there is no single diagnostic test for AECOPD, the results of the reference standard (respiratory physician review) are still, to an extent, a judgment. In addition, the sensitivity of the definition was relatively lower.

10.2.2 Recording of hospitalisations for acute exacerbations of COPD in UK primary and secondary care electronic healthcare records (Research paper VI)

The aim of the study presented in chapter 8 was to investigate how hospitalisations for AECOPD were recorded in primary and secondary care EHR, and to determine whether a valid definition of AECOPD hospitalisation in primary care EHR could be constructed.

Using discharge summaries, a definition of recording of hospitalisation for AECOPD in HES was validated. Using a combination of a specific ICD-10 code for AECOPD or LRTI in any diagnostic position, or an ICD-10 code for COPD in the first position, resulted in a definition with a sensitivity of 87.5%. This HES definition was then used as a reference standard for testing the validity of primary care EHR definitions of hospitalisation for AECOPD.

Two primary care EHR definitions were tested against the HES reference standard: 1) AECOPD hospitalisation code; and 2) AECOPD identified by the previously validated algorithm on the same day as a code suggesting hospitalisation. Both of these definitions had very modest PPVs (<55%), and had even lower sensitivities (<6%). Delay in recording of hospitalisation by GPs could not account for the low apparent validity. Many of the AECOPD hospitalisations appeared to be recorded using either an AECOPD code, or a code suggesting hospitalisation, but not both. Further, there was evidence that many hospitalisations for AECOPD were recorded using even less specific codes.

One of the major strengths of this study was the size, we included information from linked data for over 27,182 patients with COPD. The study was limited however by the lack of information on PPV for the HES definition of AECOPD hospitalisation. However, when several different possible definitions of HES were used as a reference standard in sensitivity analysis, this did not change the findings.

10.2.3 Recommendations for practice

In future, studies should use the validated definition of AECOPD in UK primary care EHR presented here. These will not only be useful for observational studies, but may also be used for RCTs run within the EHR. Researchers should not attempt to identify AECOPD using prescription of either antibiotics or oral steroids alone, or a symptom definition of AECOPD alone, as these definitions are associated with a low PPV. These definitions will also be useful for identifying AECOPD for service planning and for national and local audits. To identify hospitalisations for AECOPD, researchers should use linked primary and secondary care data, as definitions based on primary care data alone are not likely to be valid.

Although accurate coding of AECOPD and hospitalisations for AECOPD in EHR is important for secondary users of data, it is also important for clinical care. Given the importance of AECOPD for decisions on patient management, GPs should have easy access to information on the number of recent AECOPD that patients have had. Primary care clinicians should therefore consider coding AECOPD in a more precise way.

10.2.4 Recommendations for research

There is room for improvement in GP recording of AECOPD. Possible solutions to this are the use of training or incentives for GPs to improve the way they code diagnoses, or a reduction in the number of Read codes available. Other researchers may wish to investigate whether these solutions are effective.

In the future, researchers may wish to investigate the PPV of HES definitions of AECOPD. In particular, attention should be paid to investigating the misclassification between AECOPD and admissions to hospital for pneumonia for those with COPD.

Validity of primary care definitions of cause-specific hospitalisation for other diseases may also be poor, and further research should be conducted on the validity of primary and secondary care recording of hospitalisation for other diseases.

10.3 Aim 3: Improve the understanding of the relationship between AECOPD and risk of MI

10.3.1 Risk of myocardial infarction associated with acute exacerbations of COPD: A self-controlled case series (Research paper VII)

The ultimate aim of this thesis, and the aim of the study presented in Chapter 9 was to investigate the risk of MI associated with AECOPD. This study extended the findings of previous studies (Donaldson et al. 2010, Halpin et al. 2011) by providing a more precise estimate of the size and duration of the effect of AECOPD on MI. In addition, increased power meant that this study was able to investigate effect modification of the effect of AECOPD on the risk of MI. The use of linked data also meant that effect modification by severity of AECOPD on the risk of MI could be investigated.

The self-controlled case series findings indicated that AECOPD are temporally associated with risk of MI. The risk of MI increases immediately after onset of AECOPD, and peaks at a relative risk of around 2.8 for the first 3 days following onset of AECOPD before declining to almost baseline levels after around four weeks. The effect of AECOPD was higher (around an 8 fold increase in risk of MI in the first 3 days following AECOPD onset) for those events which resulted in hospitalisation, demonstrating a dose response relationship between severity of AECOPD and risk of MI.

Both exacerbator phenotype and GOLD stage of airflow limitation modified the effect of AECOPD on risk of MI, with the effect of AECOPD on risk of MI being higher for infrequent

exacerbators and those with more severe airflow limitation. In addition, the effect of AECOPD on risk of MI was higher for non-STEMIs than STEMIs.

One of the major strengths of this study was the within-person nature of the comparisons, which meant that fixed confounders were implicitly controlled for. In addition, validated definitions of both AECOPD and MI were used.

The study also had a relatively large size, which meant power was available to precisely estimate the magnitude and duration of the increased risk of MI following AECOPD. Increased power also meant that stratified analysis could be carried out to investigate potential effect modification, which may inform future studies into the pathophysiology around the increased risk of MI and into interventions to mitigate this risk.

Although confounding from fixed factors was eliminated by the study design, there may still have been confounding from time-varying confounders. Although this was minimised by adjusting for age bands, confounders which vary very closely in time with AECOPD, such as medicines, may still have been an issue.

Misclassification of AECOPD and MI may have biased the results of this study. A particular concern is that an MI may have been originally coded as an AECOPD before being coded as an MI, this would induce a spurious association between AECOPD and MI. Although validated definitions of AECOPD and MI were used, this may still have been a problem for this study. This is unlikely to have explained the whole association, however. In addition, when the exposure time following AECOPD was segmented, the risk of MI was higher for several weeks following onset of AECOPD, and this pattern is unlikely to have occurred if the association were entirely spurious. The algorithm used to identify AECOPD had a relatively lower sensitivity (63%) which would have meant that up to around one third of time which should have been "exposed time" is likely to have been classified as baseline time. This is not likely to be an explanation for the findings of the self-controlled case series, however, as this misclassification would probably have resulted in bias towards, rather than away from, the null.

10.3.3 Recommendations for practice

There is a large burden of CVD in those with COPD, and preventing MI associated with AECOPD by preventing AECOPD may be a good way to reduce CVD in those with COPD. As the MIs associated with AECOPD in this study did not seem to be "harvested", that is the period of higher risk was not followed by a period of lower risk, preventing MI associated with AECOPD may be a good strategy for lowering MI overall in those with COPD. Clinicians should be aware that the weeks following AECOPD (or apparent AECOPD) are a period of

higher risk of MI for people with COPD. This is especially true for AECOPD which result in hospitalisation.

10.3.4 Recommendations for research

The mechanism behind the increased risk of MI associated with AECOPD is currently unclear, and the findings from this study are compatible both with increased risk due to increased systemic inflammation or increasing airflow limitation during AECOPD. Future studies should investigate these possibilities.

Age was not found to be an effect modifier for the effect of AECOPD on the risk of MI. The effect of COPD on risk of MI appears to be higher for younger patients (Feary et al. 2010), and as found in previous chapters, the impact of age on mortality (and prediction of mortality) is higher for younger patients. The effect of AECOPD on risk of MI does not appear to explain this, and researchers should investigate other reasons for this effect.

Although this study did not find that cardiovascular medicines modified the risk of MI associated with COPD, this study defined use of these medicines at baseline in order to prevent bias. The investigation of potential effect modification by these medicines would perhaps be better investigated using time-varying effect modifiers in a cohort study. Future studies should also be conducted to investigate any potential effect modification by COPD medicines in a similar way.

COPD patients are at high risk of developing pneumonia (Crim et al 2009), and as these events are likely to represent a higher inflammatory burden than AECOPD, they may be associated with an even higher risk of MI. Future studies should investigate this potential relationship, and any factors which might modify the risk of MI associated with pneumonia.

Recent work on AECOPD has focussed on different distinct "clusters" of AECOPD defined by different inflammatory patterns or causes (Bafadhel et al. 2011), future researchers may wish to investigate whether the risk of MI associated with AECOPD is modified by type of AECOPD.

10.4 Overall conclusions

There is a large burden of cardiovascular disease in those with COPD. People with COPD are at higher risk of cardiovascular disease than people without COPD, and cardiovascular disease is a common cause of death for people with COPD. People with COPD are at higher risk of MI than people without COPD.

People with COPD are also at higher risk of death following MI than people who do not have COPD. This increased risk of death may be partly explained by differences in recognition and management between people with and without COPD. Current risk scores which stratify risk of death following MI do not perform as well in people with COPD compared to those without COPD, and tend to underestimate risk of death for people with COPD. More accurate prediction of risk of death for people with COPD may result in more people with COPD being considered for more aggressive treatment.

AECOPD and hospitalisations for AECOPD can be identified accurately in EHR, however primary care EHR data should not be used alone to identify hospitalisations for AECOPD.

The weeks following AECOPD represent a period of increased risk of MI for people with COPD. This risk peak in the first three days following AECOPD onset and persists for at least four weeks before returning to almost baseline levels. The effect of AECOPD on the risk of MI is higher for AECOPD which result in hospitalisation, for infrequent exacerbators, those with more severe airflow limitation, and following non-STEMI.

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Appendices

Appendix A – Additional material for Chapter 3 – Research paper I

MEDLINE search strategy

1. Lung Diseases, Obstructive/
2. exp Pulmonary Disease, Chronic Obstructive/
3. (chronic$ adj3 bronchiti$).tw.
4. (obstruct$ adj3 (pulmonary or lung$ or airway$ or airflow$ or bronch$ or respirat$)).tw.
5. COPD.tw.
6. COAD.tw.
7. COBD.tw.
8. AECB.tw.
9. emphysema$.tw.
10. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11. exp Myocardial Infarction/
12. MI.tw.
13. acs.tw.
14. exp Acute Coronary Syndrome/
15. (myocardial adj3 infarction$).tw.
16. (heart adj3 attack$).tw.
17. (acute adj3 coronary adj3 syndrome$).tw.
18. (coronary adj3 infarc$).tw.
19. (myocardial adj3 thrombos$).tw.
20. (coronary adj3 thrombos$).tw.
21. 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
22. 10 and 21

Quality assessment detailed study (or analysis) level results.

Risk of MI associated with COPD

Comparability between the exposed and unexposed groups was a major problem, with none of the reports being completely classed as low risk of bias for this item. The main reason for studies being high risk of bias for this item was that they did not adjust for smoking status as this was not available in several of the administrative healthcare databases which were used in these studies. The case control analyses reported in Rodriguez 2010(Rodriguez, Wallander et al. 2010) and Schneider 2010(Schneider, Bothner et al. 2010), however, were assessed as lower risk of bias for comparability between groups. Another common problem was lack of representativeness of the exposure group. In 3/8 studies representativeness was assessed as higher risk of bias. Some of these studies only included those with a recent diagnosis of COPD

and followed up for a short period after. Others only classified patients with COPD if they attended secondary care for their COPD and so are likely only to have included patients with more severe COPD.

Risk of MI associated with AECOPD

In general the two studies included under this research question were assessed as lower risk of bias for most items. Donaldson 2010(Donaldson, Hurst et al. 2010) was unclear risk of bias for selection and representativeness of exposed and un-exposed groups as the method used to identify AECOPD has not been validated. Halpin 2011(Halpin, Decramer et al. 2011) was assessed as higher risk of bias for selection of unexposed time as this compared only to 30 days prior to the AECOPD, not the entire stable period. This study was also considered to be at higher risk of bias under the "other bias" item as it appeared to be very underpowered (in total only 14 MIs were included, 1 during the 30 day pre-exacerbation period, and 13 in the 30 day post-exacerbation period) resulting in a very wide confidence interval (IRR 95% CI 1.71-99.1).

Risk of death after MI associated with COPD

Comparability between groups was again a problem for several of the studies included under this research question. Only 4/10 full text studies were assessed as lower risk of bias for comparability between groups. Again, the major problem was that several of the studies did not adjust for smoking status. Some studies were assessed as unclear risk of bias under some of the items of the selection domain as the definition of COPD used was unclear.

Figures S1-S3. Detailed study level risk of bias assessment.

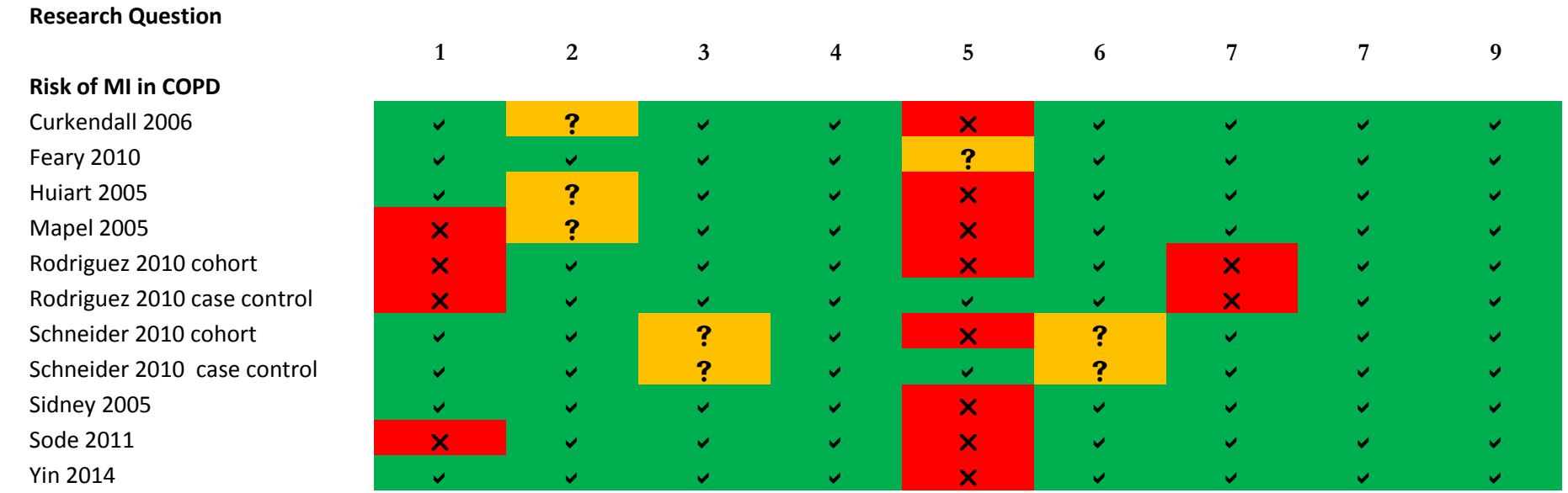

Figure S1. Detailed study level risk of bias assessment for the studies reporting risk of MI associated with COPD.

Figure S2. Detailed study level risk of bias assessment for the studies reporting risk of MI associated with AECOPD.

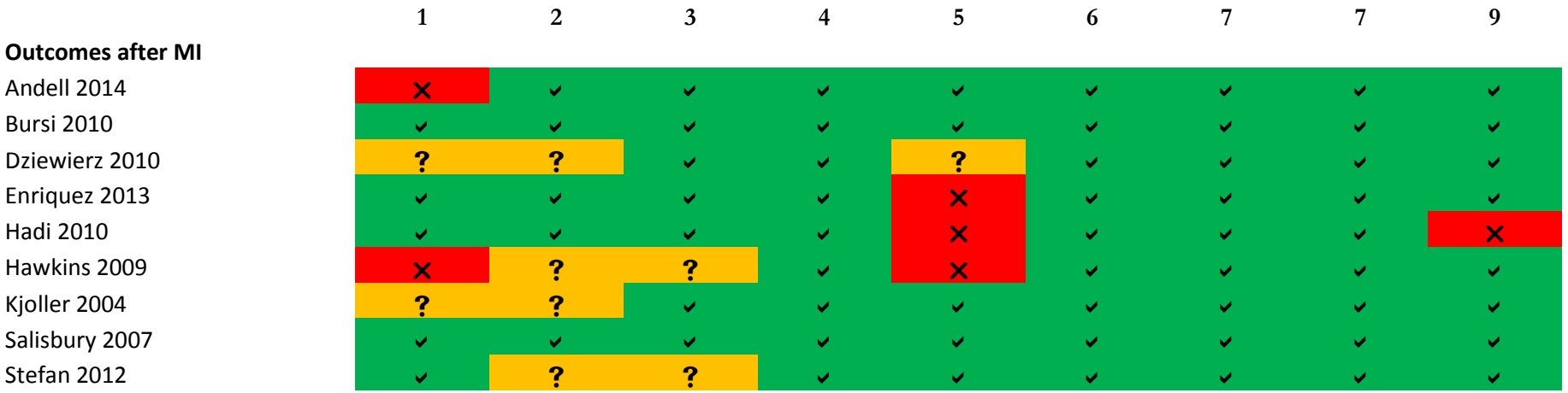

Figure S3. Detailed study level risk of bias assessment for the studies reporting risk of death following MI.

Key for figures S1-3

Selection	
Representativeness of exposed/cases	1
Selection of non-exposed/controls	2
Ascertainment of exposure/cases	3
Outcome of interest not present at start of study	4
Comparibility	

Comparability of groups on basis of desgin/analysis	5
Outcome	
Assessment of outcome	6
Follow up long enough for outcomes to occur	7
Adequacy of follow up	8
Other	9

✔ lower risk of bias ? unclear risk of bias ✘ higher risk of bias

.

Appendix B – Additional material for Chapter 4 – Research paper II

Supplementary figure – directed acyclic graph

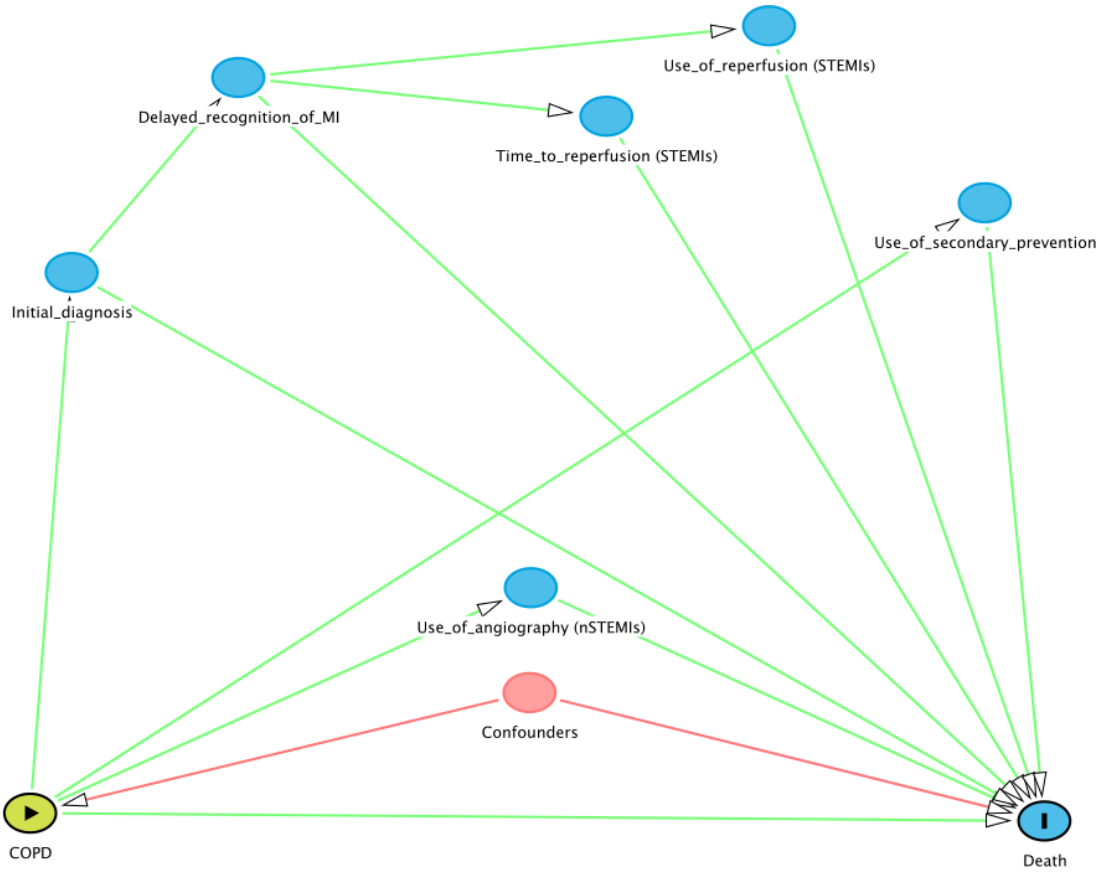

Figure S1. Directed acyclic graph used in the development of regression models.

Sensitivity analyses

As a sensitivity analysis, mortality after an MI was investigated comparing those who, for the purposes of this study, we presumed had asthma (those with a record of obstructive airway disease but no smoking history).

Additional analysis in optimal and sub-optimal care groups

We also compared mortality at 180 days for COPD patients and non-COPD patients within strata of optimal care, adjusted for age, sex, year, smoking status and co-morbidities. For STEMIs, patients were categorised as having optimal care if they had no delay in diagnosis, use of reperfusion and use of secondary prevention. For non-STEMIs, patients were categorised as having optimal care if they had no delay in diagnosis, use of angiography in-hospital, and use of secondary prevention. Sub-optimal care was defined as any factor missing from optimal care. We compared optimally treated COPD patients to optimally treated non-COPD patients; and non-optimally treated COPD patients to non-optimally treated non-COPD patients. We also compared mortality between those with optimal care and non-optimal care at 180 days among COPD patients.

Results

Difference in time to reperfusion between COPD patients and non-COPD patients among those without a delay in diagnosis

The difference in time to reperfusion between COPD and non-COPD patients was not apparent among patients who did not have a delay in diagnosis (median time to reperfusion 35.0 minutes (IQR, 21.8-63.4) for COPD patients, and 35.0 minutes (IQR, 21.8-61.2) for non-COPD patients). Adjusted analysis also showed no difference in time to reperfusion for COPD patients compared to non-COPD patients among those who did not have a delay in diagnosis (ratio of geometric means 1.03, 95% CI 1.00 to 1.05).

Sensitivity analysis with asthmatic patients

When in-hospital mortality after an MI was investigated for people who we presume to have asthma were compared to non-asthmatics, no difference in mortality was found in analysis adjusted for age, sex, smoking status, calendar year, co-morbidities and drugs on arrival (OR 1.05, 95% CI 0.89-1.24 for STEMIs; OR 1.05, 95% CI 0.91-1.22 for non-STEMIs).

Additional analysis in optimal and sub-optimal care groups

After a STEMI, the effect of COPD on mortality at 180 days in the non-optimal care group (OR 1.39, 1.29-1.51; non-optimally treated COPD patients compared to non-optimally treated non-COPD patients) was comparable to that in the optimal care group (OR 1.44, 1.08-1.94; optimally treated COPD patients compared to optimally treated non-COPD patients). After a non-STEMI, the effect of COPD on mortality at 180 days in the non-optimal care group (OR 1.53, 1.45-1.61; non-optimally treated COPD patients compared to non-optimally treated non-COPD patients) was lower than that in the optimal care group (OR 1.80, 1.36-2.37; optimally treated COPD patients compared to optimally treated non-COPD patients). Among COPD patients, having optimal treatment was associated with lower risk of death at 180 days after both a STEMI (OR 0.31, 0.23-0.42; optimally treated COPD patients compared to non-optimally treated COPD patients) and a non-STEMI (OR 0.34, 0.26-.43; optimally treated COPD patients compared to non-optimally treated COPD patients).

Appendix C – Additional material for Chapter 6 – Research paper IV

Table S1 Predicted and observed mortality using normal GRACE model stratified by year of admission.

	2006-2008			2009-2010			2012-2013		
GRACE predicted risk decile	**Average predicted mortality (%)**	**Observed mortality - non-COPD (%)**	**Observed mortality – COPD (%)**	**Average predicted mortality (%)**	**Observed mortality - non-COPD (%)**	**Observed mortality – COPD (%)**	**Average predicted mortality (%)**	**Observed mortality - non-COPD (%)**	**Observed mortality – COPD (%)**
1	1.3	0.8	0.8	1.3	0.5	0.7	1.3	0.6	1.1
2	2.5	1.6	3.2	2.5	1.3	2.4	2.5	1.0	1.7
3	4.0	3.0	5.9	4.0	2.5	3.8	4.0	1.7	4.5
4	5.0	3.9	7.6	5.0	3.2	6.0	5.0	2.5	6.0
5	6.5	5.5	9.2	6.5	4.6	7.3	6.4	3.3	6.2
6	8.9	8.6	13.3	8.9	7.2	12.6	8.9	5.4	10.4
7	12.4	12.4	18.7	12.4	11.1	17.9	12.4	8.4	13.7
8	17.2	18.8	24.8	17.2	16.8	22.0	17.2	14.4	18.4
9	26.6	30.3	35.3	26.6	27.5	32.5	26.6	23.0	27.8
10	48.5	46.6	50.8	48.3	44.5	48.0	48.7	39.8	43.6

Table S2 Changes in level of risk for COPD patients after modifications after a STEMI

	Multiplying risk by 1.3		
GRACE score predicted risk of death	**Low risk (<3%)**	**Moderate risk (3-6%)**	**High risk (≥6%)**
Low risk (<3%)	791 (60.4%)	519 (39.6%)	0 (0.0%)
Moderate risk (3-6%)	0 (0.0%)	499 (32.8%)	1,022 (67.2%)
High risk (≥6%)	0 (0.0%)	0 (0.0%)	5,564 (100.0%)
	Adding COPD into MINAP derived GRACE model		
GRACE score predicted risk of death	**Low risk (<3%)**	**Moderate risk (3-6%)**	**High risk (≥6%)**
Low risk (<3%)	1,171 (89.5%)	138 (10.5%)	7 (0.5%)
Moderate risk (3-6%)	423 (27.8%)	909 (59.8%)	188 (12.4%)
High risk (≥6%)	10 (0.2%)	587 (10.7%)	4,902 (89.1%)

Table S3 Changes in level of risk for COPD patients after modifications after a non-STEMI

	Multiplying risk by 1.3		
GRACE score predicted risk of death	**Low risk (<3%)**	**Moderate risk (3-6%)**	**High risk (≥6%)**
Low risk (<3%)	1,742 (65.3%)	924 (34.7%)	0 (0.0%)
Moderate risk (3-6%)	0 (0.0%)	912 (36.2%)	1,611 (63.9%)
High risk (≥6%)	0 (0.0%)	0 (0.0%)	10,603 (100.0%)
	Adding COPD into MINAP derived GRACE model		
GRACE score predicted risk of death	**Low risk (<3%)**	**Moderate risk (3-6%)**	**High risk (≥6%)**
Low risk (<3%)	1,909 (71.7%)	698 (26.2%)	55 (2.1%)
Moderate risk (3-6%)	184 (7.3%)	1,227 (48.8%)	1,105 (43.9%)
High risk (≥6%)	4 (0.0%)	289 (2.8%)	10,176 (97.2%)

Table S4 Changes in level of risk for COPD patients after modifications after unstable angina

	Multiplying risk by 1.3		
GRACE score predicted risk of death	**Low risk (<3%)**	**Moderate risk (3-6%)**	**High risk (≥6%)**
Low risk (<3%)	1,569 (70.3%)	664 (29.7%)	0 (0.0%)
Moderate risk (3-6%)	0 (0.0%)	589 (37.7%)	972 (62.3%)
High risk (≥6%)	0 (0.0%)	0 (0.0%)	4, 623 (100.0%)
	Adding COPD into MINAP derived GRACE model		
GRACE score predicted risk of death	**Low risk (<3%)**	**Moderate risk (3-6%)**	**High risk (≥6%)**
Low risk (<3%)	1,362 (61.1%)	746 (33.5%)	122 (5.5%)
Moderate risk (3-6%)	74 (4.8%)	656 (42.2%)	824 (53.0%)
High risk (≥6%)	1 (0.0%)	118 (2.6%)	4,449 (97.4%)

Multiple imputation and missing data

There were significant levels of missing data for creatinine (40%), systolic blood pressure (11%), and heart rate (11%). Missingness was associated with year of event, and was greatly reduced in events after 2008 (<10% missingness for all three variables).

As an additional analysis, we multiply imputed [1] values for serum creatinine, heart rate, and systolic blood pressure where these were missing. Predictor variables were all other GRACE score variables, COPD status and death at 6 months. As the missing variables were all continuous, we performed multiple imputation using multivariate normal regression using the "mi impute mvn" command in Stata 14.1 MP. We imputed 30 additional datasets and used these to test our modifications to the GRACE score estimated probability of death. We did this using logistic regression to compare mortality at 6 months after admission

The findings from the multiple imputation analysis indicated that GRACE scores underestimate the risk of death for people with COPD, that adding COPD to the GRACE score model would

fix this problem, and that multiplying GRACE score predicted probability of death by 1.3 was a good approximation to adding COPD to the model.

Table S5 Results of multiple imputation analysis

GRACE model or modification	OR (95% CI)
Normal GRACE model	1.39 (1.36-1.43)
Normal GRACE model x 1.3 for COPD patients	0.95 (0.92-0.98)
MINAP derived model	1.34 (1.30-1.39)
MINAP derived model with smoking	1.42 (1.36-1.47)
MINAP derived model with COPD	1.02 (0.99-1.06)

References

1. Carpenter JR, Kenward MG. Multiple imputation and its application. New York: Wiley, 2013

Appendix D– Additional material for Chapter 7 – Research paper V:

Supplementary table 1 Comparison of responders and non-responders

Characteristic	Responder N	Responder %	non responder N	Non responder %	Chi^2 p-value
Age group					0.073
≤55	212	21.5	111	28.0	
55 to 64	359	36.3	133	33.5	
65 to 74	301	30.5	107	27.0	
≥ 75	116	11.7	46	11.6	
Sex					0.850
Male	481	48.7	191	48.1	
Female	507	51.3	206	51.9	
MRC breathlessness scale					0.170
≥3	449	47.3	195	51.5	
< 3	501	52.7	184	48.6	
BMI					0.520
< 19	39	4.0	17	4.3	
19 - 25	353	35.7	129	32.5	
≥25	596	60.3	251	63.2	
Record of cardiovascular disease					0.090
No	731	74.0	311	78.3	
Yes	257	26.0	86	21.7	
Record of asthma					0.380
No	482	48.8	204	51.4	
Yes	506	51.2	193	48.6	
Record of GORD					0.260
No	729	73.8	281	70.8	
Yes	259	26.2	116	29.2	
GOLD stage					0.330
1	76	12.8	39	16.7	
2	285	48.1	113	48.5	
3	185	31.3	61	26.2	
4	46	7.8	20	8.6	
Smoking status					0.220
Ex-smoker	447	45.2	194	48.9	
Current smoker	541	54.8	203	51.1	

Index of multiple deprivation quintile					<0.001
1 (least deprived)	152	15.4	32	8.1	
2	213	21.6	55	14.0	
3	188	19.1	64	16.2	
4	216	21.9	100	25.4	
5 (most deprived)	216	21.9	143	36.3	

Supplementary Table 2. PPV and sensitivity for algorithms not excluding annual review dates and dates on which rescue packs were prescribed

Algorithm	N events identified	N events confirmed by reference standard	PPV (95% CI)	N events identified in last year	N extra events identified by GPs in last year	Sensitivity (95% CI)
1.OCS prescription for 5-14 days	1285	910	70.8 (68.3 - 73.3)	180	465	27.9 (24.5 - 31.5)
2.Antibiotic prescription for 5-14 days	6283	3796	60.4 (59.2 - 61.6)	426	219	66.1 (62.3 - 69.7)
3.OCS and antibiotic prescription for 5-14 days	919	705	76.7 (73.8 - 79.4)	142	503	22.0 (18.9 - 25.4)
4. Symptom definition	341	137	40.2 (34.9 - 45.6)	16	629	2.5 (1.4 - 4.0)
5. Symptom definition and OCS prescription	156	106	68.0 (60.0 - 75.2)	14	631	2.2 (1.2 - 3.6)
6. Symptom definition and antibiotic prescription	108	74	68.5 (58.9 - 77.1)	11	634	1.7 (0.9 - 3.0)
7. Symptom definition and OCS & antibiotic prescription	90	64	71.1 (60.6 - 80.2)	10	635	1.6 (0.8 - 2.8)
8. LRTI code	1809	1435	79.3 (77.4 - 81.2)	132	513	20.5 (17.4 - 23.8)
9. LRTI code and OCS prescription	1617	1311	81.1 (79.1 – 83.0)	116	529	18.0 (15.1 - 21.2)

10. LRTI code and antibiotic prescription	411	362	88.1 (84.6 - 91.1)	73	572	11.3 (9.0 - 14.0)
11. LRTI code and OCS & antibiotic prescription	388	342	88.1 (84.5 - 91.2)	70	575	10.9 (8.6 - 13.5)
12. AECOPD code	966	905	93.7 (92.0 - 95.1)	147	498	22.8 (19.6 - 26.2)
13. AECOPD code and OCS prescription	698	667	95.6 (93.8 – 97.0)	105	540	16.3 (13.5 - 19.4)
14. AECOPD code and antibiotic prescription	466	443	95.1 (92.7 - 96.9)	98	547	15.2 (12.5 - 18.2)

Supplementary Table 3 PPVs for algorithms stratified by deprivation

Algorithm	N events identified	N events confirmed by reference standard	PPV (95% CI)	N events identified	N events confirmed by reference standard	PPV (95% CI)
	Less deprived			More deprived		
1.OCS prescription	612	453	74.0 (70.4 - 77.5)	540	388	71.9 (67.9 - 75.6)
2.Antibiotic prescription	3160	1955	61.9 (60.1 - 63.6)	2680	1604	59.9 (58.0 - 61.7)
3.OCS and antibiotic prescription	441	359	81.4 (77.5 - 84.9)	382	294	77.0 (72.4 - 81.1)
4. Symptom definition	60	32	53.3 (40.0 - 66.3)	82	60	73.2 (62.2 - 82.4)
5. Symptom definition and OCS prescription	30	24	80.0 (61.4 - 92.3)	58	55	94.8 (85.6 - 98.9)
6. Symptom definition and antibiotic prescription	12	10	83.3 (51.6 - 97.9)	45	43	95.6 (84.9 - 99.5)
7. Symptom definition and OCS & antibiotic prescription	9	8	88.9 (51.8 - 99.7)	39	39	100.0 (91.0 - 100.0)
8. LRTI code	909	714	78.5 (75.7 - 81.2)	836	675	80.7 (77.9 - 83.4)
9. LRTI code and OCS prescription	804	649	80.7 (77.8 - 83.4)	754	619	82.1 (79.2 - 84.8)
10. LRTI code and antibiotic prescription	191	168	88.0 (82.5 - 92.2)	202	179	88.6 (83.4 - 92.6)
11. LRTI code and OCS & antibiotic prescription	177	155	87.6 (81.8 - 92.0)	194	172	88.7 (83.3 - 92.8)
12. AECOPD code	502	476	94.8 (92.5 - 96.6)	383	374	97.7 (95.6 - 98.9)
13. AECOPD code and OCS prescription	365	350	95.9 (93.3 - 97.7)	273	268	98.2 (95.8 - 99.4)

14. AECOPD code and antibiotic prescription	243	231	95.1 (91.5 - 97.4)	180	177	98.3 (95.2 - 99.7)
15. AECOPD code and OCS & antibiotic prescription	214	205	95.8 (92.2 - 98.1)	163	160	98.2 (94.7 - 99.6)

Supplementary Table 4 PPVs for algorithms stratified by GOLD stage

Algorithm	N events identified	N events confirmed by reference standard	PPV (95% CI)	N events identified	N events confirmed by reference standard	PPV (95% CI)
	GOLD 1-2			GOLD 3-4		
1.OCS prescription	839	621	74.0 (70.9 - 77.0)	313	220	70.3 (64.9 - 75.3)
2.Antibiotic prescription	4484	2672	59.6 (58.1 - 61.0)	1356	887	65.4 (62.8 - 67.9)
3.OCS and antibiotic prescription	608	487	80.1 (76.7 - 83.2)	215	166	77.2 (71.0 - 82.6)
4. Symptom definition	103	62	60.2 (50.1 - 69.7)	39	30	76.9 (60.7 - 88.9)
5. Symptom definition and OCS prescription	62	55	88.7 (78.1 - 95.3)	26	24	92.3 (74.9 - 99.1)
6. Symptom definition and antibiotic prescription	41	40	97.6 (87.1 - 99.9)	16	13	81.3 (54.4 - 96.0)
7. Symptom definition and OCS & antibiotic prescription	35	35	100.0 (90.0 - 100.0)	13	12	92.3 (64.0 - 99.8)
8. LRTI code	1372	1075	78.4 (76.1 - 80.5)	373	314	84.2 (80.1 - 87.7)
9. LRTI code and OCS prescription	1229	986	80.2 (77.9 - 82.4)	329	282	85.7 (81.5 - 89.3)
10. LRTI code and antibiotic prescription	298	263	88.3 (84.0 - 91.7)	95	84	88.4 (80.2 - 94.1)
11. LRTI code and OCS & antibiotic prescription	285	251	88.1 (83.7 - 91.6)	86	76	88.4 (79.7 - 94.3)
12. AECOPD code	617	594	96.3 (94.5 - 97.6)	268	256	95.5 (92.3 - 97.7)
13. AECOPD code and OCS prescription	445	432	97.1 (95.1 - 98.4)	193	186	96.4 (92.7 - 98.5)

14. AECOPD code and antibiotic prescription	304	294	96.7 (94.0 - 98.4)	119	114	95.8 (90.5 - 98.6)
15. AECOPD code and OCS & antibiotic prescription	270	263	97.4 (94.7 - 99.0)	107	102	95.3 (89.4 - 98.5)

Supplementary Table 5 PPVs for algorithms stratified by record for asthma

Algorithm	N events identified	N events confirmed by reference standard	PPV (95% CI)	N events identified	N events confirmed by reference standard	PPV (95% CI)
	Asthma record			No asthma record		
1.OCS prescription	639	468	73.2 (69.6 - 76.6)	513	373	72.7 (68.6 - 76.5)
2.Antibiotic prescription	3085	1897	61.5 (59.7 - 63.2)	2755	1662	60.3 (58.5 - 62.2)
3.OCS and antibiotic prescription	444	359	80.9 (76.9 - 84.4)	379	294	77.6 (73.0 - 81.7)
4. Symptom definition	80	56	70.0 (58.7 - 79.7)	62	36	58.1 (44.8 - 70.5)
5. Symptom definition and OCS prescription	51	47	92.2 (81.1 - 97.8)	37	32	86.5 (71.2 - 95.5)
6. Symptom definition and antibiotic prescription	36	34	94.4 (81.3 - 99.3)	21	19	90.5 (69.6 - 98.8)
7. Symptom definition and OCS & antibiotic prescription	30	29	96.7 (82.8 - 99.9)	18	18	100.0 (81.5 - 100.0)
8. LRTI code	925	751	81.2 (78.5 - 83.7)	820	638	77.8 (74.8 - 80.6)
9. LRTI code and OCS prescription	832	685	82.3 (79.6 - 84.9)	726	583	80.3 (77.2 - 83.1)
10. LRTI code and antibiotic prescription	233	208	89.3 (84.6 - 92.9)	160	139	86.9 (80.6 - 91.7)
11. LRTI code and OCS & antibiotic prescription	217	193	88.9 (84.0 - 92.8)	154	134	87.0 (80.7 - 91.9)
12. AECOPD code	481	454	94.4 (91.9 - 96.3)	404	396	98.0 (96.1 - 99.1)
13. AECOPD code and OCS prescription	339	324	95.6 (92.8 - 97.5)	299	294	98.3 (96.1 - 99.5)

14. AECOPD code and antibiotic prescription	224	211	94.2 (90.3 - 96.9)	199	197	99.0 (96.4 - 99.9)
15. AECOPD code and OCS & antibiotic prescription	192	182	94.8 (90.6 - 97.5)	185	183	98.9 (96.1 - 99.9)

Supplementary Table 6 PPVs for algorithms stratified by record for GORD

Algorithm	N events identified	N events confirmed by reference standard	PPV (95% CI)	N events identified	N events confirmed by reference standard	PPV (95% CI)
	GORD record			No GORD record		
1.OCS prescription	272	199	73.2 (67.5 - 78.3)	880	642	73.0 (69.9 - 75.9)
2.Antibiotic prescription	1623	941	58.0 (55.5 - 60.4)	4217	2618	62.1 (60.6 - 63.5)
3.OCS and antibiotic prescription	197	155	78.7 (72.3 - 84.2)	626	498	79.6 (76.2 - 82.6)
4. Symptom definition	37	22	59.5 (42.1 - 75.2)	105	70	66.7 (56.8 - 75.6)
5. Symptom definition and OCS prescription	22	19	86.4 (65.1 - 97.1)	66	60	90.9 (81.3 - 96.6)
6. Symptom definition and antibiotic prescription	13	11	84.6 (54.6 - 98.1)	44	42	95.5 (84.5 - 99.4)
7. Symptom definition and OCS & antibiotic prescription	12	11	91.7 (61.5 - 99.8)	36	36	100.0 (90.3 - 100.0)
8. LRTI code	484	369	76.2 (72.2 - 80.0)	1261	1020	80.9 (78.6 - 83.0)
9. LRTI code and OCS prescription	424	337	79.5 (75.3 - 83.2)	1134	931	82.1 (79.7 - 84.3)
10. LRTI code and antibiotic prescription	90	78	86.7 (77.9 - 92.9)	303	269	88.8 (84.7 - 92.1)
11. LRTI code and OCS & antibiotic prescription	82	71	86.6 (77.3 - 93.1)	289	256	88.6 (84.3 - 92.0)

12. AECOPD code	235	223	94.9 (91.3 - 97.3)	650	627	96.5 (94.7 - 97.7)
13. AECOPD code and OCS prescription	161	155	96.3 (92.1 - 98.6)	477	463	97.1 (95.1 - 98.4)
14. AECOPD code and antibiotic prescription	103	96	93.2 (86.5 - 97.2)	320	312	97.5 (95.1 - 98.9)
15. AECOPD code and OCS & antibiotic prescription	91	86	94.5 (87.6 - 98.2)	286	279	97.6 (95.0 - 99.0)

Supplementary Table 7 PPVs for algorithms stratified by record for CVD

Algorithm	N events identified	N events confirmed by reference standard	PPV (95% CI)	N events identified	N events confirmed by reference standard	PPV (95% CI)
	CVD record			No CVD record		
1.OCS prescription	296	198	66.9 (61.2 - 72.2)	856	643	75.1 (72.1 - 78.0)
2.Antibiotic prescription	1536	924	60.2 (57.7 - 62.6)	4304	2635	61.2 (59.7 - 62.7)
3.OCS and antibiotic prescription	198	153	77.3 (70.8 - 82.9)	625	500	80.0 (76.6 - 83.1)
4. Symptom definition	44	28	63.6 (47.8 - 77.6)	98	64	65.3 (55.0 - 74.6)
5. Symptom definition and OCS prescription	27	25	92.6 (75.7 - 99.1)	61	54	88.5 (77.8 - 95.3)
6. Symptom definition and antibiotic prescription	15	15	100.0 (78.2 - 100.0)	42	38	90.5 (77.4 - 97.3)
7. Symptom definition and OCS & antibiotic prescription	15	15	100.0 (78.2 - 100.0)	33	32	97.0 (84.2 - 99.9)
8. LRTI code	478	365	76.4 (72.3 - 80.1)	1267	1024	80.8 (78.5 - 83.0)
9. LRTI code and OCS prescription	415	325	78.3 (74.0 - 82.2)	1143	943	82.5 (80.2 - 84.7)
10. LRTI code and antibiotic prescription	106	92	86.8 (78.8 - 92.6)	287	255	88.9 (84.6 - 92.2)
11. LRTI code and OCS & antibiotic prescription	100	86	86.0 (77.6 - 92.1)	271	241	88.9 (84.6 - 92.4)
12. AECOPD code	245	234	95.5 (92.1 - 97.7)	640	616	96.3 (94.5 - 97.6)

13. AECOPD code and OCS prescription	159	152	95.6 (91.1 - 98.2)	479	466	97.3 (95.4 - 98.5)
14. AECOPD code and antibiotic prescription	107	103	96.3 (90.7 - 99.0)	316	305	96.5 (93.9 - 98.2)
15. AECOPD code and OCS & antibiotic prescription	95	91	95.8 (89.6 - 98.8)	282	274	97.2 (94.5 - 98.8)

Supplementary Table 8 PPVs for algorithms stratified by BMI

Algorithm	N events identified	N events confirmed by reference standard	PPV (95% CI)	N events identified	N events confirmed by reference standard	PPV (95% CI)	N events identified	N events confirmed by reference standard	PPV (95% CI)
	BMI <19			**BMI 19-25**			**BMI ≥25**		
1.OCS prescription	54	40	74.1 (60.3 - 85.0)	445	344	77.3 (73.1 - 81.1)	653	457	70.0 (66.3 - 73.5)
2.Antibiotic prescription	252	169	67.1 (60.9 - 72.8)	2081	1330	63.9 (61.8 - 66.0)	3507	2060	58.7 (57.1 - 60.4)
3.OCS and antibiotic prescription	41	34	82.9 (67.9 - 92.8)	307	255	83.1 (78.4 - 87.1)	475	364	76.6 (72.6 - 80.4)
4. Symptom definition	10	6	60.0 (26.2 - 87.8)	34	23	67.6 (49.5 - 82.6)	98	63	64.3 (54.0 - 73.7)
5. Symptom definition and OCS prescription	5	5	100.0 (47.8 - 100.0)	21	18	85.7 (63.7 - 97.0)	62	56	90.3 (80.1 - 96.4)
6. Symptom definition and antibiotic prescription	7	5	71.4 (29.0 - 96.3)	10	9	90.0 (55.5 - 99.7)	40	39	97.5 (86.8 - 99.9)
7. Symptom definition and OCS & antibiotic prescription	4	4	100.0 (39.8 - 100.0)	9	8	88.9 (51.8 - 99.7)	35	35	100.0 (90.0 - 100.0)
8. LRTI code	76	57	75.0 (63.7 - 84.2)	541	454	83.9 (80.5 - 86.9)	1128	878	77.8 (75.3 - 80.2)
9. LRTI code and OCS prescription	71	54	76.1 (64.5 - 85.4)	481	413	85.9 (82.4 - 88.9)	1006	801	79.6 (77.0 - 82.1)
10. LRTI code and antibiotic prescription	17	11	64.7 (38.3 - 85.8)	134	128	95.5 (90.5 - 98.3)	242	208	86.0 (80.9 - 90.1)

11. LRTI code and OCS & antibiotic prescription	16	10	62.5 (35.4 - 84.8)	122	116	95.1 (89.6 - 98.2)	233	201	86.3 (81.2 - 90.4)
12. AECOPD code	40	39	97.5 (86.8 - 99.9)	376	360	95.7 (93.2 - 97.5)	469	451	96.2 (94.0 - 97.7)
13. AECOPD code and OCS prescription	29	28	96.6 (82.2 - 99.9)	283	275	97.2 (94.5 - 98.8)	326	315	96.6 (94.0 - 98.3)
14. AECOPD code and antibiotic prescription	18	18	100.0 (81.5 - 100.0)	183	180	98.4 (95.3 - 99.7)	222	210	94.6 (90.7 - 97.2)
15. AECOPD code and OCS & antibiotic prescription	16	16	100.0 (79.4 - 100.0)	167	164	98.2 (94.8 - 99.6)	194	185	95.4 (91.4 - 97.9)

Supplementary Table 9 PPVs for algorithms stratified by sex

Algorithm	N events identified	N events confirmed by reference standard	PPV (95% CI)	N events identified	N events confirmed by reference standard	PPV (95% CI)
	Female			Male		
1.OCS prescription	609	469	77.0 (73.5 - 80.3)	536	367	68.5 (64.3 - 72.4)
2.Antibiotic prescription	3015	1843	61.1 (59.4 - 62.9)	2777	1687	60.7 (58.9 - 62.6)
3.OCS and antibiotic prescription	433	352	81.3 (77.3 - 84.9)	385	296	76.9 (72.3 - 81.0)
4. Symptom definition	66	41	62.1 (49.3 - 73.8)	75	51	68.0 (56.2 - 78.3)
5. Symptom definition and OCS prescription	40	34	85.0 (70.2 - 94.3)	48	45	93.8 (82.8 - 98.7)
6. Symptom definition and antibiotic prescription	28	25	89.3 (71.8 - 97.7)	29	28	96.6 (82.2 - 99.9)
7. Symptom definition and OCS & antibiotic prescription	23	22	95.7 (78.1 - 99.9)	25	25	100.0 (86.3 - 100.0)
8. LRTI code	913	732	80.2 (77.4 - 82.7)	818	646	79.0 (76.0 - 81.7)
9. LRTI code and OCS prescription	811	662	81.6 (78.8 - 84.2)	736	597	81.1 (78.1 - 83.9)
10. LRTI code and antibiotic prescription	217	193	88.9 (84.0 - 92.8)	175	153	87.4 (81.6 - 92.0)
11. LRTI code and OCS & antibiotic prescription	203	181	89.2 (84.1 - 93.1)	167	145	86.8 (80.7 - 91.6)
12. AECOPD code	456	439	96.3 (94.1 - 97.8)	420	402	95.7 (93.3 - 97.4)
13. AECOPD code and OCS prescription	326	316	96.9 (94.4 - 98.5)	307	297	96.7 (94.1 - 98.4)

14. AECOPD code and antibiotic prescription	224	218	97.3 (94.3 - 99.0)	196	187	95.4 (91.5 - 97.9)
15. AECOPD code and OCS & antibiotic prescription	195	190	97.4 (94.1 - 99.2)	179	172	96.1 (92.1 - 98.4)

Supplementary Table 10 PPVs for algorithms stratified by smoking status

Algorithm	N events identified	N events confirmed by reference standard	PPV (95% CI)	N events identified	N events confirmed by reference standard	PPV (95% CI)
	Ex-smoker			Current smoker		
1.OCS prescription	490	344	70.2 (65.9 - 74.2)	662	497	75.1 (71.6 - 78.3)
2.Antibiotic prescription	2621	1601	61.1 (59.2 - 63.0)	3219	1958	60.8 (59.1 - 62.5)
3.OCS and antibiotic prescription	345	271	78.6 (73.8 - 82.8)	478	382	79.9 (76.0 - 83.4)
4. Symptom definition	58	45	77.6 (64.7 - 87.5)	84	47	56.0 (44.7 - 66.8)
5. Symptom definition and OCS prescription	39	37	94.9 (82.7 - 99.4)	49	42	85.7 (72.8 - 94.1)
6. Symptom definition and antibiotic prescription	27	24	88.9 (70.8 - 97.6)	30	29	96.7 (82.8 - 99.9)
7. Symptom definition and OCS & antibiotic prescription	21	20	95.2 (76.2 - 99.9)	27	27	100.0 (87.2 - 100.0)
8. LRTI code	805	663	82.4 (79.5 - 84.9)	940	726	77.2 (74.4 - 79.9)
9. LRTI code and OCS prescription	722	607	84.1 (81.2 - 86.7)	836	661	79.1 (76.1 - 81.8)
10. LRTI code and antibiotic prescription	166	143	86.1 (79.9 - 91.0)	227	204	89.9 (85.2 - 93.5)
11. LRTI code and OCS & antibiotic prescription	161	139	86.3 (80.0 - 91.2)	210	188	89.5 (84.6 - 93.3)
12. AECOPD code	406	392	96.6 (94.3 - 98.1)	479	458	95.6 (93.4 - 97.3)
13. AECOPD code and OCS prescription	283	273	96.5 (93.6 - 98.3)	355	345	97.2 (94.9 - 98.6)

14. AECOPD code and antibiotic prescription	171	164	95.9 (91.7 - 98.3)	252	244	96.8 (93.8 - 98.6)
15. AECOPD code and OCS & antibiotic prescription	147	140	95.2 (90.4 - 98.1)	230	225	97.8 (95.0 - 99.3)

Supplementary Table 11 PPVs for algorithms stratified by age group

Algorithm	N events identified	N events confirmed by reference standard	PPV (95% CI)	N events identified	N events confirmed by reference standard	PPV (95% CI)	N events identified	N events confirmed by reference standard	PPV (95% CI)	N events identified	N events confirmed by reference standard	PPV (95% CI)
	≤55			55 to 64			65 to 74			≥ 75		
1.OCS prescription	288	205	71.2 (65.6 - 76.3)	424	318	75.0 (70.6 - 79.1)	340	245	72.1 (67.0 - 76.8)	100	73	73.0 (63.2 - 81.4)
2.Antibiotic prescription	1234	691	56.0 (53.2 - 58.8)	2127	1341	63.0 (61.0 - 65.1)	1818	1130	62.2 (59.9 - 64.4)	661	397	60.1 (56.2 - 63.8)
3.OCS and antibiotic prescription	210	168	80.0 (73.9 - 85.2)	300	230	76.7 (71.5 - 81.3)	247	200	81.0 (75.5 - 85.7)	66	55	83.3 (72.1 - 91.4)
4. Symptom definition	24	15	62.5 (40.6 - 81.2)	47	31	66.0 (50.7 - 79.1)	45	26	57.8 (42.2 - 72.3)	26	20	76.9 (56.4 - 91.0)
5. Symptom definition and OCS prescription	15	12	80.0 (51.9 - 95.7)	28	26	92.9 (76.5 - 99.1)	26	24	92.3 (74.9 - 99.1)	19	17	89.5 (66.9 - 98.7)
6. Symptom definition and antibiotic prescription	8	8	100.0 (63.1 - 100.0)	19	17	89.5 (66.9 - 98.7)	17	15	88.2 (63.6 - 98.5)	13	13	100.0 (75.3 - 100.0)
7. Symptom definition and OCS &	7	7	100.0 (59.0 - 100.0)	15	15	100.0 (78.2 - 100.0)	15	14	93.3 (68.1 - 99.8)	11	11	100.0 (71.5 - 100.0)

antibiotic prescription												
8. LRTI code	377	288	76.4 (71.8 - 80.6)	645	501	77.7 (74.3 - 80.8)	530	440	83.0 (79.5 - 86.1)	193	160	82.9 (76.8 - 87.9)
9. LRTI code and OCS prescription	336	265	78.9 (74.1 - 83.1)	580	463	79.8 (76.3 - 83.0)	473	402	85.0 (81.4 - 88.1)	169	138	81.7 (75.0 - 87.2)
10. LRTI code and antibiotic prescription	106	93	87.7 (79.9 - 93.3)	129	115	89.1 (82.5 - 93.9)	112	97	86.6 (78.9 - 92.3)	46	42	91.3 (79.2 - 97.6)
11. LRTI code and OCS & antibiotic prescription	97	86	88.7 (80.6 - 94.2)	121	107	88.4 (81.3 - 93.5)	108	93	86.1 (78.1 - 92.0)	45	41	91.1 (78.8 - 97.5)
12. AECOPD code	135	129	95.6 (90.6 - 98.4)	385	372	96.6 (94.3 - 98.2)	281	269	95.7 (92.7 - 97.8)	84	80	95.2 (88.3 - 98.7)
13. AECOPD code and OCS prescription	95	92	96.8 (91.0 - 99.3)	289	281	97.2 (94.6 - 98.8)	200	193	96.5 (92.9 - 98.6)	54	52	96.3 (87.3 - 99.5)
14. AECOPD code and antibiotic prescription	78	75	96.2 (89.2 - 99.2)	196	190	96.9 (93.5 - 98.9)	114	109	95.6 (90.1 - 98.6)	35	34	97.1 (85.1 - 99.9)

15. AECOPD code and OCS & antibiotic prescription	70	68	97.1 (90.1 - 99.7)	176	170	96.6 (92.7 - 98.7)	101	98	97.0 (91.6 - 99.4)	30	29	96.7 (82.8 - 99.9)

Lower respiratory tract infection diagnostic codes

Medical code	Read term
68	Chest infection
312	Acute bronchitis
556	Influenza
1019	Acute bronchiolitis
1382	Acute viral bronchitis unspecified
2157	Flu like illness
2476	Chest cold
2581	Chest infection NOS
3358	Lower resp tract infection
5947	Influenza like illness
5978	Acute wheezy bronchitis
6124	Acute lower respiratory tract infection
6181	Obliterating fibrous bronchiolitis
8980	Influenza-like symptoms
9043	Acute pneumococcal bronchitis
11072	Acute purulent bronchitis
14791	Influenza with gastrointestinal tract involvement
15774	Influenza with laryngitis
16388	Influenza NOS
17185	Acute bronchiolitis with bronchospasm
17359	Chest infection - unspecified bronchitis
17917	Acute bronchiolitis NOS
18451	Acute bronchiolitis due to respiratory syncytial virus
20198	Acute bronchitis NOS
21061	Chronic obstruct pulmonary dis with acute lower resp infectn
21145	Acute croupous bronchitis
21492	Acute haemophilus influenzae bronchitis
23488	Influenza with respiratory manifestations NOS
24316	Chest infection with infectious disease EC
24800	Acute bacterial bronchitis unspecified
26125	Bronchiolitis obliterans
29273	Acute bronchitis due to parainfluenza virus
29617	Influenza with pharyngitis
29669	Acute bronchitis and bronchiolitis
31363	Influenza with other manifestations NOS
37447	Acute lower respiratory tract infection
41137	Acute bronchitis or bronchiolitis NOS
41589	Acute obliterating bronchiolitis
43362	Acute streptococcal bronchitis
43625	Influenza with other respiratory manifestation
46157	Influenza with encephalopathy

47472	Influenza with other manifestations
48593	Acute bronchitis due to respiratory syncytial virus
49794	Acute neisseria catarrhalis bronchitis
54533	Acute capillary bronchiolitis
63697	Avian influenza virus nucleic acid detection
64890	Acute bronchitis due to rhinovirus
65916	Acute bronchitis due to echovirus
66228	Acute bronchiolitis due to other specified organisms
66397	[X]Other acute lower respiratory infections
69192	Acute exudative bronchiolitis
71370	Acute pseudomembranous bronchitis
73100	[X]Acute bronchitis due to other specified organisms
91123	Parainfluenza type 3 nucleic acid detection
93153	Acute bronchitis due to coxsackievirus
94130	Parainfluenza type 1 nucleic acid detection
94858	Parainfluenza type 2 nucleic acid detection
94930	Avian influenza
96017	Influenza B virus detected
96018	Influenza H3 virus detected
96019	Influenza H1 virus detected
96286	Human parainfluenza virus detected
97062	Influenza A virus, other or untyped strain detected
97279	[X]Influenza+other manifestations, virus not identified
97605	[X]Influenza+oth respiratory manifestatns,virus not identifd
97936	[X]Influenza+other manifestations,influenza virus identified
98102	Influenza A (H1N1) swine flu
98103	Possible influenza A virus H1N1 subtype
98115	Suspected swine influenza
98125	Suspected influenza A virus subtype H1N1 infection
98129	Influenza due to Influenza A virus subtype H1N1
98143	Influenza A virus H1N1 subtype detected
98156	Influenza H5 virus detected
98257	[X]Flu+oth respiratory manifestations,'flu virus identified
99214	[X]Acute bronchiolitis due to other specified organisms
101775	Acute membranous bronchitis
102918	Influenza H2 virus detected

Acute exacerbation of COPD diagnostic codes

Medical code	Read term
1446	Acute exacerbation of chronic obstructive airways disease
7884	Chron obstruct pulmonary dis wth acute exacerbation, unspec

Cough codes

Medical code	Read term
92	Cough
292	Chesty cough
1025	Bronchial cough
1160	[D]Cough
1234	Productive cough NOS
1273	C/O - cough
3068	Night cough present
3645	Coughing up phlegm
4070	Morning cough
4836	Nocturnal cough / wheeze
4931	Dry cough
7706	Productive cough -clear sputum
7707	Cough symptom NOS
7708	Productive cough-yellow sputum
7773	Productive cough -green sputum
8239	[D]Cough with haemorrhage
18907	Cough with fever
22318	Difficulty in coughing up sputum
29318	Evening cough
60903	Cough aggravates symptom
100515	Cough swab

Breathlessness codes

Medical code	Read term
735	[D]Breathlessness
741	[D]Shortness of breath
1429	Breathlessness
2563	[D]Respiratory distress
2575	Short of breath on exertion
2737	Respiratory distress syndrome
2931	Difficulty breathing
3092	[D]Dyspnoea
4822	Shortness of breath
5175	Breathlessness symptom
5349	Shortness of breath symptom
5896	Dyspnoea - symptom
6326	Breathless - moderate exertion
6434	Paroxysmal nocturnal dyspnoea
7000	O/E - dyspnoea
7534	O/E - respiratory distress
7683	Breathless - lying flat
7932	Breathless - mild exertion
9297	[D]Respiratory insufficiency
18116	Nocturnal dyspnoea
21801	Breathlessness NOS
22094	Short of breath dressing/undressing
24889	Breathless - strenuous exertion
31143	Breathless - at rest
40813	Unable to complete a sentence in one breath
53771	Dyspnoea on exertion

Sputum codes

Medical codes	Read term
292	Chesty cough
1025	Bronchial cough
1234	Productive cough NOS
1251	[D]Abnormal sputum
3645	Coughing up phlegm
3727	Sputum sent for C/S
7706	Productive cough -clear sputum
7708	Productive cough-yellow sputum
7773	Productive cough -green sputum
8287	Sputum sample obtained
8760	[D]Positive culture findings in sputum
9807	Sputum - symptom
11072	Acute purulent bronchitis
14271	Sputum culture
14272	Sputum microscopy
14273	Sputum appearance
14804	Sputum appears infected
15430	[D]Sputum abnormal - colour
16026	Sputum examination: abnormal
18964	Sputum clearance
20086	[D]Sputum abnormal - amount
22318	Difficulty in coughing up sputum
23252	Sputum microscopy NOS
23582	[D]Abnormal sputum NOS
24181	Sputum: mucopurulent
30754	Yellow sputum
30904	Sputum sent for examination
36515	[D]Abnormal sputum - tenacious
36880	Green sputum
43270	Sputum evidence of infection
44214	[D]Sputum abnormal - odour
49144	Sputum: pus cells present
49694	Sputum: organism on gram stain
54177	Sputum: excessive - mucoid
100484	Volume of sputum
100524	Moderate sputum
100629	White sputum
100647	Copious sputum
100931	Brown sputum
101782	Profuse sputum
103209	Grey sputum

COPD specific oral corticosteroid codes

Product code	Product name
95	prednisolone 5mg tablets
1063	prednesol 5mg tablet (sovereign medical ltd)
2044	prednisone 2.5 mg tab
2368	prednisolone 2.5mg tablet
2390	prednisolone e/c 1 mg tab
2799	prednisolone 10 mg tab
2949	prednisone 5mg tablets
3059	prednisolone 50 mg tab
3345	sintisone tablet (pharmacia ltd)
3557	prednisone 1mg tablets
7584	prednisolone 4 mg tab
7710	prednisolone 15 mg tab
7934	prednisone 30 mg tab
9727	prednisolone 50mg tablets
13522	prednisolone 2 mg tab
13615	prednisone 10 mg tab
16724	prednisone 50 mg tab
20095	precortisyl forte 25mg tablet (aventis pharma)
20670	prednisolone e/c
21833	decortisyl 5mg tablet (roussel laboratories ltd)
23512	precortisyl 5mg tablet (hoechst marion roussel)
24716	prednisolone e/c
25272	precortisyl 1mg tablet (hoechst marion roussel)
27889	prednisolone
27959	prednisolone
27962	deltastab 1mg tablet (waymade healthcare plc)
28376	prednisolone 2.5mg gastro-resistant tablet (biorex laboratories ltd)
28859	deltastab 5mg tablet (waymade healthcare plc)
30390	deltastab 2 mg tab
30971	decortisyl 25 mg tab
31327	prednisolone steaglate 6.65mg tablet
33691	prednisolone 5mg gastro-resistant tablet (biorex laboratories ltd)
33988	prednisolone 5mg tablet (co-pharma ltd)
33990	prednisolone 5mg tablet (ivax pharmaceuticals uk ltd)
34109	prednisolone 5 mg gastro-resistant tablet
34631	prednisolone 1mg tablet (co-pharma ltd)
34914	prednisolone 1mg tablet (celltech pharma europe ltd)
38407	prednisolone 20mg tablet
43544	prednisone 5mg tablet (knoll ltd)
44380	prednisone 1mg modified-release tablets
44723	prednisone 5mg modified-release tablets
44802	lodotra 5mg modified-release tablets (napp pharmaceuticals ltd)
44803	lodotra 2mg modified-release tablets (napp pharmaceuticals ltd)
45302	prednisolone 5mg tablet (biorex laboratories ltd)

46711	prednisone 2mg modified-release tablets
47142	prednisolone 5mg soluble tablet (amdipharm plc)
54432	lodotra 1mg modified-release tablets (napp pharmaceuticals ltd)

COPD specific antibiotic codes

Product code	Product name
22029	amiclav 250mg/125mg tablets (ashbourne pharmaceuticals ltd)
11634	amix 125 oral suspension (ashbourne pharmaceuticals ltd)
11613	amix 250 capsules (ashbourne pharmaceuticals ltd)
21844	amix 250 oral suspension (ashbourne pharmaceuticals ltd)
18786	amix 500 capsules (ashbourne pharmaceuticals ltd)
29697	amopen 125mg/5ml liquid (yorkshire pharmaceuticals ltd)
30498	amopen 250mg capsule (yorkshire pharmaceuticals ltd)
31423	amopen 250mg/5ml liquid (yorkshire pharmaceuticals ltd)
17711	amopen 500mg capsule (yorkshire pharmaceuticals ltd)
12378	amoram 125mg/5ml oral suspension (lpc medical (uk) ltd)
9243	amoram 250mg capsules (lpc medical (uk) ltd)
22438	amoram 250mg/5ml oral suspension (lpc medical (uk) ltd)
22415	amoram 500mg capsules (lpc medical (uk) ltd)
8906	amoxicillin 125mg / clavulanic acid 31mg/5ml oral suspension
13285	amoxicillin 125mg / clavulanic acid 31mg/5ml oral suspension
53942	amoxicillin 125mg / clavulanic acid 62.5mg/5ml oral suspension
41835	amoxicillin 125mg powder (ivax pharmaceuticals uk ltd)
3742	amoxicillin 125mg sugar free chewable tablets
13848	amoxicillin 125mg sugar free powder
485	amoxicillin 125mg/1.25ml oral suspension paediatric
42822	amoxicillin 125mg/5ml mixture (celltech pharma europe ltd)
28872	amoxicillin 125mg/5ml mixture (crosspharma ltd)
41818	amoxicillin 125mg/5ml oral solution (berk pharmaceuticals ltd)
42240	amoxicillin 125mg/5ml oral solution (co-pharma ltd)
29337	amoxicillin 125mg/5ml oral solution (neo laboratories ltd)
62	amoxicillin 125mg/5ml oral suspension
33690	amoxicillin 125mg/5ml oral suspension (a a h pharmaceuticals ltd)
34857	amoxicillin 125mg/5ml oral suspension (actavis uk ltd)
42545	amoxicillin 125mg/5ml oral suspension (almus pharmaceuticals ltd)
50002	amoxicillin 125mg/5ml oral suspension (bristol laboratories ltd)
32622	amoxicillin 125mg/5ml oral suspension (generics (uk) ltd)
23238	amoxicillin 125mg/5ml oral suspension (ivax pharmaceuticals uk ltd)
48038	amoxicillin 125mg/5ml oral suspension (kent pharmaceuticals ltd)
52685	amoxicillin 125mg/5ml oral suspension (phoenix healthcare distribution ltd)
28875	amoxicillin 125mg/5ml oral suspension (ranbaxy (uk) ltd)
43229	amoxicillin 125mg/5ml oral suspension (sandoz ltd)
55047	amoxicillin 125mg/5ml oral suspension (sandoz ltd)
28870	amoxicillin 125mg/5ml oral suspension (teva uk ltd)
56561	amoxicillin 125mg/5ml oral suspension (waymade healthcare plc)
503	amoxicillin 125mg/5ml oral suspension sugar free
33696	amoxicillin 125mg/5ml oral suspension sugar free (a a h pharmaceuticals ltd)
34679	amoxicillin 125mg/5ml oral suspension sugar free (actavis uk ltd)

53078	amoxicillin 125mg/5ml oral suspension sugar free (alliance healthcare (distribution) ltd)
36054	amoxicillin 125mg/5ml oral suspension sugar free (almus pharmaceuticals ltd)
52122	amoxicillin 125mg/5ml oral suspension sugar free (bristol laboratories ltd)
31014	amoxicillin 125mg/5ml oral suspension sugar free (generics (uk) ltd)
24150	amoxicillin 125mg/5ml oral suspension sugar free (ivax pharmaceuticals uk ltd)
34384	amoxicillin 125mg/5ml oral suspension sugar free (kent pharmaceuticals ltd)
52857	amoxicillin 125mg/5ml oral suspension sugar free (phoenix healthcare distribution ltd)
29858	amoxicillin 125mg/5ml oral suspension sugar free (sandoz ltd)
34638	amoxicillin 125mg/5ml oral suspension sugar free (teva uk ltd)
55626	amoxicillin 125mg/5ml oral suspension sugar free (waymade healthcare plc)
1391	amoxicillin 250mg / clavulanic acid 125mg tablets
7636	amoxicillin 250mg / clavulanic acid 62mg/5ml oral suspension
13262	amoxicillin 250mg / clavulanic acid 62mg/5ml oral suspension
42809	amoxicillin 250mg capsule (c p pharmaceuticals ltd)
31661	amoxicillin 250mg capsule (co-pharma ltd)
28882	amoxicillin 250mg capsule (crosspharma ltd)
34435	amoxicillin 250mg capsule (ddsa pharmaceuticals ltd)
33222	amoxicillin 250mg capsule (lagap)
32872	amoxicillin 250mg capsule (mepra-pharm)
34714	amoxicillin 250mg capsule (neo laboratories ltd)
45267	amoxicillin 250mg capsule (regent laboratories ltd)
9	amoxicillin 250mg capsules
25484	amoxicillin 250mg capsules (a a h pharmaceuticals ltd)
33343	amoxicillin 250mg capsules (actavis uk ltd)
54796	amoxicillin 250mg capsules (boston healthcare ltd)
54491	amoxicillin 250mg capsules (bristol laboratories ltd)
30745	amoxicillin 250mg capsules (generics (uk) ltd)
34042	amoxicillin 250mg capsules (ivax pharmaceuticals uk ltd)
30528	amoxicillin 250mg capsules (kent pharmaceuticals ltd)
54271	amoxicillin 250mg capsules (mawdsley-brooks & company ltd)
51536	amoxicillin 250mg capsules (milpharm ltd)
30743	amoxicillin 250mg capsules (ranbaxy (uk) ltd)
48006	amoxicillin 250mg capsules (sandoz ltd)
23967	amoxicillin 250mg capsules (teva uk ltd)
54185	amoxicillin 250mg capsules (wockhardt uk ltd)
870	amoxicillin 250mg sugar free chewable tablets
42815	amoxicillin 250mg/5ml mixture (celltech pharma europe ltd)
33570	amoxicillin 250mg/5ml mixture (crosspharma ltd)
40238	amoxicillin 250mg/5ml mixture (mepra-pharm)
45317	amoxicillin 250mg/5ml oral solution (neo laboratories ltd)
427	amoxicillin 250mg/5ml oral suspension

33165	amoxicillin 250mg/5ml oral suspension (a a h pharmaceuticals ltd)
34760	amoxicillin 250mg/5ml oral suspension (actavis uk ltd)
41090	amoxicillin 250mg/5ml oral suspension (almus pharmaceuticals ltd)
55018	amoxicillin 250mg/5ml oral suspension (bristol laboratories ltd)
33689	amoxicillin 250mg/5ml oral suspension (generics (uk) ltd)
32640	amoxicillin 250mg/5ml oral suspension (ivax pharmaceuticals uk ltd)
51382	amoxicillin 250mg/5ml oral suspension (phoenix healthcare distribution ltd)
55499	amoxicillin 250mg/5ml oral suspension (ranbaxy (uk) ltd)
56223	amoxicillin 250mg/5ml oral suspension (sandoz ltd)
37755	amoxicillin 250mg/5ml oral suspension (sandoz ltd)
53924	amoxicillin 250mg/5ml oral suspension (sigma pharmaceuticals plc)
27725	amoxicillin 250mg/5ml oral suspension (teva uk ltd)
585	amoxicillin 250mg/5ml oral suspension sugar free
34232	amoxicillin 250mg/5ml oral suspension sugar free (a a h pharmaceuticals ltd)
40243	amoxicillin 250mg/5ml oral suspension sugar free (actavis uk ltd)
54222	amoxicillin 250mg/5ml oral suspension sugar free (alliance healthcare (distribution) ltd)
42732	amoxicillin 250mg/5ml oral suspension sugar free (almus pharmaceuticals ltd)
49065	amoxicillin 250mg/5ml oral suspension sugar free (bristol laboratories ltd)
31535	amoxicillin 250mg/5ml oral suspension sugar free (generics (uk) ltd)
33699	amoxicillin 250mg/5ml oral suspension sugar free (ivax pharmaceuticals uk ltd)
34855	amoxicillin 250mg/5ml oral suspension sugar free (kent pharmaceuticals ltd)
34775	amoxicillin 250mg/5ml oral suspension sugar free (teva uk ltd)
17746	amoxicillin 375mg soluble tablets
1140	amoxicillin 3g oral powder sachets sugar free
33383	amoxicillin 3g oral powder sachets sugar free (a a h pharmaceuticals ltd)
40168	amoxicillin 3g oral powder sachets sugar free (kent pharmaceuticals ltd)
28130	amoxicillin 3g oral powder sachets sugar free (teva uk ltd)
41734	amoxicillin 3g powder (actavis uk ltd)
15192	amoxicillin 400mg / clavulanic acid 57mg/5ml sugar free oral suspension
5662	amoxicillin 500mg / clarithromycin 500mg / lansoprazole 30mg triple pack
13216	amoxicillin 500mg / clavulanic acid 125mg tablets
38684	amoxicillin 500mg capsule (c p pharmaceuticals ltd)
35570	amoxicillin 500mg capsule (crosspharma ltd)
34885	amoxicillin 500mg capsule (ddsa pharmaceuticals ltd)
44854	amoxicillin 500mg capsule (lagap)
34912	amoxicillin 500mg capsule (neo laboratories ltd)
48	amoxicillin 500mg capsules
33692	amoxicillin 500mg capsules (a a h pharmaceuticals ltd)
53627	amoxicillin 500mg capsules (accord healthcare ltd)
26157	amoxicillin 500mg capsules (actavis uk ltd)
52820	amoxicillin 500mg capsules (alliance healthcare (distribution) ltd)

47640	amoxicillin 500mg capsules (almus pharmaceuticals ltd)
55527	amoxicillin 500mg capsules (boston healthcare ltd)
52771	amoxicillin 500mg capsules (bristol laboratories ltd)
23740	amoxicillin 500mg capsules (generics (uk) ltd)
29463	amoxicillin 500mg capsules (ivax pharmaceuticals uk ltd)
33706	amoxicillin 500mg capsules (kent pharmaceuticals ltd)
52058	amoxicillin 500mg capsules (medreich plc)
54725	amoxicillin 500mg capsules (milpharm ltd)
34852	amoxicillin 500mg capsules (ranbaxy (uk) ltd)
31801	amoxicillin 500mg capsules (sandoz ltd)
34001	amoxicillin 500mg capsules (teva uk ltd)
55394	amoxicillin 500mg capsules (wockhardt uk ltd)
1722	amoxicillin 500mg dispersible tablets
2281	amoxicillin 500mg sugar free chewable tablets
4582	amoxicillin 750mg soluble tablets
9343	amoxicillin 750mg sugar free powder
439	amoxicillin with clavulanic acid dispersible tablets
2171	amoxil 125mg/1.25ml paediatric oral suspension (glaxosmithkline uk ltd)
2153	amoxil 125mg/5ml syrup sucrose free (glaxosmithkline uk ltd)
133	amoxil 250mg capsules (glaxosmithkline uk ltd)
1812	amoxil 250mg/5ml syrup sucrose free (glaxosmithkline uk ltd)
2174	amoxil 3g oral powder sachets sucrose free (glaxosmithkline uk ltd)
847	amoxil 500mg capsules (glaxosmithkline uk ltd)
49590	amoxil 500mg capsules (lexon (uk) ltd)
51436	amoxil 500mg capsules (mawdsley-brooks & company ltd)
56700	amoxil 500mg capsules (necessity supplies ltd)
15148	amoxil 500mg dispersible tablet (smithkline beecham plc)
4010	amoxil 750mg sachets (glaxosmithkline uk ltd)
4154	amoxil fiztab 125mg tablet (bencard)
1637	amoxil fiztab 250mg tablet (bencard)
7737	amoxil fiztab 500mg tablet (bencard)
31571	amoxycillin
32505	amoxycillin
27897	amoxycillin
7592	amoxycillin 125 mg cap
22469	amoxycillin 125mg/31mg clavulanic acid
25034	amoxycillin 125mg/62mg clavulanic acid
7581	amoxycillin 125mg/62mg clavulanic acid syr
27886	amoxycillin 250/clavulanic acid 125 disp
19795	amoxycillin 250mg/clavulanic acid 125mg
1570	amoxycillin 500 mg tab
2902	amoxycillin fiztab 125 mg tab
1393	amoxycillin fiztab 250 mg tab
22293	amoxycillin trihydrate sachet
21982	amoxycillin trihydrate sachet
31286	amoxymed 125mg/5ml oral solution (medipharma ltd)

3669	amoxymed 250mg capsule (medipharma ltd)
33109	amrit 125mg/5ml liquid (bhr pharmaceuticals ltd)
27714	amrit 250mg capsule (bhr pharmaceuticals ltd)
33110	amrit 250mg/5ml liquid (bhr pharmaceuticals ltd)
33112	amrit 500mg capsule (bhr pharmaceuticals ltd)
27495	arpimycin 125mg/5ml liquid (rosemont pharmaceuticals ltd)
36544	arpimycin 125mg/5ml oral suspension (rosemont pharmaceuticals ltd)
24220	arpimycin 250mg/5ml liquid (rosemont pharmaceuticals ltd)
36514	arpimycin 250mg/5ml oral suspension (rosemont pharmaceuticals ltd)
37022	arpimycin 500mg/5ml liquid (rosemont pharmaceuticals ltd)
415	augmentin 125/31 sf oral suspension (glaxosmithkline uk ltd)
50595	augmentin 125/31 sf oral suspension (mawdsley-brooks & company ltd)
51164	augmentin 125/31 sf oral suspension (waymade healthcare plc)
569	augmentin 250/62 sf oral suspension (glaxosmithkline uk ltd)
52666	augmentin 250/62 sf oral suspension (sigma pharmaceuticals plc)
2507	augmentin 375mg dispersible tablets (glaxosmithkline uk ltd)
49063	augmentin 375mg tablets (doncaster pharmaceuticals ltd)
399	augmentin 375mg tablets (glaxosmithkline uk ltd)
48683	augmentin 375mg tablets (lexon (uk) ltd)
49374	augmentin 375mg tablets (mawdsley-brooks & company ltd)
49048	augmentin 375mg tablets (waymade healthcare plc)
50279	augmentin 625mg tablets (doncaster pharmaceuticals ltd)
509	augmentin 625mg tablets (glaxosmithkline uk ltd)
49656	augmentin 625mg tablets (lexon (uk) ltd)
52207	augmentin 625mg tablets (mawdsley-brooks & company ltd)
49321	augmentin 625mg tablets (sigma pharmaceuticals plc)
49683	augmentin 625mg tablets (waymade healthcare plc)
5341	augmentin-duo 400/57 oral suspension (glaxosmithkline uk ltd)
56591	augmentin-duo 400/57 oral suspension (lexon (uk) ltd)
51194	augmentin-duo 400/57 oral suspension (sigma pharmaceuticals plc)
31007	aureomycin powder (wyeth pharmaceuticals)
25127	avelox 400mg tablets (bayer plc)
26289	bacticlor mr 375mg tablets (ranbaxy (uk) ltd)
4895	benzoyl peroxide 5% / erythromycin 3% gel
21802	berkmycen 250mg tablet (berk pharmaceuticals ltd)
17093	bisolvomycin capsule (boehringer ingelheim ltd)
13910	cefaclor 125mg/5ml liquid (generics (uk) ltd)
14607	cefaclor 125mg/5ml liquid (lagap)
1038	cefaclor 125mg/5ml oral suspension
39703	cefaclor 125mg/5ml oral suspension (a a h pharmaceuticals ltd)
34913	cefaclor 125mg/5ml oral suspension (genus pharmaceuticals ltd)
32235	cefaclor 125mg/5ml oral suspension (ranbaxy (uk) ltd)
7526	cefaclor 125mg/5ml oral suspension sugar free
56610	cefaclor 125mg/5ml oral suspension sugar free (phoenix healthcare distribution ltd)
9520	cefaclor 250mg capsule (lagap)

366	cefaclor 250mg capsules
30772	cefaclor 250mg capsules (ranbaxy (uk) ltd)
20420	cefaclor 250mg/5ml liquid (generics (uk) ltd)
20409	cefaclor 250mg/5ml liquid (lagap)
3737	cefaclor 250mg/5ml oral suspension
46973	cefaclor 250mg/5ml oral suspension (genus pharmaceuticals ltd)
48025	cefaclor 250mg/5ml oral suspension (ranbaxy (uk) ltd)
9293	cefaclor 250mg/5ml oral suspension sugar free
3180	cefaclor 375mg modified-release tablets
34838	cefaclor 375mg modified-release tablets (a a h pharmaceuticals ltd)
20881	cefaclor 375mg modified-release tablets (ranbaxy (uk) ltd)
4689	cefaclor 500mg capsule (lagap)
2976	cefaclor 500mg capsules
43425	cefaclor 500mg capsules (a a h pharmaceuticals ltd)
55211	cefaclor 500mg capsules (kent pharmaceuticals ltd)
30771	cefaclor 500mg capsules (ranbaxy (uk) ltd)
8051	cefaclor 500mg modified-release tablets
12248	cefalexin 125mg/1.25ml paediatric drops
1693	cefalexin 125mg/5ml oral suspension
29748	cefalexin 125mg/5ml oral suspension (a a h pharmaceuticals ltd)
32181	cefalexin 125mg/5ml oral suspension (actavis uk ltd)
53945	cefalexin 125mg/5ml oral suspension (alliance healthcare (distribution) ltd)
39417	cefalexin 125mg/5ml oral suspension (generics (uk) ltd)
32642	cefalexin 125mg/5ml oral suspension (kent pharmaceuticals ltd)
36578	cefalexin 125mg/5ml oral suspension (ranbaxy (uk) ltd)
33329	cefalexin 125mg/5ml oral suspension (teva uk ltd)
6651	cefalexin 125mg/5ml oral suspension sugar free
19144	cefalexin 125mg/5ml oral suspension sugar free (teva uk ltd)
1384	cefalexin 125mg/5ml suspension
18451	cefalexin 1g tablets
33802	cefalexin 250mg capsule (berk pharmaceuticals ltd)
155	cefalexin 250mg capsules
34253	cefalexin 250mg capsules (a a h pharmaceuticals ltd)
19152	cefalexin 250mg capsules (actavis uk ltd)
54864	cefalexin 250mg capsules (alliance healthcare (distribution) ltd)
52283	cefalexin 250mg capsules (arrow generics ltd)
19160	cefalexin 250mg capsules (generics (uk) ltd)
19133	cefalexin 250mg capsules (ivax pharmaceuticals uk ltd)
41736	cefalexin 250mg capsules (kent pharmaceuticals ltd)
52282	cefalexin 250mg capsules (milpharm ltd)
24090	cefalexin 250mg capsules (pliva pharma ltd)
36599	cefalexin 250mg capsules (ranbaxy (uk) ltd)
9690	cefalexin 250mg capsules (teva uk ltd)
40747	cefalexin 250mg chewable tablets
1146	cefalexin 250mg tablets

33334	cefalexin 250mg tablets (a a h pharmaceuticals ltd)
36330	cefalexin 250mg tablets (actavis uk ltd)
47163	cefalexin 250mg tablets (arrow generics ltd)
36701	cefalexin 250mg tablets (generics (uk) ltd)
31825	cefalexin 250mg tablets (ivax pharmaceuticals uk ltd)
9698	cefalexin 250mg tablets (teva uk ltd)
41825	cefalexin 250mg/5ml oral solution (c p pharmaceuticals ltd)
1860	cefalexin 250mg/5ml oral suspension
42008	cefalexin 250mg/5ml oral suspension (a a h pharmaceuticals ltd)
45221	cefalexin 250mg/5ml oral suspension (actavis uk ltd)
29464	cefalexin 250mg/5ml oral suspension (generics (uk) ltd)
41192	cefalexin 250mg/5ml oral suspension (ranbaxy (uk) ltd)
41968	cefalexin 250mg/5ml oral suspension (teva uk ltd)
6671	cefalexin 250mg/5ml oral suspension sugar free
34133	cefalexin 250mg/5ml oral suspension sugar free (teva uk ltd)
1713	cefalexin 250mg/5ml suspension
44755	cefalexin 500mg capsule (berk pharmaceuticals ltd)
400	cefalexin 500mg capsules
32643	cefalexin 500mg capsules (a a h pharmaceuticals ltd)
19138	cefalexin 500mg capsules (actavis uk ltd)
52851	cefalexin 500mg capsules (alliance healthcare (distribution) ltd)
19184	cefalexin 500mg capsules (generics (uk) ltd)
9664	cefalexin 500mg capsules (ivax pharmaceuticals uk ltd)
36569	cefalexin 500mg capsules (kent pharmaceuticals ltd)
54955	cefalexin 500mg capsules (milpharm ltd)
19161	cefalexin 500mg capsules (ranbaxy (uk) ltd)
29281	cefalexin 500mg capsules (teva uk ltd)
865	cefalexin 500mg tablets
29202	cefalexin 500mg tablets (a a h pharmaceuticals ltd)
22321	cefalexin 500mg tablets (generics (uk) ltd)
31827	cefalexin 500mg tablets (ivax pharmaceuticals uk ltd)
9689	cefalexin 500mg tablets (teva uk ltd)
2227	cefalexin 500mg/5ml oral suspension
17150	ceporex 125mg/1.25ml drops (glaxo laboratories ltd)
7560	ceporex 125mg/5ml liquid (galen ltd)
3609	ceporex 125mg/5ml oral solution (galen ltd)
41106	ceporex 125mg/5ml syrup (co-pharma ltd)
12235	ceporex 1g tablet (galen ltd)
192	ceporex 250mg capsule (galen ltd)
40884	ceporex 250mg capsules (co-pharma ltd)
8019	ceporex 250mg tablet (galen ltd)
41049	ceporex 250mg tablets (co-pharma ltd)
8625	ceporex 250mg/5ml liquid (galen ltd)
8008	ceporex 250mg/5ml oral solution (galen ltd)
40945	ceporex 250mg/5ml syrup (co-pharma ltd)
2661	ceporex 500mg capsule (galen ltd)

40915	ceporex 500mg capsules (co-pharma ltd)
8085	ceporex 500mg tablet (galen ltd)
40914	ceporex 500mg tablets (co-pharma ltd)
5859	ceporex 500mg/5ml oral solution (galen ltd)
41230	ceporex 500mg/5ml syrup (co-pharma ltd)
7881	chlortetracycline 250mg capsules
36689	chlortetracycline hcl syr
12016	chymocyclar capsule (rorer pharmaceuticals ltd)
27016	ciprofloxacin
498	ciprofloxacin 100mg tablets
42507	ciprofloxacin 100mg tablets (a a h pharmaceuticals ltd)
48031	ciprofloxacin 100mg tablets (almus pharmaceuticals ltd)
54555	ciprofloxacin 100mg tablets (doncaster pharmaceuticals ltd)
54674	ciprofloxacin 100mg tablets (phoenix healthcare distribution ltd)
39913	ciprofloxacin 100mg tablets (sandoz ltd)
52309	ciprofloxacin 100mg tablets (sigma pharmaceuticals plc)
52945	ciprofloxacin 200mg/100ml solution for infusion vials
56439	ciprofloxacin 200mg/100ml solution for infusion vials (a a h pharmaceuticals ltd)
34647	ciprofloxacin 250mg tablet (neo laboratories ltd)
281	ciprofloxacin 250mg tablets
29343	ciprofloxacin 250mg tablets (a a h pharmaceuticals ltd)
50601	ciprofloxacin 250mg tablets (accord healthcare ltd)
34308	ciprofloxacin 250mg tablets (actavis uk ltd)
51537	ciprofloxacin 250mg tablets (alliance healthcare (distribution) ltd)
54393	ciprofloxacin 250mg tablets (arrow generics ltd)
54701	ciprofloxacin 250mg tablets (bristol laboratories ltd)
56381	ciprofloxacin 250mg tablets (co-pharma ltd)
43814	ciprofloxacin 250mg tablets (dr reddy's laboratories (uk) ltd)
33989	ciprofloxacin 250mg tablets (generics (uk) ltd)
41561	ciprofloxacin 250mg tablets (ivax pharmaceuticals uk ltd)
54302	ciprofloxacin 250mg tablets (medreich plc)
34448	ciprofloxacin 250mg tablets (niche generics ltd)
34694	ciprofloxacin 250mg tablets (pliva pharma ltd)
34559	ciprofloxacin 250mg tablets (sandoz ltd)
34478	ciprofloxacin 250mg tablets (teva uk ltd)
34655	ciprofloxacin 250mg tablets (wockhardt uk ltd)
4091	ciprofloxacin 250mg/5ml oral suspension
10304	ciprofloxacin 2mg/ml infusion
45341	ciprofloxacin 500mg tablet (neo laboratories ltd)
34322	ciprofloxacin 500mg tablet (niche generics ltd)
583	ciprofloxacin 500mg tablets
29458	ciprofloxacin 500mg tablets (a a h pharmaceuticals ltd)
52501	ciprofloxacin 500mg tablets (accord healthcare ltd)
34605	ciprofloxacin 500mg tablets (actavis uk ltd)
49445	ciprofloxacin 500mg tablets (almus pharmaceuticals ltd)

56789	ciprofloxacin 500mg tablets (apc pharmaceuticals & chemicals (europe) ltd)
52616	ciprofloxacin 500mg tablets (arrow generics ltd)
53641	ciprofloxacin 500mg tablets (co-pharma ltd)
50055	ciprofloxacin 500mg tablets (doncaster pharmaceuticals ltd)
53088	ciprofloxacin 500mg tablets (dr reddy's laboratories (uk) ltd)
30707	ciprofloxacin 500mg tablets (generics (uk) ltd)
42174	ciprofloxacin 500mg tablets (ivax pharmaceuticals uk ltd)
55917	ciprofloxacin 500mg tablets (medreich plc)
43557	ciprofloxacin 500mg tablets (pliva pharma ltd)
53878	ciprofloxacin 500mg tablets (ranbaxy (uk) ltd)
43797	ciprofloxacin 500mg tablets (sandoz ltd)
45285	ciprofloxacin 500mg tablets (teva uk ltd)
34494	ciprofloxacin 500mg tablets (wockhardt uk ltd)
34973	ciprofloxacin 750mg tablet (niche generics ltd)
1837	ciprofloxacin 750mg tablets
29472	ciprofloxacin 750mg tablets (a a h pharmaceuticals ltd)
43517	ciprofloxacin 750mg tablets (actavis uk ltd)
52099	ciprofloxacin 750mg tablets (bristol laboratories ltd)
56856	ciprofloxacin 750mg tablets (ranbaxy (uk) ltd)
28544	ciprofloxaxin 400mg/200ml in glucose 5% infusion
9154	ciproxin 100mg tablets (bayer plc)
1202	ciproxin 250mg tablets (bayer plc)
52353	ciproxin 250mg tablets (doncaster pharmaceuticals ltd)
53519	ciproxin 250mg tablets (lexon (uk) ltd)
163	ciproxin 250mg/5ml oral suspension (bayer plc)
728	ciproxin 500mg tablets (bayer plc)
52807	ciproxin 500mg tablets (mawdsley-brooks & company ltd)
52177	ciproxin 500mg tablets (sigma pharmaceuticals plc)
49839	ciproxin 500mg tablets (waymade healthcare plc)
7752	ciproxin 750mg tablets (bayer plc)
45591	clarie xl 500mg tablets (teva uk ltd)
10326	clarithromycin 125mg granules straws
331	clarithromycin 125mg/5ml oral suspension
45795	clarithromycin 125mg/5ml oral suspension (a a h pharmaceuticals ltd)
54903	clarithromycin 125mg/5ml oral suspension (alliance healthcare (distribution) ltd)
51831	clarithromycin 125mg/5ml oral suspension (phoenix healthcare distribution ltd)
41453	clarithromycin 125mg/5ml oral suspension (ranbaxy (uk) ltd)
53168	clarithromycin 125mg/5ml oral suspension (sandoz ltd)
26059	clarithromycin 187.5mg granules straws
765	clarithromycin 250mg granules sachets
17645	clarithromycin 250mg granules straws
537	clarithromycin 250mg tablets
34650	clarithromycin 250mg tablets (a a h pharmaceuticals ltd)
54472	clarithromycin 250mg tablets (accord healthcare ltd)

48163	clarithromycin 250mg tablets (actavis uk ltd)
52158	clarithromycin 250mg tablets (alliance healthcare (distribution) ltd)
54882	clarithromycin 250mg tablets (almus pharmaceuticals ltd)
52719	clarithromycin 250mg tablets (apotex uk ltd)
53086	clarithromycin 250mg tablets (doncaster pharmaceuticals ltd)
34394	clarithromycin 250mg tablets (generics (uk) ltd)
51154	clarithromycin 250mg tablets (kent pharmaceuticals ltd)
53153	clarithromycin 250mg tablets (phoenix healthcare distribution ltd)
53688	clarithromycin 250mg tablets (ranbaxy (uk) ltd)
47582	clarithromycin 250mg tablets (sandoz ltd)
50946	clarithromycin 250mg tablets (sigma pharmaceuticals plc)
54269	clarithromycin 250mg tablets (somex pharma)
34533	clarithromycin 250mg tablets (teva uk ltd)
54897	clarithromycin 250mg tablets (tillomed laboratories ltd)
53144	clarithromycin 250mg tablets (wockhardt uk ltd)
5357	clarithromycin 250mg/5ml oral suspension
54241	clarithromycin 250mg/5ml oral suspension (a a h pharmaceuticals ltd)
55148	clarithromycin 250mg/5ml oral suspension (alliance healthcare (distribution) ltd)
34811	clarithromycin 250mg/5ml oral suspension (ranbaxy (uk) ltd)
53179	clarithromycin 250mg/5ml oral suspension (sandoz ltd)
54208	clarithromycin 250mg/5ml oral suspension (sigma pharmaceuticals plc)
55428	clarithromycin 250mg/5ml oral suspension (waymade healthcare plc)
54529	clarithromycin 500mg modified-release tablet (hillcross pharmaceuticals ltd)
6803	clarithromycin 500mg modified-release tablets
681	clarithromycin 500mg tablets
38163	clarithromycin 500mg tablets (a a h pharmaceuticals ltd)
51426	clarithromycin 500mg tablets (accord healthcare ltd)
48023	clarithromycin 500mg tablets (actavis uk ltd)
49939	clarithromycin 500mg tablets (alliance healthcare (distribution) ltd)
53715	clarithromycin 500mg tablets (almus pharmaceuticals ltd)
53776	clarithromycin 500mg tablets (doncaster pharmaceuticals ltd)
34608	clarithromycin 500mg tablets (generics (uk) ltd)
53703	clarithromycin 500mg tablets (kent pharmaceuticals ltd)
46488	clarithromycin 500mg tablets (ranbaxy (uk) ltd)
40784	clarithromycin 500mg tablets (sandoz ltd)
53109	clarithromycin 500mg tablets (somex pharma)
34974	clarithromycin 500mg tablets (teva uk ltd)
53875	clarithromycin 500mg tablets (tillomed laboratories ltd)
11433	clarithromycin 500mg with lansoprazole 30mg and amoxicillin 500mg triple pack
6497	clarithromycin 500mg with metronidazole 400mg with lansoprazole 30mg triple pack
28349	clarosip 125mg granules for oral suspension straws (grunenthal ltd)
31689	clarosip 187.5mg granules for oral suspension straws (grunenthal ltd)
31690	clarosip 250mg granules for oral suspension straws (grunenthal ltd)

9925	clavulanic acid 125mg with amoxicillin 250mg tablets
13239	clavulanic acid 125mg with amoxicillin 500mg tablets
24006	clavulanic acid 31mg with amoxcillin 125mg/5ml oral suspension
21775	clavulanic acid 31mg with amoxicillin 125mg/5ml sugar free oral suspension
20432	clavulanic acid 57mg with amoxicillin 400mg/5ml sugar free suspension
42485	clavulanic acid 62mg with amoxicillin 250mg/5ml oral suspension
16612	clavulanic acid 62mg with amoxicillin 250mg/5ml sugar free suspension
24093	clavulanic acid with amoxicillin dispersible tablets
12504	clomocycline 170mg capsules
10200	co-amoxiclav 125mg/31mg/5ml oral suspension
54052	co-amoxiclav 125mg/31mg/5ml oral suspension (a a h pharmaceuticals ltd)
54732	co-amoxiclav 125mg/31mg/5ml oral suspension (generics (uk) ltd)
1638	co-amoxiclav 125mg/31mg/5ml oral suspension sugar free
43548	co-amoxiclav 125mg/31mg/5ml oral suspension sugar free (a a h pharmaceuticals ltd)
54324	co-amoxiclav 125mg/31mg/5ml oral suspension sugar free (actavis uk ltd)
54452	co-amoxiclav 125mg/31mg/5ml oral suspension sugar free (alliance healthcare (distribution) ltd)
54808	co-amoxiclav 125mg/31mg/5ml oral suspension sugar free (almus pharmaceuticals ltd)
28874	co-amoxiclav 125mg/31mg/5ml oral suspension sugar free (ivax pharmaceuticals uk ltd)
56884	co-amoxiclav 125mg/31mg/5ml oral suspension sugar free (phoenix healthcare distribution ltd)
34680	co-amoxiclav 125mg/31mg/5ml oral suspension sugar free (ranbaxy (uk) ltd)
34972	co-amoxiclav 125mg/31mg/5ml oral suspension sugar free (sandoz ltd)
829	co-amoxiclav 250mg/125mg dispersible tablets sugar free
545	co-amoxiclav 250mg/125mg tablets
30786	co-amoxiclav 250mg/125mg tablets (a a h pharmaceuticals ltd)
19209	co-amoxiclav 250mg/125mg tablets (actavis uk ltd)
51623	co-amoxiclav 250mg/125mg tablets (alliance healthcare (distribution) ltd)
48147	co-amoxiclav 250mg/125mg tablets (almus pharmaceuticals ltd)
34297	co-amoxiclav 250mg/125mg tablets (generics (uk) ltd)
28871	co-amoxiclav 250mg/125mg tablets (ivax pharmaceuticals uk ltd)
33693	co-amoxiclav 250mg/125mg tablets (kent pharmaceuticals ltd)
50446	co-amoxiclav 250mg/125mg tablets (phoenix healthcare distribution ltd)
30783	co-amoxiclav 250mg/125mg tablets (ranbaxy (uk) ltd)
19414	co-amoxiclav 250mg/125mg tablets (sandoz ltd)
34734	co-amoxiclav 250mg/125mg tablets (teva uk ltd)
55312	co-amoxiclav 250mg/125mg tablets (waymade healthcare plc)
46915	co-amoxiclav 250mg/125mg tablets (zentiva)
7364	co-amoxiclav 250mg/62mg/5ml oral suspension
54708	co-amoxiclav 250mg/62mg/5ml oral suspension (a a h pharmaceuticals ltd)
54780	co-amoxiclav 250mg/62mg/5ml oral suspension (generics (uk) ltd)

524	co-amoxiclav 250mg/62mg/5ml oral suspension sugar free
42227	co-amoxiclav 250mg/62mg/5ml oral suspension sugar free (a a h pharmaceuticals ltd)
51678	co-amoxiclav 250mg/62mg/5ml oral suspension sugar free (almus pharmaceuticals ltd)
37304	co-amoxiclav 250mg/62mg/5ml oral suspension sugar free (ivax pharmaceuticals uk ltd)
40320	co-amoxiclav 250mg/62mg/5ml oral suspension sugar free (ranbaxy (uk) ltd)
46918	co-amoxiclav 250mg/62mg/5ml oral suspension sugar free (sandoz ltd)
34234	co-amoxiclav 250mg/62mg/5ml oral suspension sugar free (teva uk ltd)
56578	co-amoxiclav 250mg/62mg/5ml oral suspension sugar free (waymade healthcare plc)
6687	co-amoxiclav 400mg/57mg/5ml oral suspension sugar free
51637	co-amoxiclav 400mg/57mg/5ml oral suspension sugar free (a a h pharmaceuticals ltd)
641	co-amoxiclav 500mg/125mg tablets
33701	co-amoxiclav 500mg/125mg tablets (a a h pharmaceuticals ltd)
50742	co-amoxiclav 500mg/125mg tablets (actavis uk ltd)
50341	co-amoxiclav 500mg/125mg tablets (alliance healthcare (distribution) ltd)
53609	co-amoxiclav 500mg/125mg tablets (apc pharmaceuticals & chemicals (europe) ltd)
53996	co-amoxiclav 500mg/125mg tablets (aurobindo pharma ltd)
30705	co-amoxiclav 500mg/125mg tablets (generics (uk) ltd)
29356	co-amoxiclav 500mg/125mg tablets (ivax pharmaceuticals uk ltd)
40148	co-amoxiclav 500mg/125mg tablets (kent pharmaceuticals ltd)
49610	co-amoxiclav 500mg/125mg tablets (medreich plc)
54591	co-amoxiclav 500mg/125mg tablets (phoenix healthcare distribution ltd)
34493	co-amoxiclav 500mg/125mg tablets (ranbaxy (uk) ltd)
32910	co-amoxiclav 500mg/125mg tablets (sandoz ltd)
29353	co-amoxiclav 500mg/125mg tablets (teva uk ltd)
44154	co-amoxiclav 500mg/125mg tablets (zentiva)
21860	cyclodox 100mg capsule (berk pharmaceuticals ltd)
21878	demix 100 capsules (ashbourne pharmaceuticals ltd)
21828	demix 50 capsules (ashbourne pharmaceuticals ltd)
2428	distaclor 125mg/5ml liquid (dista products ltd)
25384	distaclor 125mg/5ml oral suspension (flynn pharma ltd)
4576	distaclor 250mg capsule (dista products ltd)
9219	distaclor 250mg/5ml liquid (dista products ltd)
22042	distaclor 250mg/5ml oral suspension (flynn pharma ltd)
7889	distaclor 375mg modified-release tablet (dista products ltd)
319	distaclor 500mg capsule (dista products ltd)
18243	distaclor 500mg capsules (flynn pharma ltd)
3523	distaclor 500mg modified-release tablet (dista products ltd)
20992	distaclor mr 375mg tablets (flynn pharma ltd)
21038	doxatet 100mg tablet (manufacturer unknown)
2884	doxycycline (as hyclate) 100mg dispersible tablets

970	doxycycline (as hyclate) 100mg tablets
12987	doxycycline (as hyclate) 50mg capsules with microgranules
23819	doxycycline (as hyclate) 50mg capsules with microgranules
8724	doxycycline (as hyclate) 50mg/5ml oral solution
41560	doxycycline 100mg capsule (ivax pharmaceuticals uk ltd)
34594	doxycycline 100mg capsule (neo laboratories ltd)
34423	doxycycline 100mg capsule (pliva pharma ltd)
41605	doxycycline 100mg capsule (sandoz ltd)
1046	doxycycline 100mg capsules
24149	doxycycline 100mg capsules (a a h pharmaceuticals ltd)
34300	doxycycline 100mg capsules (actavis uk ltd)
49737	doxycycline 100mg capsules (alliance healthcare (distribution) ltd)
46807	doxycycline 100mg capsules (almus pharmaceuticals ltd)
32066	doxycycline 100mg capsules (generics (uk) ltd)
24126	doxycycline 100mg capsules (ivax pharmaceuticals uk ltd)
33671	doxycycline 100mg capsules (kent pharmaceuticals ltd)
53310	doxycycline 100mg capsules (sigma pharmaceuticals plc)
30739	doxycycline 100mg capsules (teva uk ltd)
55519	doxycycline 100mg capsules (waymade healthcare plc)
6396	doxycycline 100mg dispersible tablets sugar free
26747	doxycycline 100mg tablet (neo laboratories ltd)
40796	doxycycline 40mg modified-release capsules
264	doxycycline 50mg capsules
34175	doxycycline 50mg capsules (a a h pharmaceuticals ltd)
48095	doxycycline 50mg capsules (actavis uk ltd)
53973	doxycycline 50mg capsules (alliance healthcare (distribution) ltd)
34765	doxycycline 50mg capsules (generics (uk) ltd)
40391	doxycycline 50mg capsules (ivax pharmaceuticals uk ltd)
32419	doxycycline 50mg capsules (teva uk ltd)
23405	doxylar 100mg capsules (sandoz ltd)
23432	doxylar 50mg capsules (sandoz ltd)
17226	economycin 250mg capsule (ddsa pharmaceuticals ltd)
26111	economycin 250mg tablet (ddsa pharmaceuticals ltd)
40980	efracea 40mg modified-release capsules (galderma (uk) ltd)
4489	erycen 250mg tablet (berk pharmaceuticals ltd)
23017	erycen 500mg tablet (berk pharmaceuticals ltd)
318	erymax 250mg capsule (elan pharma)
10190	erymax 250mg gastro-resistant capsules (teva uk ltd)
14511	erymax sprinkle 125mg capsule (elan pharma)
9434	erymin 250mg/5ml oral suspension (elan pharma)
48017	erythoden 125mg/5ml liquid (stevenden healthcare)
41389	erythoden 250mg/5ml liquid (stevenden healthcare)
39616	erythrocin 250 tablets (amdipharm plc)
480	erythrocin 250mg tablet (abbott laboratories ltd)
1072	erythrocin 500 500mg tablet (abbott laboratories ltd)
39613	erythrocin 500 tablets (amdipharm plc)

53449	erythrocin 500 tablets (lexon (uk) ltd)
51984	erythrocin 500 tablets (mawdsley-brooks & company ltd)
53004	erythrocin 500 tablets (necessity supplies ltd)
50693	erythrocin 500 tablets (sigma pharmaceuticals plc)
50223	erythrocin 500 tablets (stephar (u.k.) ltd)
27768	erythrolar 250mg tablet (lagap)
50205	erythrolar 250mg tablets (ennogen pharma ltd)
4153	erythrolar 250mg/5ml liquid (lagap)
23954	erythrolar 500mg tablet (lagap)
49301	erythrolar 500mg tablets (ennogen pharma ltd)
3209	erythromid 250mg tablet (abbott laboratories ltd)
9148	erythromid ds 500mg tablet (abbott laboratories ltd)
1376	erythromycin 100 mg syr
7792	erythromycin 12 mg syr
14429	erythromycin 125mg sprinkle capsules
34231	erythromycin 125mg/5ml liquid (berk pharmaceuticals ltd)
33248	erythromycin 125mg/5ml liquid (ivax pharmaceuticals uk ltd)
397	erythromycin 125mg/5ml oral suspension
9656	erythromycin 2% gel
1969	erythromycin 250 mg mix
29154	erythromycin 250mg capsule (actavis uk ltd)
103	erythromycin 250mg gastro-resistant capsules
33686	erythromycin 250mg gastro-resistant capsules (a a h pharmaceuticals ltd)
50580	erythromycin 250mg gastro-resistant capsules (actavis uk ltd)
50694	erythromycin 250mg gastro-resistant capsules (alliance healthcare (distribution) ltd)
55133	erythromycin 250mg gastro-resistant capsules (kent pharmaceuticals ltd)
49952	erythromycin 250mg gastro-resistant capsules (phoenix healthcare distribution ltd)
34512	erythromycin 250mg gastro-resistant capsules (teva uk ltd)
55397	erythromycin 250mg gastro-resistant capsules (waymade healthcare plc)
34837	erythromycin 250mg gastro-resistant tablet (co-pharma ltd)
63	erythromycin 250mg gastro-resistant tablets
24127	erythromycin 250mg gastro-resistant tablets (a a h pharmaceuticals ltd)
33703	erythromycin 250mg gastro-resistant tablets (abbott laboratories ltd)
29344	erythromycin 250mg gastro-resistant tablets (actavis uk ltd)
52906	erythromycin 250mg gastro-resistant tablets (alliance healthcare (distribution) ltd)
42661	erythromycin 250mg gastro-resistant tablets (almus pharmaceuticals ltd)
52952	erythromycin 250mg gastro-resistant tablets (co-pharma ltd)
42296	erythromycin 250mg gastro-resistant tablets (dr reddy's laboratories (uk) ltd)
34334	erythromycin 250mg gastro-resistant tablets (generics (uk) ltd)
24129	erythromycin 250mg gastro-resistant tablets (ivax pharmaceuticals uk ltd)
53986	erythromycin 250mg gastro-resistant tablets (medreich plc)
55483	erythromycin 250mg gastro-resistant tablets (milpharm ltd)

52428	erythromycin 250mg gastro-resistant tablets (phoenix healthcare distribution ltd)
31530	erythromycin 250mg gastro-resistant tablets (ranbaxy (uk) ltd)
34479	erythromycin 250mg gastro-resistant tablets (sovereign medical ltd)
33685	erythromycin 250mg gastro-resistant tablets (teva uk ltd)
34873	erythromycin 250mg tablet (berk pharmaceuticals ltd)
34189	erythromycin 250mg tablet (c p pharmaceuticals ltd)
553	erythromycin 250mg.5ml oral suspension
47242	erythromycin 250mg/5ml liquid (c p pharmaceuticals ltd)
41584	erythromycin 250mg/5ml liquid (ivax pharmaceuticals uk ltd)
3408	erythromycin 500 mg cap
401	erythromycin 500mg ec gastro-resistant tablets
34869	erythromycin 500mg tablet (c p pharmaceuticals ltd)
41604	erythromycin 500mg tablet (hillcross pharmaceuticals ltd)
26365	erythromycin 500mg tablet (ivax pharmaceuticals uk ltd)
55300	erythromycin 500mg tablet (teva uk ltd)
47676	erythromycin 500mg/5ml liquid (c p pharmaceuticals ltd)
2326	erythromycin 500mg/5ml oral suspension
37796	erythromycin estolate 125mg/5ml suspension
9903	erythromycin estolate 250mg capsules
40073	erythromycin estolate 250mg/5ml suspension
37694	erythromycin estolate 500mg tablets
2429	erythromycin ethyl succinate 125mg/5ml oral suspension
13167	erythromycin ethyl succinate 125mg/5ml oral suspension (a a h pharmaceuticals ltd)
49978	erythromycin ethyl succinate 125mg/5ml oral suspension (focus pharmaceuticals ltd)
50948	erythromycin ethyl succinate 125mg/5ml oral suspension (phoenix healthcare distribution ltd)
47126	erythromycin ethyl succinate 125mg/5ml oral suspension (pinewood healthcare)
34779	erythromycin ethyl succinate 125mg/5ml oral suspension (sandoz ltd)
4672	erythromycin ethyl succinate 125mg/5ml oral suspension sugar free
33697	erythromycin ethyl succinate 125mg/5ml oral suspension sugar free (a a h pharmaceuticals ltd)
42659	erythromycin ethyl succinate 125mg/5ml oral suspension sugar free (abbott laboratories ltd)
55589	erythromycin ethyl succinate 125mg/5ml oral suspension sugar free (alliance healthcare (distribution) ltd)
48101	erythromycin ethyl succinate 125mg/5ml oral suspension sugar free (focus pharmaceuticals ltd)
33695	erythromycin ethyl succinate 125mg/5ml oral suspension sugar free (generics (uk) ltd)
34795	erythromycin ethyl succinate 125mg/5ml oral suspension sugar free (ivax pharmaceuticals uk ltd)
45870	erythromycin ethyl succinate 125mg/5ml oral suspension sugar free (pinewood healthcare)
33705	erythromycin ethyl succinate 125mg/5ml oral suspension sugar free (teva uk ltd)

2376	erythromycin ethyl succinate 250mg/5ml oral suspension
13120	erythromycin ethyl succinate 250mg/5ml oral suspension (a a h pharmaceuticals ltd)
32902	erythromycin ethyl succinate 250mg/5ml oral suspension (kent pharmaceuticals ltd)
46696	erythromycin ethyl succinate 250mg/5ml oral suspension (sandoz ltd)
2225	erythromycin ethyl succinate 250mg/5ml oral suspension sugar free
32898	erythromycin ethyl succinate 250mg/5ml oral suspension sugar free (a a h pharmaceuticals ltd)
46154	erythromycin ethyl succinate 250mg/5ml oral suspension sugar free (abbott laboratories ltd)
52860	erythromycin ethyl succinate 250mg/5ml oral suspension sugar free (alliance healthcare (distribution) ltd)
33694	erythromycin ethyl succinate 250mg/5ml oral suspension sugar free (generics (uk) ltd)
30177	erythromycin ethyl succinate 250mg/5ml oral suspension sugar free (ivax pharmaceuticals uk ltd)
34853	erythromycin ethyl succinate 250mg/5ml oral suspension sugar free (teva uk ltd)
733	erythromycin ethyl succinate 500mg tablets
2226	erythromycin ethyl succinate 500mg/5ml oral suspension
30980	erythromycin ethyl succinate 500mg/5ml oral suspension (kent pharmaceuticals ltd)
14171	erythromycin ethyl succinate 500mg/5ml oral suspension sugar free
31514	erythromycin ethyl succinate 500mg/5ml oral suspension sugar free (abbott laboratories ltd)
25595	erythromycin ethyl succinate 500mg/5ml oral suspension sugar free (ivax pharmaceuticals uk ltd)
27203	erythromycin ethyl succinate 500mg/5ml oral suspension sugar free (teva uk ltd)
25751	erythromycin ethylsuccinate (coated) 250mg/5ml oral suspension sugar free
30234	erythromycin ethylsuccinate 125mg sachets
12330	erythromycin ethylsuccinate 1g sachets
13635	erythromycin ethylsuccinate 250mg sachets
15713	erythromycin ethylsuccinate 500mg sachets
1037	erythromycin ethylsuccinate sf 125 mg/5ml sus
3907	erythromycin sf sach 250 mg
438	erythromycin stearate 250mg tablets
2350	erythromycin stearate 500mg tablets
3572	erythroped 250mg powder (abbott laboratories ltd)
16747	erythroped 250mg sachets (abbott laboratories ltd)
105	erythroped 250mg/5ml liquid (abbott laboratories ltd)
532	erythroped 250mg/5ml oral suspension (abbott laboratories ltd)
4596	erythroped a 1g sachets (abbott laboratories ltd)
327	erythroped a 500mg tablet (abbott laboratories ltd)
39632	erythroped a 500mg tablets (amdipharm plc)
54098	erythroped a 500mg tablets (lexon (uk) ltd)
56203	erythroped a 500mg tablets (sigma pharmaceuticals plc)

4372	erythroped forte 500mg sachets (abbott laboratories ltd)
993	erythroped forte 500mg/5ml liquid (abbott laboratories ltd)
4610	erythroped forte 500mg/5ml oral suspension (abbott laboratories ltd)
39642	erythroped forte sf 500mg/5ml oral suspension (amdipharm plc)
3042	erythroped pi 125mg sachets (abbott laboratories ltd)
997	erythroped pi 125mg/5ml liquid (abbott laboratories ltd)
825	erythroped pi 125mg/5ml oral suspension (abbott laboratories ltd)
39623	erythroped pi sf 125mg/5ml oral suspension (amdipharm plc)
39669	erythroped sf 250mg/5ml oral suspension (amdipharm plc)
18930	flemoxin 375mg soluble tablet (paines & byrne ltd)
24396	flemoxin 750mg soluble tablet (paines & byrne ltd)
14386	galenamox 125mg/5ml oral suspension (galen ltd)
14371	galenamox 250mg capsules (galen ltd)
14407	galenamox 250mg/5ml oral suspension (galen ltd)
14396	galenamox 500mg capsules (galen ltd)
18682	ilosone 125mg/5ml liquid (dista products ltd)
17207	ilosone 250mg capsule (dista products ltd)
19330	ilosone 250mg/5ml liquid (dista products ltd)
18643	ilosone 500mg tablet (dista products ltd)
23244	ilotycin 250mg tablet (eli lilly and company ltd)
12541	imperacin 250mg tablet (astrazeneca uk ltd)
7485	keflex 125mg/5ml liquid (eli lilly and company ltd)
27072	keflex 125mg/5ml oral suspension (flynn pharma ltd)
7430	keflex 250mg capsule (eli lilly and company ltd)
11989	keflex 250mg capsules (flynn pharma ltd)
9157	keflex 250mg tablet (eli lilly and company ltd)
830	keflex 250mg tablets (flynn pharma ltd)
10455	keflex 250mg/5ml liquid (eli lilly and company ltd)
28722	keflex 250mg/5ml oral suspension (flynn pharma ltd)
12276	keflex 500mg capsule (eli lilly and company ltd)
24618	keflex 500mg capsules (flynn pharma ltd)
9603	keflex 500mg tablet (eli lilly and company ltd)
31110	keflex 500mg tablets (flynn pharma ltd)
26233	keftid 125mg/5ml oral suspension (co-pharma ltd)
26207	keftid 250mg capsules (co-pharma ltd)
41853	keftid 250mg/5ml oral suspension (co-pharma ltd)
26236	keftid 500mg capsules (co-pharma ltd)
33304	kerymax 250mg gastro-resistant capsules (kent pharmaceuticals ltd)
26989	kiflone 125mg/5ml oral solution (berk pharmaceuticals ltd)
21835	kiflone 250mg capsule (berk pharmaceuticals ltd)
21979	kiflone 250mg/5ml oral solution (berk pharmaceuticals ltd)
27017	kiflone 500mg capsule (berk pharmaceuticals ltd)
26992	kiflone 500mg tablet (berk pharmaceuticals ltd)
3736	klaricid 125mg/5ml oral suspension (abbott laboratories ltd)
2719	klaricid 250mg tablets (abbott laboratories ltd)
52411	klaricid 250mg tablets (necessity supplies ltd)

9583	klaricid 250mg/5ml oral suspension (abbott laboratories ltd)
6623	klaricid 500 tablets (abbott laboratories ltd)
14816	klaricid adult 250mg granules sachets (abbott laboratories ltd)
38997	klaricid paediatric 125mg/5ml oral suspension (abbott laboratories ltd)
39010	klaricid paediatric 250mg/5ml oral suspension (abbott laboratories ltd)
6121	klaricid xl 500mg tablets (abbott laboratories ltd)
15290	lansoprazole with amoxicillin and clarithromycin 30mg + 500mg + 500mg triple pack
7439	ledermycin 150mg capsule (wyeth pharmaceuticals)
16613	ledermycin 150mg capsules (mercury pharma group ltd)
22076	ledermycin 300mg tablet (wyeth pharmaceuticals)
6295	levofloxacin 250mg tablets
55708	levofloxacin 250mg tablets (actavis uk ltd)
56012	levofloxacin 250mg tablets (dr reddy's laboratories (uk) ltd)
5238	levofloxacin 500mg tablets
53673	levofloxacin 500mg/100ml infusion bags
19001	megaclor 170mg capsule (pharmax ltd)
6306	moxifloxacin 400mg tablets
17222	mysteclin oral solution (bristol-myers squibb pharmaceuticals ltd)
15071	nordox 100mg capsule (sankyo pharma uk ltd)
8393	novobiocin/tetracycline 125 mg cap
25752	nystatin with tetracycline hc capsule
9361	oxymycin 250mg tablets (dr reddy's laboratories (uk) ltd)
2458	oxytetracycline 100 mg tab
9034	oxytetracycline 125mg/5ml syrup
8285	oxytetracycline 250 mg syr
132	oxytetracycline 250mg capsules
34888	oxytetracycline 250mg tablet (c p pharmaceuticals ltd)
77	oxytetracycline 250mg tablets
34044	oxytetracycline 250mg tablets (a a h pharmaceuticals ltd)
34040	oxytetracycline 250mg tablets (actavis uk ltd)
34336	oxytetracycline 250mg tablets (ivax pharmaceuticals uk ltd)
40483	oxytetracycline 250mg tablets (sandoz ltd)
34141	oxytetracycline 250mg tablets (teva uk ltd)
28291	oxytetracycline 3%/hydrocortisone 1%
10542	oxytetracycline hcl/hydrocortisone .5 % ear
17703	oxytetramix 250 tablets (ashbourne pharmaceuticals ltd)
30520	primacine 125mg/5ml liquid (pinewood healthcare)
39118	primacine 250mg/5ml liquid (pinewood healthcare)
27504	primacine 500mg/5ml liquid (pinewood healthcare)
27681	ranclav 125mg/31mg/5ml sf oral suspension (ranbaxy (uk) ltd)
25370	ranclav 375mg tablets (ranbaxy (uk) ltd)
22017	respillin 125mg/5ml oral solution (opd pharm)
22015	respillin 125mg/5ml oral solution (opd pharm)
24203	respillin 250mg capsule (opd pharm)
24200	respillin 500mg capsule (opd pharm)

31428	retcin 250mg tablet (ddsa pharmaceuticals ltd)
21808	rommix 125mg/5ml oral suspension sugar free (ashbourne pharmaceuticals ltd)
11611	rommix 250 ec tablets (ashbourne pharmaceuticals ltd)
25278	rommix 500mg tablet (ashbourne pharmaceuticals ltd)
24097	rondomycin 150mg capsule (pfizer ltd)
18109	sebomin mr 100mg capsules (actavis uk ltd)
37440	sebren mr 100mg capsules (teva uk ltd)
19693	sustamycin 250mg capsule (boehringer mannheim uk ltd)
17693	tavanic 250mg tablets (sanofi)
6206	tavanic 500mg tablets (sanofi)
27254	tenkorex 500mg capsule (opd pharm)
7455	terramycin 250mg capsule (pfizer ltd)
17467	terramycin 250mg tablets (pfizer ltd)
9014	tetrabid-organon 250mg capsule (organon laboratories ltd)
8219	tetrachel 250mg capsule (berk pharmaceuticals ltd)
3816	tetrachel 250mg tablet (berk pharmaceuticals ltd)
25017	tetracycline
56044	tetracycline 125mg/5ml oral solution
8284	tetracycline 125mg/5ml syrup
21804	tetracycline 125mg/5ml syrup
41547	tetracycline 250mg capsule (berk pharmaceuticals ltd)
121	tetracycline 250mg capsules
34011	tetracycline 250mg capsules
56181	tetracycline 250mg tablet (celltech pharma europe ltd)
45271	tetracycline 250mg tablet (numark management ltd)
386	tetracycline 250mg tablets
43538	tetracycline 250mg tablets (a a h pharmaceuticals ltd)
41636	tetracycline 250mg tablets (actavis uk ltd)
54214	tetracycline 250mg tablets (alliance healthcare (distribution) ltd)
53117	tetracycline 250mg tablets (almus pharmaceuticals ltd)
48100	tetracycline 250mg tablets (teva uk ltd)
2922	tetracycline 250mg with nystatin 250000units tablets
2636	tetracycline 500 mg cap
3528	tetracycline 500 mg tab
21654	tetracycline ear/eye
21629	tetracycline eye
31425	tetracycline hcl/pancreatic concentrate cap
28736	tetracycline hydrochloride/amphotericin syr
15355	tetracycline with chlortetracycline & demeclocycline tablets
25071	tetracycline with nystatin capsules
4951	tetralysal 300 capsules (galderma (uk) ltd)
20054	tetralysal 408mg capsule (pharmacia ltd)
25280	tiloryth 250mg gastro-resistant capsules (tillomed laboratories ltd)
268	vibramycin 100mg capsules (pfizer ltd)
3152	vibramycin 100mg dispersible tablet (pfizer ltd)

10454	vibramycin 50mg/5ml oral solution (pfizer ltd)
9267	vibramycin acne pack 50mg capsules (pfizer ltd)
56198	vibramycin-d 100mg dispersible tablets (mawdsley-brooks & company ltd)
14904	vibramycin-d 100mg dispersible tablets (pfizer ltd)
52967	vibramycin-d 100mg dispersible tablets (stephar (u.k.) ltd)
53135	vibramycin-d 100mg dispersible tablets (waymade healthcare plc)
26392	vibrox 100mg capsules (kent pharmaceuticals ltd)
21829	zoxycil 250mg capsule (trinity pharmaceuticals ltd)
26262	zoxycil 500mg capsule (trinity pharmaceuticals ltd)

Codes used to identify annual reviews and rescue pack prescriptions

Annual review and rescue pack prescription codes

Medical code	Read term
9520	Chronic obstructive pulmonary disease monitoring
10043	Asthma annual review
11287	Chronic obstructive pulmonary disease annual review
25997	Deferred antibiotic therapy
28743	Number of COPD exacerbations in past year
100459	Advance supply of steroid medication
101042	Issue of chronic obstructive pulmonary disease rescue pack

Table S1. PPV and sensitivity of CPRD strategies to identify hospitalisations for AECOPD using different HES definitions as reference standard using day of admission in HES only

HES AECOPD definition	**CPRD strategy**	**PPV (95% CI)**	**Sensitivity (95% CI)**
AECOPD hospitalisation or LRTI code in any position or COPD in first position in any FCE	**AECOPD identified by algorithm**	0.7% (0.7-0.7%)	7.2% (6.9-7.6%)
	Non-specific hospitalisation code	10.3% (10.1-10.6%)	27.1% (26.5-27.7%)
Either specific AECOPD code in any position or COPD code in 1st position	**AECOPD identified by algorithm**	0.6% (0.6-0.6%)	7.2% (6.9-7.6%)
	Non-specific hospitalisation code	9.1% (8.9-9.3%)	27.6% (27.0-28.2%)
Either specific AECOPD code in first position in any finished consultant episode	**AECOPD identified by algorithm**	0.6% (0.6-0.6%)	7.4% (7.1-7.9%)
	Non-specific hospitalisation code	8.7% (8.5-8.9%)	28.1% (27.4-28.7%)

Table S2. PPV and sensitivity of CPRD strategies to identify hospitalisations for AECOPD using different HES definitions as reference standard using day of admission in HES only

HES AECOPD definition	**CPRD strategy**	**PPV (95% CI)**	**Sensitivity (95% CI)**
AECOPD hospitalisation or LRTI code in any position or COPD in first position in any FCE	**AECOPD hospitalisation code**	47.6% (44.3-50.8%)	1.9% (1.7-2.0%)
	AECOPD identified using validated algorithm & hospitalisation code	41.9% (39.8-44.0%)	3.7% (3.5-4.0%)
Either specific AECOPD code in any position or COPD code in 1st position	**AECOPD hospitalisation code**	43.6% (40.5-46.9%)	2.1% (1.9-2.3%)
	AECOPD identified using validated algorithm & hospitalisation code	36.8% (34.7-38.9%)	3.7% (3.5-4.0%)
Either specific AECOPD code in first position in any finished consultant episode	**AECOPD hospitalisation code**	46.5% (44.9-48.2%)	2.1% (1.9-2.3%)
	AECOPD identified using validated algorithm & hospitalisation code	35.3% (33.2-37.4%)	3.8% (3.5-4.1%)

Table S3. PPV and sensitivity of record of AECOPD or non-specific hospitalisation code to identify hospitalisations for AECOPD using different HES definitions as reference standard allowing 30 days after HES record of hospitalisation for AECOPD

HES AECOPD definition	**CPRD strategy**	**PPV (95% CI)**	**Sensitivity (95% CI)**
AECOPD hospitalisation or LRTI code in any position or COPD in first position in any FCE	**AECOPD identified by algorithm**	1.8% (1.7-1.8%)	34.2% (33.7-34.6%)
	Non-specific hospitalisation code	14.5% (14.3-14.6%)	53.5% (53.0-54.0%)
Either specific AECOPD code in any position or COPD code in 1st position	**AECOPD identified by algorithm**	1.5% (1.5-1.6%)	34.6% (34.1-35.1%)
	Non-specific hospitalisation code	12.6% (12.5-12.8%)	54.1% (53.6-54.6%)
Either specific AECOPD code in first position in any finished consultant episode	**AECOPD identified by algorithm**	1.5% (1.4-1.5%)	35.1% (34.6-35.6%)
	Non-specific hospitalisation code	12.0% (11.9-12.2%)	54.8% (54.3-55.3%)

Table S4. PPV and sensitivity of CPRD strategies to identify hospitalisations for AECOPD using different HES definitions as reference standard allowing 60 days after HES record of hospitalisation for AECOPD

HES AECOPD definition	**CPRD strategy**	**PPV (95% CI)**	**Sensitivity (95% CI)**
AECOPD hospitalisation or LRTI code in any position or COPD in first position in any FCE	**AECOPD hospitalisation code**	50.7% (49.1-52.3%)	4.4% (4.3-4.6%)
	AECOPD identified using validated algorithm & hospitalisation code	46.1% (44.3-47.8%)	6.1% (5.8-6.4%)
Either specific AECOPD code in any position or COPD code in 1st position	**AECOPD hospitalisation code**	49.5% (48.0-51.1%)	5.0% (4.8-5.3%)
	AECOPD identified using validated algorithm & hospitalisation code	41.2% (39.5-42.9%)	6.2% (5.9-6.6%)
Either specific AECOPD code in first position in any finished consultant episode	**AECOPD hospitalisation code**	46.6% (45.0-48.2%)	5.0% (4.8-5.3%)
	AECOPD identified using validated algorithm & hospitalisation code	39.5% (37.8-41.2%)	6.4% (6.1-6.8%)

Table S5. PPV and sensitivity of record of AECOPD or non-specific hospitalisation code to identify hospitalisations for AECOPD using different HES definitions as reference standard allowing 60 days after HES record of hospitalisation for AECOPD

HES AECOPD definition	**CPRD strategy**	**PPV (95% CI)**	**Sensitivity (95% CI)**
AECOPD hospitalisation or LRTI code in any position or COPD in first position in any FCE	**AECOPD identified by algorithm**	2.3% (2.3-2.3%)	46.3% (45.8-46.7%)
	Non-specific hospitalisation code	14.5% (14.4-14.7%)	55.9% (55.4-56.4%)
Either specific AECOPD code in any position or COPD code in 1st position	**AECOPD identified by algorithm**	2.0% (2.0-2.1%)	46.8% (46.3-47.3%)
	Non-specific hospitalisation code	12.7% (12.5-12.9%)	56.5% (56.0-57.0%)
Either specific AECOPD code in first position in any finished consultant episode	**AECOPD identified by algorithm**	1.9% (1.9-1.9%)	47.3% (46.8-47.8%)
	Non-specific hospitalisation code	12.1% (11.9-12.2%)	57.2% (56.6-57.7%)

Table S6. Generic hospitalisation Read codes.

Read term	medcode
Admit to respiratory ITU	67786
In-patient stay 9 days	62577
In-patient stay 7 days	62578
Listed for admission to hosp.	9744
Discharge from adult intensive care service	53495
In-patient stay NOS	21153
Listed for hosp admission NOS	25524
In-patient stay 10 days	62574
In-patient stay > 12 hours	62572
Died in hospital	1868
Discharge by ITU specialist	37697
In-patient stay 12 days	62579
Intensive care monitoring	45334
Emergency hospital admission	314
Hospital admission note	43828
Under care of casualty doctor	59130
Under care of ITU specialist	42924
Duration of in-patient stay	56256
Discharge to tertiary referring hospital	43900
In-patient stay 8 days	62570
Night hospital care	46759
In-patient stay 11 days	36131
Patient in hospital	61893
Inpatient care	35252
Discharged from hospital	480
Admit geriatric emergency	30002
Admit to intensive care unit	11413
Discharge by adult ITU specialist	46901
Seen in hospital ward	6527
Self-referral to hospital	21264
Death in hospital	9059

Discharge from hospital	10866
Under care of adult ITU specialist	43881
In-patient stay 1 day	43149
Admit to intensive c.u. NOS	22374
Discharged from inpatient care	4774
Refer to hospital	3975
Under care of intensive care specialist	18522
Hospital inpatient	10533
In-patient stay 6 days	62575
Hospital inpatient report	63999
Patient died in community hospital	30357
Seen by adult ITU specialist	53501
Hospital death disch. NOS	28927
Other hospital admission NOS	1047
In-patient stay 14 days	60689
Discharge by adult intensive care specialist	68130
Discharge by intensive care specialist	47108
Self-referral to hospital NOS	38567
Seen by adult intensive care specialist	40768
Discharge from intensive care service	42177
Discharge from casualty service	48490
Referral to ITU specialist	69617
In-patient stay 4 days	62576
Admit medical emergency unsp.	18512
Hospital death discharge notif	28879
In-patient stay 13 days	62569
Admission to hospital	9821
Transferred from hospital	8091
Admit hospital emergency NOS	6885
Seen by ITU specialist	53496
In-patient stay 3 days	62573
In-patient stay 5 days	57174
Discharge to hospital	41976

Discharge from adult ITU service	47585
In-patient stay 2 days	62571
Under care of adult intensive care specialist	12839
Death notif. from hospital	28801
Patient died in hospital	6897
Hospital patient	23536
Inpatient care	51466
Admit to I.T.U.	8265
Referral to intensive care specialist	42668

Table S1: Incidence rate ratios of first myocardial infarction in risk periods after an acute exacerbation of COPD (AECOPD) relative to stable periods sensitivity analysisexcluding periods before first AECOPD.

Risk period	N outcome events (MI)	IRR (95% CI)
Total risk period (91 days)	898	1.73 (1.57-1.91)
1-3 days	92	3.07 (2.47-3.82)
4-7 days	99	2.59 (2.10-3.20)
8-14 days	161	2.53 (2.13-3.01)
15-28 days	217	2.03 (1.74-2.37)
29-91 days	329	1.23 (1.08-1.39)

Table S2: Incidence rate ratios of first myocardial infarction in risk periods after an acute exacerbation of COPD (AECOPD) relative to stable periods sensitivity analysis censoring within six months of MI

Risk period	N outcome events (MI)	IRR (95% CI)
Total risk period (91 days)	695	1.53 (1.38-1.68)
1-3 days	73	2.68 (2.11-3.41)
4-7 days	66	1.91 (1.48-2.45)
8-14 days	121	2.11 (1.74-2.56)
15-28 days	172	1.80 (1.52-2.12)
29-91 days	263	1.12 (0.97-1.29)

Table S3: Incidence rate ratios of first myocardial infarction in risk periods after an acute exacerbation of COPD (AECOPD) relative to stable periods sensitivity analysis censoring within 12 months of MI

Risk period	N outcome events (MI)	IRR (95% CI)
Total risk period (91 days)	586	1.49 (1.34-1.67)
1-3 days	59	2.48 (1.90-3.25)
4-7 days	56	1.85 (1.41-2.44)
8-14 days	104	2.08 (1.69-2.56)
15-28 days	138	1.67 (1.39-2.01)
29-91 days	229	1.14 (0.98-1.32)

Table S4. Read codes for MI.

Read term	medcode
acute myocardial infarction	241
heart attack	1204
mi - acute myocardial infarction	1677
inferior myocardial infarction nos	1678
other specified anterior myocardial infarction	5387
acute non-st segment elevation myocardial infarction	10562
acute st segment elevation myocardial infarction	12229
acute myocardial infarction nos	14658
anterior myocardial infarction nos	14897
lateral myocardial infarction nos	14898
posterior myocardial infarction nos	23892
acute transmural myocardial infarction of unspecif site	29758
acute posterolateral myocardial infarction	32854
other acute myocardial infarction	34803
other acute myocardial infarction nos	46017
true posterior myocardial infarction	63467
[x]acute transmural myocardial infarction of unspecif site	96838

Table S5. Angina Read codes.

Read term	medcode
angina on effort	1414
angina pectoris	1430
unstable angina	1431
crescendo angina	4656
h/o: angina pectoris	6336
unstable angina	7347
post infarct angina	9555
variant angina pectoris	11048
acute coronary syndrome	11983
stable angina	12804
prinzmetal's angina	12986
angina control	13185
angina control - improving	14782
angina control nos	15349
angina control - poor	15373
angina at rest	17307
worsening angina	18118
nocturnal angina	18125
angina control - good	19542
angina at rest	19655
angina decubitus	20095
angina pectoris nos	25842
new onset angina	26863
angina pectoris nos	28554
angina control - worsening	29300
angina decubitus nos	29902
ischaemic chest pain	32450
refractory angina	34328
[x]other forms of angina pectoris	39546
antianginal therapy	45960
h/o: angina in last year	57062

Table S6. Read codes for stroke.

Read term	medcode
intracerebral haemorrhage nos	3535
intracerebral haemorrhage	5051
cva - cerebrovascular accid due to intracerebral haemorrhage	6960
pontine haemorrhage	7912
cerebellar haemorrhage	13564
stroke due to intracerebral haemorrhage	18604
right sided intracerebral haemorrhage, unspecified	19201
left sided intracerebral haemorrhage, unspecified	28314
external capsule haemorrhage	30045
intracerebral haemorrhage, intraventricular	30202
intracerebral haemorrhage in hemisphere, unspecified	31060
cortical haemorrhage	31595
internal capsule haemorrhage	40338
basal nucleus haemorrhage	46316
[x]other intracerebral haemorrhage	53810
intracerebral haemorrhage, multiple localized	57315
bulbar haemorrhage	62342
[x]intracerebral haemorrhage in hemisphere, unspecified	96630
lobar cerebral haemorrhage	107440
infarction - cerebral	569
cerebral infarction nos	3149
cva - cerebral artery occlusion	5363
cerebellar infarction	5602
stroke due to cerebral arterial occlusion	6155
left sided cerebral infarction	9985
right sided cerebral infarction	10504
cerebral embolism	15019
brainstem infarction nos	15252
cerebral thrombosis	16517
cerebral infarct due to thrombosis of precerebral arteries	23671
cerebral infarction due to embolism of precerebral arteries	24446
brainstem infarction	25615
infarction of basal ganglia	26424
cerebral infarction due to embolism of cerebral arteries	27975
cerebrl infarctn due/unspcf occlusn or sten/cerebrl artrs	33543
cerebral embolus	34758
cerebral infarction due to thrombosis of cerebral arteries	36717
cereb infarct due unsp occlus/stenos precerebr arteries	40758
[x]other cerebral infarction	53745
[x]occlusion and stenosis of other precerebral arteries	90572
[x]cerebrl infarctn due/unspcf occlusn or sten/cerebrl artrs	91627

[x]occlusion and stenosis of other cerebral arteries	92036
[x]cereb infarct due unsp occlus/stenos precerebr arteries	94482
subarachnoid haemorrhage	1786
subarachnoid haemorrhage from posterior communicating artery	9696
subarachnoid haemorrh from intracranial artery, unspecif	17326
subarachnoid haemorrhage from middle cerebral artery	19412
subarachnoid haemorrhage nos	23580
subarachnoid haemorrhage following injury	28807
ruptured berry aneurysm	29939
subarachnoid haemorrhage from basilar artery	41910
subarachnoid haemorrhage from anterior communicating artery	42331
subarachnoid haemorrhage from carotid siphon and bifurcation	56007
subarachnoid haemorrhage from vertebral artery	60692
[x]subarachnoid haemorrh from intracranial artery, unspecif	108630
[x]subarachnoid haemorrhage from other intracranial arteries	108668
cva unspecified	1298
stroke and cerebrovascular accident unspecified	1469
cva - cerebrovascular accident unspecified	6116
stroke unspecified	6253
left sided cva	7780
brain stem stroke syndrome	8443
right sided cva	12833
cerebellar stroke syndrome	17322
middle cerebral artery syndrome	18689
posterior cerebral artery syndrome	19260
anterior cerebral artery syndrome	19280
pure motor lacunar syndrome	33499
pure sensory lacunar syndrome	51767
subdural haemorrhage - nontraumatic	4273
subdural haematoma - nontraumatic	17734
subdural haemorrhage nos	18912
intracranial haemorrhage nos	20284
haemorrhagic stroke monitoring	28914

Figure S7. Heart failure Read codes.

Read term	medcode
h/o: heart failure	15058
h/o: heart failure in last year	46912
heart failure confirmed	9913
heart failure self-management plan agreed	106198
congestive heart failure monitoring	12366
heart failure annual review	30779
heart failure 6 month review	83502
education about deteriorating heart failure	105002
heart failure care plan discussed with patient	32945
has heart failure management plan	103732
heart failure clinical pathway	106008
preferred place of care for next exacerbation heart failure	105542
admit heart failure emergency	32898
heart failure follow-up	17851
referral to heart failure exercise programme	70619
seen in heart failure clinic	12627
seen by community heart failure nurse	19002
referred by heart failure nurse specialist	69062
malignant hypertensive heart disease with ccf	72668
benign hypertensive heart disease with ccf	52127
hypertensive heart disease nos with ccf	62718
hypertensive heart&renal dis wth (congestive) heart failure	21837
heart failure	2062
cardiac failure	1223
congestive heart failure	398
congestive cardiac failure	2906
right heart failure	10079
right ventricular failure	10154
biventricular failure	9524
acute congestive heart failure	23707
chronic congestive heart failure	32671
decompensated cardiac failure	27884
compensated cardiac failure	11424
congestive heart failure due to valvular disease	94870
left ventricular failure	884
impaired left ventricular function	5942
acute left ventricular failure	5255
acute heart failure	27964
heart failure with normal ejection fraction	101138
hfnef - heart failure with normal ejection fraction	101137
heart failure with preserved ejection fraction	106897
right ventricular failure	104275
heart failure nos	4024
cardiac failure nos	17278
post cardiac operation heart failure nos	96799
heart failure as a complication of care	66306

Table S8. Aspirin product codes

Product name	prodcode
anhydrous citric acid /aspirin /calcium 8 mg tab	24427
asasantin retard capsules (boehringer ingelheim ltd)	4679
aspav dispersible tablets (actavis uk ltd)	685
aspirin	23495
aspirin & caffeine disp 300 mg tab	12605
aspirin & codeine 500 mg tab	13598
aspirin & codeine 75 mg tab	22450
aspirin & codeine paed 75 mg tab	19724
aspirin & dover's pwdr tab	30432
aspirin & papaverutum 10 mg tab	4557
aspirin & paracetamol tab	15352
aspirin / caffeine cit./ codeine phos./ 200 mg tab	31498
aspirin /caffeine /quinine sulphate 325 mg tab	40191
aspirin /ethoheptazine citrate /meprobam 250 mg tab	23250
aspirin 100 mg sup	15517
aspirin 100mg effervescent tablets	36543
aspirin 100mg modified-release tablets	9301
aspirin 120 mg sup	30695
aspirin 125 mg sup	26792
aspirin 150 mg tab	2924
aspirin 150mg / isosorbide mononitrate 60mg modified-release tablets	21382
aspirin 162.5mg modified-release capsules	39738
aspirin 175 mg sup	26099
aspirin 200 mg sup	26424
aspirin 250 mg sup	24857
aspirin 25mg with dipyridamole 200mg modified-release capsules	10031
aspirin 300mg/lysine 245mg 300 mg tab	28238
aspirin 324mg modified-release tablets	22138
aspirin 325 mg cap	7462
aspirin 325 mg tab	8843
aspirin 325mg / caffeine 22mg tablets	24622
aspirin 37.5 mg tab	7486
aspirin 40 mg cap	111
aspirin 40 mg tab	7417
aspirin 50 mg cap	4523
aspirin 50 mg sup	20206
aspirin 500 mg sup	23491
aspirin 500mg / papaveretum 7.71mg dispersible tablets sugar free	6226
aspirin 60 mg tab	383
aspirin 600mg / caffeine 50mg oral powder sachets sugar free	12964

aspirin 600mg/glycine 300mg 600 mg tab	33075
aspirin 65 mg sup	42061
aspirin 70 mg tab	216
aspirin 75 mg sup	1486
aspirin 75mg / isosorbide mononitrate 60mg modified-release tablets	21380
aspirin 75mg dispersible tablet (a a h pharmaceuticals ltd)	31211
aspirin 75mg dispersible tablet (nucare plc)	34942
aspirin 75mg dispersible tablet (sovereign medical ltd)	33320
aspirin 75mg dispersible tablets	3
aspirin 75mg dispersible tablets (a a h pharmaceuticals ltd)	33656
aspirin 75mg dispersible tablets (actavis uk ltd)	32036
aspirin 75mg dispersible tablets (alliance healthcare (distribution) ltd)	49060
aspirin 75mg dispersible tablets (bristol laboratories ltd)	52618
aspirin 75mg dispersible tablets (ivax pharmaceuticals uk ltd)	31953
aspirin 75mg dispersible tablets (kent pharmaceuticals ltd)	33676
aspirin 75mg dispersible tablets (sigma pharmaceuticals plc)	49685
aspirin 75mg dispersible tablets (teva uk ltd)	31954
aspirin 75mg dispersible tablets (the boots company plc)	50926
aspirin 75mg dispersible tablets (thornton & ross ltd)	34434
aspirin 75mg dispersible tablets (wockhardt uk ltd)	47937
aspirin 75mg gastro-resistant tablet (galen ltd)	34796
aspirin 75mg gastro-resistant tablets	34
aspirin 75mg gastro-resistant tablets (a a h pharmaceuticals ltd)	47992
aspirin 75mg gastro-resistant tablets (actavis uk ltd)	34797
aspirin 75mg gastro-resistant tablets (almus pharmaceuticals ltd)	43709
aspirin 75mg gastro-resistant tablets (c p pharmaceuticals ltd)	34611
aspirin 75mg gastro-resistant tablets (generics (uk) ltd)	32992
aspirin 75mg gastro-resistant tablets (ivax pharmaceuticals uk ltd)	34485
aspirin 75mg gastro-resistant tablets (kent pharmaceuticals ltd)	31956
aspirin 75mg gastro-resistant tablets (sandoz ltd)	31938

aspirin 75mg gastro-resistant tablets (sterwin medicines)	33293
aspirin 75mg gastro-resistant tablets (teva uk ltd)	41512
aspirin 75mg gastro-resistant tablets (wockhardt uk ltd)	53178
aspirin 75mg gastro-resistant tablets (zanza laboratories ltd)	51561
aspirin 75mg soluble tablet (c p pharmaceuticals ltd)	40381
aspirin 75mg soluble tablet (celltech pharma europe ltd)	45643
aspirin 75mg soluble tablet (co-operative)	34385
aspirin 75mg tablet (hillcross pharmaceuticals ltd)	48021
aspirin 75mg tablets	16
aspirin 75mg tablets (a a h pharmaceuticals ltd)	50949
aspirin 75mg tablets (phoenix healthcare distribution ltd)	48974
aspirin disp 150 mg tab	9027
aspirin disp 200 mg tab	22107
aspirin disp 37.5 mg tab	8734
aspirin disp 500 mg tab	15044
aspirin disp 600 mg tab	22824
aspirin dispersible	19674
aspirin m/f 324 mg tab	28707
aspirin paed 100 mg sup	26582
aspirin paed 150 mg sup	22253
aspirin paed 81 mg tab	8424
aspirin paed mix	22864
aspirin s/r 500 mg tab	22863
aspirin sachets 30 mg	11941
aspirin soluble	19813
aspirin soluble 100 mg tab	12102
aspirin soluble 150 mg tab	2754
aspirin soluble 200 mg tab	4271
aspirin soluble 40 mg cap	7944
aspirin soluble 400 mg tab	27467
aspirin soluble 50 mg tab	15397
aspirin soluble 500 mg tab	8920
aspirin soluble 600 mg tab	15447
aspirin sr 100 mg tab	7915
aspirin sr 300 mg tab	7665
aspirin/caffeine/codeine phosphate 300 mg tab	28606
aspirin/caffeine/dextropropoxyphene naps pul	25959
aspirin/codeine phosphate/paracetamol 250 mg tab	7770

aspirin/codeine phosphate/paracetamol 300 mg tab	24498
aspirin/paracetamol tab	7769

Table S9. Beta-blocker product codes.

Product name	prodcode
atenolol 50mg tablets	5
atenolol 100mg tablets	24
atenolol 25mg tablets	26
propranolol 5mg/5ml oral solution	220
propranolol 10mg tablets	297
bisoprolol 5mg tablets	472
atenolol 50mg with chlortalidone 12.5mg tablets	581
bisoprolol 2.5mg tablets	594
bisoprolol 1.25mg tablets	599
propranolol 40mg tablets	707
metoprolol 50mg tablets	739
nebivolol 5mg tablets	751
metoprolol 100mg tablets	753
propranolol 80mg modified-release capsules	769
sotalol 40mg tablets	786
carvedilol 3.125mg tablets	817
bisoprolol 1.5mg/5ml oral suspension	822
propranolol 80mg tablets	940
half inderal la 80mg capsules (astrazeneca uk ltd)	1006
inderal 80mg tablets (astrazeneca uk ltd)	1048
inderal 40mg tablets (astrazeneca uk ltd)	1050
tenoretic 100mg/25mg tablets (astrazeneca uk ltd)	1124
tenoret 50mg/12.5mg tablets (astrazeneca uk ltd)	1288
bisoprolol 10mg tablets	1290
labetalol 400mg tablets	1295
oxprenolol 40mg tablets	1333
oxprenolol 160mg modified-release tablets	1334
propranolol 160mg modified-release capsules	1448
sotalol 80mg tablets	1572
labetalol 100mg tablets	1597
beta-adalat modified-release capsules (bayer plc)	1684
atenolol 100mg with chlortalidone 25mg tablets	1788
trasicor 80mg tablet (novartis pharmaceuticals uk ltd)	2361
inderal 10mg tablets (astrazeneca uk ltd)	2414
tenormin ls 50mg tablets (astrazeneca uk ltd)	2432
nadolol 80mg tablets	2499
tenormin 100mg tablets (astrazeneca uk ltd)	2587
tenormin 25mg tablets (astrazeneca uk ltd)	2590
carvedilol 12.5mg tablets	2629

labetalol 200mg tablets	2775
oxprenolol 80mg tablets	2780
inderal la 160mg capsules (astrazeneca uk ltd)	3005
propranolol 40mg/5ml oral solution sugar free	3087
propranolol 160mg tablets	3167
betaloc 100mg tablets (astrazeneca uk ltd)	3344
betaloc-sa 200mg tablets (astrazeneca uk ltd)	3474
oxprenolol 20mg tablets	3516
amiloride with atenolol with hydrochlorothiazide capsules	3526
monocor 5mg tablets (wyeth pharmaceuticals)	3588
sotalol 160mg with hydrochlorothiazide 25mg tablet	3691
oxprenolol 160mg tablet	3748
propanix 40mg tablet (ashbourne pharmaceuticals ltd)	3827
sotacor 80mg tablets (bristol-myers squibb pharmaceuticals ltd)	4004
slow-trasicor 160mg tablets (amdipharm plc)	4025
celectol 200mg tablet (pantheon healthcare ltd)	4265
carvedilol 6.25mg tablets	4410
trasidrex modified-release tablets (mercury pharma group ltd)	4429
atenolol 50mg / nifedipine 20mg modified-release capsules	4542
visken 5mg tablet (sovereign medical ltd)	4588
moducren tablets (merck sharp & dohme ltd)	4605
labetalol 50mg tablets	4725
emcor ls 5mg tablets (merck serono ltd)	4771
inderetic 80mg/2.5mg capsules (astrazeneca uk ltd)	4796
atenolol with amiloride and hydrochlorothiazide capsules	4983
pindolol 5mg tablets	5284
corgaretic 40mg tablets (sanofi-synthelabo ltd)	5330
propranolol 10mg/5ml oral solution sugar free	5478
bisoprolol 7.5mg tablets	5713
co-tenidone 100mg/25mg tablets	5721
beta-cardone 40mg tablets (focus pharmaceuticals ltd)	5858
monocor 10mg tablets (wyeth pharmaceuticals)	5968
atenolol 25mg/5ml oral solution sugar free	6066

beta-cardone 80mg tablets (focus pharmaceuticals ltd)	6751
carvedilol 25mg tablets	7049
metoprolol 100mg / hydrochlorothiazide 12.5mg tablets	7066
bisoprolol 3.75mg tablets	7091
trasicor 20mg tablet (novartis pharmaceuticals uk ltd)	7474
nebilet 5mg tablets (a menarini pharma uk s.r.l.)	7528
kalten capsules (m & a pharmachem ltd)	7543
bisoprolol 5mg/5ml oral suspension	7553
acebutolol 400mg tablets	7620
blocadren 10mg tablet (merck sharp & dohme ltd)	7852
timolol 10mg tablets	7853
celiprolol 400mg tablets	7974
sectral 400mg tablets (sanofi)	8023
sotalol 80mg with hydrochlorothiazide 12.5mg tablet	8061
metoprolol 200mg modified-release tablets	8068
betaloc 50mg tablets (astrazeneca uk ltd)	8071
acebutolol 200mg capsules	8113
lopresoretic tablet (novartis pharmaceuticals uk ltd)	8147
acebutolol 100mg capsules	8172
secadrex 200mg/12.5mg tablets (sanofi)	8189
celiprolol 200mg tablets	8262
trasicor 40mg tablet (novartis pharmaceuticals uk ltd)	8290
inderal 160mg tablet (astrazeneca uk ltd)	8331
inderex 160mg/5mg modified-release capsules (astrazeneca uk ltd)	8369
sectral 200mg capsules (sanofi)	8555
prestim tablet (icn pharmaceuticals france s.a.)	8623
tenif 50mg/20mg modified-release capsules (astrazeneca uk ltd)	8642
oxprenolol with cyclopenthiazide 160mg+0.25mg modified-release tablet	8673
trandate 200mg tablets (focus pharmaceuticals ltd)	8707
trandate 400mg tablets (focus pharmaceuticals ltd)	8807
nadolol 40mg tablets	8935
propanix 160mg modified-release capsule (ashbourne pharmaceuticals ltd)	8978
propranolol 160mg modified-release / bendroflumethiazide 5mg capsules	8987
trandate 100mg tablets (focus pharmaceuticals ltd)	9016
viskaldix tablets (amdipharm plc)	9143

atenolol 25mg / bendroflumethiazide 1.25mg capsules	9178
propranolol 80mg/5ml oral solution	9185
trandate 50mg tablets (focus pharmaceuticals ltd)	9273
sotalol 160mg tablets	9292
co-tenidone 50mg/12.5mg tablets	9783
atenix 50 tablets (ashbourne pharmaceuticals ltd)	10191
lopresor 50mg tablet (novartis pharmaceuticals uk ltd)	10429
co-betaloc tablets (pfizer ltd)	10627
corgard 80mg tablets (sanofi)	10716
trasicor 160mg tablet (novartis pharmaceuticals uk ltd)	10777
emcor 10mg tablets (merck serono ltd)	10892
bendroflumethiazide 5mg with nadolol 40mg tablets	11338
sotacor 160mg tablets (bristol-myers squibb pharmaceuticals ltd)	11380
propranolol 50mg/5ml oral solution	11711
metoprolol 50mg/5ml oral suspension	11793
betim 10mg tablet (icn pharmaceuticals france s.a.)	12037
propranolol 80mg / bendroflumethiazide 2.5mg capsules	12054
sectral 100mg capsules (sanofi)	12296
sotazide tablet (bristol-myers squibb pharmaceuticals ltd)	12456
berkolol 10mg tablet (berk pharmaceuticals ltd)	12495
timolol maleate with bendroflumethiazide 20mg + 5mg tablet	12517
timolol 10mg / bendroflumethiazide 2.5mg tablets	12651
sotalol 200mg tablets	13051
tenormin 25mg/5ml syrup (astrazeneca uk ltd)	13394
corgard 40mg tablets (sanofi-synthelabo ltd)	13415
beta-cardone 200mg tablets (focus pharmaceuticals ltd)	13487
lopresor 100mg tablet (novartis pharmaceuticals uk ltd)	13499
atenix co 100 tablets (ashbourne pharmaceuticals ltd)	13526
co-prenozide 160mg/0.25mg modified-release tablets	13871
cardicor 2.5mg tablets (merck serono ltd)	14030
pindolol 10mg / clopamide 5mg tablets	14057
cardicor 1.25mg tablets (merck serono ltd)	14058

eucardic 3.125mg tablets (roche products ltd)	14117
acebutolol 200mg / hydrochlorothiazide 12.5mg tablets	14126
eucardic 6.25mg tablets (roche products ltd)	14146
corgaretic 80mg tablets (sanofi-synthelabo ltd)	14438
propanix 10mg tablet (ashbourne pharmaceuticals ltd)	14552
pindolol 15mg tablets	14673
bedranol sr 80mg capsules (sandoz ltd)	14808
tolerzide tablet (bristol-myers squibb pharmaceuticals ltd)	15042
nifedipine with atenolol 20mg + 50mg capsule	15117
totamol 50mg tablet (c p pharmaceuticals ltd)	15176
metoprolol tartrate with chlortalidone tablet	15488
half-betadur cr 80mg capsule (monmouth pharmaceuticals ltd)	15619
totamol 100mg tablet (c p pharmaceuticals ltd)	15730
labrocol 400mg tablet (lagap)	16645
celectol 400mg tablet (pantheon healthcare ltd)	16776
chlortalidone 25mg with atenolol 100mg tablets	16786
syprol 5mg/5ml oral solution (rosemont pharmaceuticals ltd)	17082
monozide 10 tablets (wyeth pharmaceuticals)	17149
atenix 25 tablets (ashbourne pharmaceuticals ltd)	17322
bisoprolol 10mg / hydrochlorothiazide 6.25mg tablets	17462
cardicor 5mg tablets (merck serono ltd)	17615
spiroprop tablet (pharmacia ltd)	17783
cardicor 7.5mg tablets (merck serono ltd)	18185
co-betaloc sa tablets (pfizer ltd)	18287
eucardic 12.5mg tablets (roche products ltd)	18414
tenben 25mg/1.25mg capsules (galen ltd)	18743
totamol 25mg tablet (c p pharmaceuticals ltd)	18950
chlortalidone 12.5mg with atenolol 50mg tablets	19055
bendroflumethiazide 2.5mg with timolol maleate 10mg tablets	19142
atenolol 25mg tablets (ivax pharmaceuticals uk ltd)	19172

bisoprolol 10mg tablets (ranbaxy (uk) ltd)	19178
atenolol 50mg tablets (ivax pharmaceuticals uk ltd)	19182
atenolol 100mg tablets (teva uk ltd)	19191
bisoprolol 5mg tablets (ivax pharmaceuticals uk ltd)	19200
carvedilol 6.25mg tablets (teva uk ltd)	19202
eucardic 25mg tablets (roche products ltd)	19437
cardicor 3.75mg tablets (merck serono ltd)	19853
cardicor 10mg tablets (merck serono ltd)	19858
visken 15mg tablet (sovereign medical ltd)	20012
lopresor sr 200mg tablets (recordati pharmaceuticals ltd)	20082
metoprolol 200mg modified-release / hydrochlorothiazide 25mg tablets	20093
half beta-prograne 80mg modified-release capsules (tillomed laboratories ltd)	20468
atenix 100 tablets (ashbourne pharmaceuticals ltd)	20502
atenamin 25mg tablet (opd pharm)	20728
prestim forte tablet (leo pharma)	21025
atenamin 50mg tablet (opd pharm)	21133
hydrochlorothiazide with timolol and amiloride 25mg with 10mg with 2.5mg tablet	21182
propanix 80mg tablet (ashbourne pharmaceuticals ltd)	21838
berkolol 80mg tablet (berk pharmaceuticals ltd)	21839
berkolol 40mg tablet (berk pharmaceuticals ltd)	21866
atenix co 50 tablets (ashbourne pharmaceuticals ltd)	21873
oxyprenix sr 160mg tablets	21885
bipranix 10mg tablets (ashbourne pharmaceuticals ltd)	21905
bipranix 5mg tablets (ashbourne pharmaceuticals ltd)	21966
half propanix la 80mg modified-release capsule (ashbourne pharmaceuticals ltd)	22208
labrocol 200mg tablet (lagap)	22793
bendroflumethiazide 2.5mg with propanolol 80mg capsules	22912
bendroflumethiazide 5mg with propanolol 160mg modified-release capsules	23131
nadolol 40mg / bendroflumethiazide 5mg tablets	23134
betadur cr 160mg modified-release capsule (monmouth pharmaceuticals ltd)	23326
sloprolol 160mg capsule (c p pharmaceuticals ltd)	23587
bisoprolol 5mg tablets (teva uk ltd)	24083

trasicor 40mg tablets (amdipharm plc)	24094
antipressan 50mg tablets (teva uk ltd)	24191
antipressan 100mg tablets (teva uk ltd)	24195
berkolol 160mg tablet (berk pharmaceuticals ltd)	24218
totaretic 100mg+25mg tablet (c p pharmaceuticals ltd)	24280
rapranol sr 160mg capsules (ranbaxy (uk) ltd)	25359
prestim tablets (meda pharmaceuticals ltd)	25363
rapranol sr 80mg capsules (ranbaxy (uk) ltd)	25367
clopamide 5mg with pindolol 10mg tablets	25462
apsolox 80mg tablet (approved prescription services ltd)	25644
timolol maleate with amiloride and hydrochlorothiazide tablet	25730
antipressan 25mg tablets (teva uk ltd)	26211
propanix la 160mg modified-release capsule (ashbourne pharmaceuticals ltd)	26228
beta-prograne 160mg modified-release capsules (tillomed laboratories ltd)	26229
tenchlor 100mg/25mg tablets (teva uk ltd)	26248
lopranol la 160mg capsule (opus pharmaceuticals ltd)	26255
totaretic 50mg+12.5mg tablet (c p pharmaceuticals ltd)	26741
syprol 10mg/5ml oral solution (rosemont pharmaceuticals ltd)	26895
oxprenolol 40mg tablet (actavis uk ltd)	27357
propranolol 40mg tablets (actavis uk ltd)	27700
metoros ls 95mg tablet (geigy pharmaceuticals)	27719
nadolol 80mg / bendroflumethiazide 5mg tablets	27946
apsolol 40mg tablet (approved prescription services ltd)	27964
angilol 10mg tablet (ddsa pharmaceuticals ltd)	28048
propranolol 80mg modified-release capsule (actavis uk ltd)	28128
hydrochlorothiazide with atenolol and amiloride capsule	28177
half propatard la 80mg modified-release capsule (galen ltd)	28788
bedranol sr 160mg capsules (sandoz ltd)	28996
trasicor 80mg tablets (amdipharm plc)	29180
slow-pren 160mg tablet (ivax pharmaceuticals uk ltd)	29230
atenolol 25mg tablets (teva uk ltd)	29368
atenamin 100mg tablet (opd pharm)	29398
hydrochlorothiazide with metoprolol tartrate 12.5mg with 100mg tablet	29427

betim 10mg tablets (meda pharmaceuticals ltd)	29610
mepranix 50mg tablet (ashbourne pharmaceuticals ltd)	29762
propanix 160mg tablet (ashbourne pharmaceuticals ltd)	29763
metoros 190mg tablet (novartis pharmaceuticals uk ltd)	29998
mepranix 100mg tablet (ashbourne pharmaceuticals ltd)	30400
amiloride with timolol with hydrochlorothiazide tablets	30519
vasaten 50mg tablet (shire pharmaceuticals ltd)	30636
labetalol 200mg tablets (a a h pharmaceuticals ltd)	30770
propranolol 80mg tablets (generics (uk) ltd)	31214
tenchlor 50mg/12.5mg tablets (teva uk ltd)	31470
atenolol 25mg tablets (kent pharmaceuticals ltd)	31536
co-tenidone 50mg/12.5mg tablets (actavis uk ltd)	31708
propranolol 40mg tablets (generics (uk) ltd)	31776
angilol 80mg tablet (ddsa pharmaceuticals ltd)	31833
atenolol 100mg tablets (ivax pharmaceuticals uk ltd)	31934
co-tenidone 50mg/12.5mg tablets (a a h pharmaceuticals ltd)	32094
bisoprolol 5mg tablets (generics (uk) ltd)	32114
propranolol 80mg modified-release capsule (lagap)	32162
congescor 2.5mg tablets (tillomed laboratories ltd)	32552
vivacor 10mg tablets (lexon (uk) ltd)	32630
visken 15mg tablets (amdipharm plc)	32787
metoprolol 50mg tablets (generics (uk) ltd)	32836
atenolol 100mg tablets (generics (uk) ltd)	33079
atenolol 100mg tablets (a a h pharmaceuticals ltd)	33085
atenolol 50mg tablets (a a h pharmaceuticals ltd)	33092
atenolol 100mg tablets (wockhardt uk ltd)	33184
carvedilol 12.5mg tablets (genus pharmaceuticals ltd)	33374
probeta la 160mg capsule (trinity pharmaceuticals ltd)	33376
oxprenolol sr 160mg modified-release tablet (hillcross pharmaceuticals ltd)	33569
slo-pro 160mg capsules (generics (uk) ltd)	33602
propranolol 80mg tablets (a a h pharmaceuticals ltd)	33644

atenolol 50mg tablets (generics (uk) ltd)	33650
atenolol 25mg tablets (a a h pharmaceuticals ltd)	33657
hydrochlorothiazide with metoprolol tartrate 25mg with 200mg modified-release tablet	33659
apsolol 160mg tablet (approved prescription services ltd)	33836
bisoprolol 10mg tablets (actavis uk ltd)	33839
atenolol 50mg tablets (actavis uk ltd)	33850
congescor 1.25mg tablets (tillomed laboratories ltd)	33909
co-tenidone 100mg/25mg tablets (ivax pharmaceuticals uk ltd)	34012
co-tenidone 50mg/12.5mg tablets (ivax pharmaceuticals uk ltd)	34034
metoprolol 100mg tablets (teva uk ltd)	34092
metoprolol 50mg tablets (a a h pharmaceuticals ltd)	34094
metoprolol 100mg tablets (a a h pharmaceuticals ltd)	34125
labetalol 100mg tablet (c p pharmaceuticals ltd)	34171
labetalol 100mg tablets (a a h pharmaceuticals ltd)	34177
propranolol la 80mg modified-release capsule (approved prescription services ltd)	34185
labetalol 200mg tablet (celltech pharma europe ltd)	34188
propranolol sr 160mg modified-release capsule (c p pharmaceuticals ltd)	34208
propranolol 160mg tablets (actavis uk ltd)	34214
atenolol 50mg tablets (sandoz ltd)	34265
atenolol 50mg tablets (teva uk ltd)	34365
sotalol 40mg tablets (a a h pharmaceuticals ltd)	34371
propranolol 10mg tablets (a a h pharmaceuticals ltd)	34378
metoprolol 50mg tablets (teva uk ltd)	34407
metoprolol 50mg tablets (actavis uk ltd)	34430
atenolol 50mg tablets (wockhardt uk ltd)	34443
co-tenidone 50mg/12.5mg tablets (generics (uk) ltd)	34449
atenolol 25mg tablets (generics (uk) ltd)	34492
carvedilol 12.5mg tablets (actavis uk ltd)	34501
metoprolol 100mg tablets (generics (uk) ltd)	34509
sotalol 80mg tablets (generics (uk) ltd)	34520
atenolol 25mg tablets (wockhardt uk ltd)	34575
metoprolol 50mg tablets (ivax pharmaceuticals uk ltd)	34584
atenolol 25mg tablets (sandoz ltd)	34585
sotalol 40mg tablets (teva uk ltd)	34600

sotalol 40mg tablet (tillomed laboratories ltd)	34640
sotalol 80mg tablets (sandoz ltd)	34690
atenolol 50mg tablets (kent pharmaceuticals ltd)	34695
carvedilol 6.25mg tablets (actavis uk ltd)	34740
carvedilol 3.125mg tablets (ivax pharmaceuticals uk ltd)	34741
atenolol 100mg tablets (sandoz ltd)	34754
propranolol 10mg tablets (actavis uk ltd)	34783
propranolol 10mg tablets (teva uk ltd)	34804
bisoprolol 10mg tablets (generics (uk) ltd)	34821
co-tenidone 50mg/12.5mg tablets (teva uk ltd)	34825
metoprolol 100mg tablets (actavis uk ltd)	34854
propranolol 80mg capsule (ivax pharmaceuticals uk ltd)	34867
propranolol 40mg tablets (teva uk ltd)	34868
atenolol 50mg tablet (berk pharmaceuticals ltd)	34882
propranolol 160mg modified-release capsule (sandoz ltd)	34884
metoprolol 50mg tablet (berk pharmaceuticals ltd)	34890
co-tenidone 100mg/25mg tablets (a a h pharmaceuticals ltd)	34899
metoprolol 50mg tablets (sandoz ltd)	34925
propranolol 160mg modified-release capsule (lagap)	34945
propranolol 160mg modified-release capsule (actavis uk ltd)	34949
bisoprolol 5mg tablets (actavis uk ltd)	34963
atenolol 25mg tablets (tillomed laboratories ltd)	34976
celectol 200mg tablets (zentiva)	35054
trasicor 20mg tablets (amdipharm plc)	35062
visken 5mg tablets (amdipharm plc)	35695
sotalol 25mg/5ml oral suspension	35710
labrocol 100mg tablet (lagap)	35778
propranolol 80mg modified-release capsules (a a h pharmaceuticals ltd)	35938
celectol 400mg tablets (zentiva)	35940
atenolol 50mg tablets (tillomed laboratories ltd)	36261
propranolol 10mg tablets (generics (uk) ltd)	36576
propranolol sr 160mg modified-release capsule (hillcross pharmaceuticals ltd)	36603
bisoprolol 2.5mg tablets (a a h pharmaceuticals ltd)	37118
co-tenidone 100mg/25mg tablets (generics (uk) ltd)	37725
bisoprolol 2.5mg tablet (teva uk ltd)	37837

propranolol 50mg/5ml oral solution (rosemont pharmaceuticals ltd)	38433
bisoprolol 7.5mg tablets (a a h pharmaceuticals ltd)	38991
propranolol 80mg modified-release capsules (teva uk ltd)	39233
sotalol 80mg tablets (a a h pharmaceuticals ltd)	39423
bisoprolol 0.625mg/5ml oral solution	39646
vivacor 5mg tablets (lexon (uk) ltd)	39846
metoprolol 100mg tablets (ivax pharmaceuticals uk ltd)	40167
labetalol 400mg tablets (a a h pharmaceuticals ltd)	40240
propranolol la 160mg capsule (approved prescription services ltd)	40241
nebivolol 2.5mg tablets	40761
propranolol 40mg tablets (a a h pharmaceuticals ltd)	41555
co-tenidone 100mg/25mg tablets (teva uk ltd)	41572
bisoprolol 10mg tablets (teva uk ltd)	41591
celiprolol 200mg tablets (teva uk ltd)	41740
labetalol 100mg tablets (generics (uk) ltd)	41827
syprol 50mg/5ml oral solution (rosemont pharmaceuticals ltd)	42152
celiprolol 200mg tablets (generics (uk) ltd)	42795
bisoprolol 1.25mg tablets (generics (uk) ltd)	43251
propranolol 10mg tablets (ivax pharmaceuticals uk ltd)	43525
sotalol 40mg tablets (ivax pharmaceuticals uk ltd)	43549
bisoprolol 5mg tablet (pliva pharma ltd)	43564
bisoprolol 2.5mg/5ml oral suspension	44000
labetalol 200mg tablets (actavis uk ltd)	44083
nebivolol 2.5mg tablets (a a h pharmaceuticals ltd)	44808
atenolol 25mg tablets (actavis uk ltd)	44858
labetalol 400mg tablets (sandoz ltd)	45250
metoprolol tartrate oral solution	45289
propranolol 40mg tablets (ivax pharmaceuticals uk ltd)	45297
acebutolol 400mg tablets (a a h pharmaceuticals ltd)	45309
propranolol sr 80mg modified-release capsule (c p pharmaceuticals ltd)	45343
propranolol 10mg tablets (almus pharmaceuticals ltd)	45494
syprol 40mg/5ml oral solution (rosemont pharmaceuticals ltd)	45765
beta-prograne 160mg modified-release capsules (teva uk ltd)	45877

half beta-prograne 80mg modified-release capsules (teva uk ltd)	46363
lopresor 50mg tablets (recordati pharmaceuticals ltd)	46614
lopresor 100mg tablets (recordati pharmaceuticals ltd)	46740
atenolol 100mg tablets (kent pharmaceuticals ltd)	46908
atenolol 100mg tablets (actavis uk ltd)	46931
carvedilol 3.125mg tablets (actavis uk ltd)	46935
carvedilol 3.125mg tablets (a a h pharmaceuticals ltd)	46936
co-tenidone 100mg/25mg tablets (actavis uk ltd)	46952
bisoprolol 2.5mg tablets (generics (uk) ltd)	47041
carvedilol 5mg/5ml oral suspension	47107
nebivolol 2.5mg tablets (glenmark generics (europe) ltd)	47300
metoprolol tartrate 12.5mg/5ml oral suspension	47536
half beta-prograne 80mg modified-release capsules (actavis uk ltd)	47543
labetalol 400mg tablet (approved prescription services ltd)	47673
labetalol 200mg tablet (c p pharmaceuticals ltd)	47674
bedranol sr 80mg capsules (almus pharmaceuticals ltd)	47833
atenolol 25mg tablets (almus pharmaceuticals ltd)	47870
bedranol sr 160mg capsules (almus pharmaceuticals ltd)	47907
propranolol 50mg/5ml oral solution sugar free	48682
carvedilol 3.125mg/5ml oral suspension	49142
propranolol 5mg/5ml oral solution sugar free	49863
atenolol 25mg tablets (bristol laboratories ltd)	49953
congescor 2.5mg tablets (teva uk ltd)	50224
congescor 1.25mg tablets (teva uk ltd)	50300
bisoprolol 1.25mg tablet (teva uk ltd)	50403
bisoprolol 2.5mg tablets (chanelle medical uk ltd)	50514
atenolol 25mg tablets (alliance healthcare (distribution) ltd)	50702
metoprolol 12.5mg/5ml oral suspension	51447
sotalol 25mg/5ml oral solution	51492
bisoprolol 1.25mg tablets (actavis uk ltd)	51528
atenolol 25mg/5ml oral solution sugar free (alliance healthcare (distribution) ltd)	51643
atenolol 25mg tablets (co-pharma ltd)	51998

bedranol sr 160mg capsule (lagap)	52136
atenolol 25mg tablets (crescent pharma ltd)	52310
atenolol 50mg tablets (almus pharmaceuticals ltd)	52500
bisoprolol 1.25mg tablets (almus pharmaceuticals ltd)	52548
inderal la 160mg capsules (sigma pharmaceuticals plc)	52609
bisoprolol 5mg tablets (alliance healthcare (distribution) ltd)	52635
bisoprolol 2.5mg/5ml oral solution	52686
beta-adalat modified-release capsules (lexon (uk) ltd)	52728
propranolol 40mg tablets (kent pharmaceuticals ltd)	52777
atenolol 50mg tablets (alliance healthcare (distribution) ltd)	53204
atenolol 50mg tablets (bristol laboratories ltd)	53215
bisoprolol 10mg tablets (a a h pharmaceuticals ltd)	53334
atenolol 50mg tablets (accord healthcare ltd)	53414

Table S10. Statin product codes

Product name	prodcode
simvastatin 20mg tablets	25
atorvastatin 10mg tablets	28
simvastatin 10mg tablets	42
simvastatin 40mg tablets	51
atorvastatin 20mg tablets	75
fluvastatin 20mg capsules	379
pravastatin 10mg tablets	490
rosuvastatin 10mg tablets	713
pravastatin 20mg tablets	730
atorvastatin 40mg tablets	745
simvador 40mg tablets (discovery pharmaceuticals ltd)	802
simvastatin 20mg/5ml oral solution sugar free	818
pravastatin 40mg tablets	1219
lipostat 10mg tablets (bristol-myers squibb pharmaceuticals ltd)	1221
lipostat 40mg tablets (bristol-myers squibb pharmaceuticals ltd)	1223
fluvastatin 40mg capsules	2137
zocor 10mg tablets (merck sharp & dohme ltd)	2718
lipitor 40mg tablets (pfizer ltd)	2955
lipitor 10mg tablets (pfizer ltd)	3411
lipostat 20mg tablets (bristol-myers squibb pharmaceuticals ltd)	3690
simvastatin 80mg tablets	5148
atorvastatin 80mg tablets	5775
lescol xl 80mg tablets (novartis pharmaceuticals uk ltd)	5985
zocor 40mg tablets (merck sharp & dohme ltd)	6168
rosuvastatin 20mg tablets	6213
zocor 20mg tablets (merck sharp & dohme ltd)	7196
crestor 10mg tablets (astrazeneca uk ltd)	7347
lipitor 20mg tablets (pfizer ltd)	7374
rosuvastatin 5mg tablets	7554
lescol 20mg capsules (novartis pharmaceuticals uk ltd)	8380
lescol 40mg capsules (novartis pharmaceuticals uk ltd)	9153
rosuvastatin 40mg tablets	9897
simvador 20mg tablets (discovery pharmaceuticals ltd)	9920
crestor 40mg tablets (astrazeneca uk ltd)	9930
fluvastatin 80mg modified-release tablets	11627
simvador 10mg tablets (discovery pharmaceuticals ltd)	13041

crestor 20mg tablets (astrazeneca uk ltd)	15252
lipitor 80mg tablets (pfizer ltd)	17683
crestor 5mg tablets (astrazeneca uk ltd)	17688
zocor 80mg tablets (merck sharp & dohme ltd)	22579
zocor heart-pro 10mg tablet (mcneil products ltd)	31930
simvastatin 80mg tablets (a a h pharmaceuticals ltd)	32909
pravastatin 10mg tablet (dr reddy's laboratories (uk) ltd)	32921
simvastatin 20mg tablets (a a h pharmaceuticals ltd)	33082
simvastatin 20mg tablets (generics (uk) ltd)	34312
simvastatin 20mg tablets (teva uk ltd)	34316
simvastatin 40mg tablets (generics (uk) ltd)	34353
simvastatin 20mg tablets (ivax pharmaceuticals uk ltd)	34366
simvastatin 40mg tablets (teva uk ltd)	34376
simvastatin 40mg tablets (ivax pharmaceuticals uk ltd)	34381
simvastatin 20mg tablet (ratiopharm uk ltd)	34476
simvastatin 10mg tablets (ivax pharmaceuticals uk ltd)	34481
simvastatin 40mg tablets (a a h pharmaceuticals ltd)	34502
simvastatin 10mg tablets (generics (uk) ltd)	34535
simvastatin 40mg tablet (ratiopharm uk ltd)	34545
simvastatin 10mg tablet (ratiopharm uk ltd)	34560
simvastatin 20mg tablet (niche generics ltd)	34746
simvastatin 20mg tablets (wockhardt uk ltd)	34814
pravastatin 40mg tablets (a a h pharmaceuticals ltd)	34820
simvastatin 40mg tablet (niche generics ltd)	34879
simvastatin 20mg tablets (kent pharmaceuticals ltd)	34891
simvastatin 40mg tablets (wockhardt uk ltd)	34907
simvastatin 10mg tablets (a a h pharmaceuticals ltd)	34955
simvastatin 40mg tablets (actavis uk ltd)	34969
pravastatin 20mg tablets (teva uk ltd)	36377
simvastatin 40mg tablets (sandoz ltd)	37434
simvastatin 20mg tablets (dexcel-pharma ltd)	39060
simvastatin 40mg/5ml oral solution sugar free	39652
simvastatin 20mg/5ml oral suspension (martindale pharmaceuticals ltd)	39675
simvador 80mg tablets (discovery pharmaceuticals ltd)	39870

simvastatin 10mg tablets (teva uk ltd)	40340
pravastatin 20mg tablets (a a h pharmaceuticals ltd)	40382
simvastatin 20mg tablets (ranbaxy (uk) ltd)	40601
simvastatin 80mg tablets (teva uk ltd)	41657
pravastatin 10mg tablets (teva uk ltd)	43218
simvastatin 20mg/5ml oral suspension sugar free (rosemont pharmaceuticals ltd)	44528
simvastatin 40mg tablets (dexcel-pharma ltd)	44650
ranzolont 10mg tablets (ranbaxy (uk) ltd)	44878
simvastatin 40mg tablets (kent pharmaceuticals ltd)	45219
simvastatin 20mg tablets (sandoz ltd)	45235
simvastatin 20mg tablets (actavis uk ltd)	45245
simvastatin 40mg tablets (arrow generics ltd)	45346
simvastatin 40mg tablets (almus pharmaceuticals ltd)	46878
simvastatin 80mg tablets (arrow generics ltd)	46956
atorvastatin 20mg chewable tablets sugar free	47065
atorvastatin 10mg chewable tablets sugar free	47090
lipitor 20mg chewable tablets (pfizer ltd)	47630
lipitor 10mg chewable tablets (pfizer ltd)	47721
simvastatin 10mg tablets (arrow generics ltd)	47774
simvastatin 10mg tablets (tillomed laboratories ltd)	47948
pravastatin 40mg tablets (generics (uk) ltd)	47988
simvastatin 20mg tablets (arrow generics ltd)	48018
simvastatin 10mg tablets (kent pharmaceuticals ltd)	48051
simvastatin 10mg tablets (ranbaxy (uk) ltd)	48058
simvastatin 10mg tablets (actavis uk ltd)	48078
pravastatin 40mg tablets (teva uk ltd)	48097
simvastatin 20mg/5ml oral suspension sugar free	48221
atorvastatin 60mg tablets	48346
simvastatin 40mg/5ml oral suspension sugar free	48431
atorvastatin 10mg/5ml oral solution	48518
simvastatin 40mg tablets (alliance healthcare (distribution) ltd)	48867
atorvastatin 30mg tablets	48973
simvastatin 40mg tablets (bristol laboratories ltd)	49061
simvastatin 20mg tablets (alliance healthcare (distribution) ltd)	49062

atorvastatin 20mg tablets (a a h pharmaceuticals ltd)	49558
simvastatin 80mg tablets (almus pharmaceuticals ltd)	49587
atorvastatin 40mg tablets (alliance healthcare (distribution) ltd)	49751
atorvastatin 10mg tablets (zentiva)	50236
atorvastatin 40mg tablets (pfizer ltd)	50272
simvastatin 40mg tablets (relonchem ltd)	50483
simvastatin 20mg tablets (relonchem ltd)	50564
simvastatin 40mg tablets (aurobindo pharma ltd)	50670
simvastatin 40mg tablets (accord healthcare ltd)	50703
simvastatin 20mg tablets (medreich plc)	50754
atorvastatin 20mg tablets (pfizer ltd)	50788
atorvastatin 20mg tablets (dexcel-pharma ltd)	50790
simvastatin 40mg tablets (somex pharma)	50882
pravastatin 10mg tablets (sigma pharmaceuticals plc)	50925
atorvastatin 40mg tablets (teva uk ltd)	50963
simvastatin 10mg tablets (medreich plc)	51085
atorvastatin 10mg tablets (a a h pharmaceuticals ltd)	51134
simvastatin 40mg tablets (medreich plc)	51166
atorvastatin 40mg tablets (arrow generics ltd)	51200
simvastatin 10mg tablets (alliance healthcare (distribution) ltd)	51233
atorvastatin 20mg tablets (arrow generics ltd)	51359
simvastatin 20mg tablets (aurobindo pharma ltd)	51483
atorvastatin 20mg tablets (consilient health ltd)	51622
pravastatin 40mg tablets (medreich plc)	51676
simvastatin 10mg tablets (sigma pharmaceuticals plc)	51715
atorvastatin 40mg tablets (consilient health ltd)	51876
pravastatin 20mg tablets (medreich plc)	51890
atorvastatin 40mg tablets (wockhardt uk ltd)	52097
simvastatin 40mg tablets (ranbaxy (uk) ltd)	52098
atorvastatin 20mg tablets (aspire pharma ltd)	52168
atorvastatin 20mg tablets (actavis uk ltd)	52211
simvastatin 20mg tablets (accord healthcare ltd)	52257
atorvastatin 40mg tablets (dr reddy's laboratories (uk) ltd)	52397

atorvastatin 40mg tablets (a a h pharmaceuticals ltd)	52398
atorvastatin 80mg tablets (actavis uk ltd)	52459
atorvastatin 40mg tablets (aspire pharma ltd)	52460
simvastatin 10mg tablets (wockhardt uk ltd)	52625
simvastatin 10mg/5ml oral suspension	52676
pravastatin 20mg tablets (alliance healthcare (distribution) ltd)	52755
simvastatin 20mg tablets (sigma pharmaceuticals plc)	52812
atorvastatin 80mg tablets (dr reddy's laboratories (uk) ltd)	52821
simvastatin 20mg tablets (bristol laboratories ltd)	52953
simvastatin 80mg tablets (medreich plc)	52962
simvastatin 20mg tablets (somex pharma)	53087
zocor 40mg tablets (lexon (uk) ltd)	53340
simvastatin 10mg tablets (aurobindo pharma ltd)	53415
crestor 10mg tablets (doncaster pharmaceuticals ltd)	53460
lipitor 80mg tablets (mawdsley-brooks & company ltd)	53594

Appendix G - Proof of retention of copyright for research papers

I retained copyright for each of the published articles presented in this thesis and licensed these under CC BY 4.0, which allows distribution and adaption of the work, provided the original work is properly cited (http://creativecommons.org/licenses/by/4.0/). Proof of this is presented in the following pages.

Epidemiology

Risk of myocardial infarction (MI) and death following MI in people with chronic obstructive pulmonary disease (COPD): a systematic review and meta-analysis

Kieran J Rothnie[1,2], **Ruoling Yan**[3], **Liam Smeeth**[2], **Jennifer K Quint**[1,2]

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Abstract

Objectives Cardiovascular disease is an important comorbidity in patients with chronic obstructive pulmonary disease (COPD). We aimed to systematically review the evidence for: (1) risk of myocardial infarction (MI) in people with COPD; (2) risk of MI associated with acute exacerbation of COPD (AECOPD); (3) risk of death after MI in people with COPD.

Design Systematic review and meta-analysis.

Methods MEDLINE, EMBASE and SCI were searched up to January 2015. Two reviewers screened abstracts and full text records, extracted data and assessed studies for risk of bias. We used the generic inverse variance method to pool effect estimates, where possible. Evidence was synthesised in a narrative review where meta-analysis was not possible.

Results Searches yielded 8362 records, and 24 observational studies were included. Meta-analysis showed increased risk of MI associated with COPD (HR 1.72, 95% CI 1.22 to 2.42) for cohort analyses, but not in case–control studies: OR 1.18 (0.80 to 1.76). Both included studies that investigated the risk of MI associated with AECOPD found an increased risk of MI after AECOPD (incidence rate ratios, IRR 2.27, 1.10 to 4.70, and IRR 13.04, 1.71 to 99.7). Meta-analysis showed weak evidence for increased risk of death for patients with COPD in hospital after MI (OR 1.13, 0.97 to 1.31). However, meta-analysis showed an increased risk of death after MI for patients with COPD during follow-up (HR 1.26, 1.13 to 1.40).

Conclusions There is good evidence that COPD is associated with increased risk of MI; however, it is unclear to what extent this association is due to smoking status. There is some evidence that the risk of MI is higher during AECOPD than stable periods. There is poor evidence that COPD is associated with increased in hospital mortality after an MI, and good evidence that longer term mortality is higher for patients with COPD after an MI.

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Research paper II

Original article

Closing the mortality gap after a myocardial infarction in people with and without chronic obstructive pulmonary disease

OPEN ACCESS

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Received 27 November 2014
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Abstract

Objective Patients with chronic obstructive pulmonary disease (COPD) have increased mortality following myocardial infarction (MI) compared with patients without COPD. We investigated the extent to which differences in recognition and management after MI could explain the mortality difference.

Methods 300 161 patients with a first MI between 2003 and 2013 were identified in the UK Myocardial Ischaemia National Audit Project database. Logistic regression was used to compare mortality in hospital and at 180 days postdischarge between patients with and without COPD. Variables relating to inhospital factors (delay in diagnosis, use of reperfusion and time to reperfusion/use of angiography) and use of secondary prevention were sequentially added to models.

Results Mortality was higher for patients with COPD both inhospital (4.6% vs 3.2%) and at 180 days (12.8% vs 7.7%). After adjusting for inhospital factors, the effect of COPD on inhospital mortality after MI was reduced for both ST-elevation myocardial infarctions (STEMIs) and non-STEMIs (STEMIs OR 1.24 (95% CI 1.10 to 1.41) to 1.13 (95% CI 0.99 to 1.29); non-STEMIs OR 1.34 (95% CI 1.24 to 1.45) to 1.16 (95% CI 1.07 to 1.26)). Adjusting for inhospital factors reduced the effect of COPD on mortality after non-STEMI at 180 days (OR 1.56 (95% CI 1.47 to 1.65) to 1.37 (95% CI 1.31 to 1.44)). Adjusting for use of secondary prevention also reduced the effect of COPD on mortality at 180 days for STEMIs and non-STEMIs (STEMIs OR 1.45 (95% CI 1.31 to 1.61) to 1.25 (95% CI 1.11 to 1.41); non-STEMIs OR 1.37 (95% CI 1.31 to 1.44) to 1.26 (95% CI 1.17 to 1.35).

Conclusions Delayed diagnosis, timing and use of reperfusion of a STEMI, use of angiography after a non-STEMI and use of secondary prevention medicines are all potential explanations for the mortality gap after MI in people with COPD.

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COPD and acute myocardial infarction: effects on presentation, management and outcomes

Kieran J. Rothnie, Jennifer K. Quint

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Article | Information & metrics | Explore

Abstract

Cardiovascular disease is a common cause of death in patients with chronic obstructive pulmonary disease (COPD) and is a key target for improving outcomes. However, there are concerns that patients with COPD may not have enjoyed the same mortality reductions from acute myocardial infarction (AMI) in recent decades as the general population. This has generated interest in how COPD patients present with AMI and how their management and outcomes compare to non-COPD patients. The evidence points to an increased risk of death after AMI in patients with COPD, but it is unclear to what extent this is attributable to COPD itself or to modifiable factors including under-treatment with guideline-recommended interventions and drugs. We review the evidence for differences between COPD and non-COPD patients in terms of the presentation of AMI, its treatment and outcomes both in-hospital and in the longer term.

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Special populations

Original article

Predicting mortality after acute coronary syndromes in people with chronic obstructive pulmonary disease

OPEN ACCESS

Kieran J Rothnie[1,2], **Liam Smeeth**[2,3], **Neil Pearce**[2], **Emily Herrett**[2], **Adam Timmis**[3,4], **Harry Hemingway**[3,5], **Jadwiga Wedzicha**[6], **Jennifer K Quint**[1,2]

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Abstract

Objective To assess the accuracy of Global Registry of Acute Coronary Events (GRACE) scores in predicting mortality at 6 months for people with chronic obstructive pulmonary disease (COPD) and to investigate how it might be improved.

Methods Data were obtained on 481 849 patients with acute coronary syndrome admitted to UK hospitals between January 2003 and June 2013 from the Myocardial Ischaemia National Audit Project (MINAP) database. We compared risk of death between patients with COPD and those without COPD at 6 months, adjusting for predicted risk of death. We then assessed whether several modifications improved the accuracy of the GRACE score for people with COPD.

Results The risk of death after adjusting for GRACE score predicted that risk of death was higher for patients with COPD than that for other patients (RR 1.29, 95% CI 1.28 to 1.33). Adding smoking into the GRACE score model did not improve accuracy for patients with COPD. Either adding COPD into the model (relative risk (RR) 1.00, 0.94 to 1.02) or multiplying the GRACE score by 1.3 resulted in better performance (RR 0.99, 0.96 to 1.01).

Conclusions GRACE scores underestimate risk of death for people with COPD. A more accurate prediction of risk of death can be obtained by adding COPD into the GRACE score equation, or by multiplying the GRACE score predicted risk of death by 1.3 for people with COPD. This means that one third of patients with COPD currently classified as low risk should be classified as moderate risk, and could be considered for more aggressive early treatment after non-ST-segment elevation myocardial infarction or unstable angina.

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Research paper V

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